STUDIES ON NEURAL REGULATION OF BLOOD PRESSURE IN HYPERTENSION

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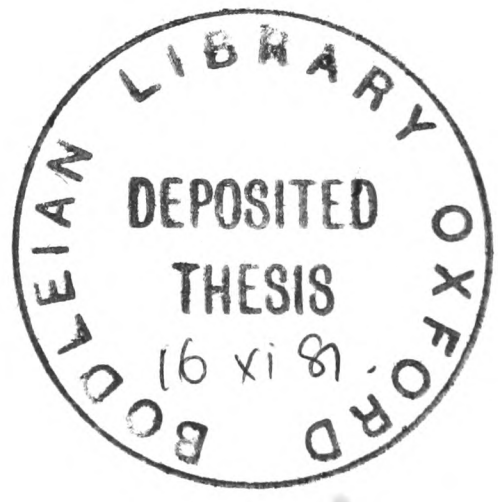

Studies on Neural Regulation of Blood Pressure in Hypertension

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ABSTRACT

Resetting of baroreceptor afferent firing in hypertensive animals, and the reduction in baroreflex regulation of the heart rate seen in man, are thought to be secondary to changes in vascular distensibility in hypertension.

Diminished baroreflex sensitivity should be reflected in a withdrawal of inhibition of sympathetic nervous function. This hypothesis was investigated in 62 hypertensive subjects using three indirect indices of sympathetic nervous activity: (1) the haemodynamic responses to mental and physical exercise, (2) plasma noradrenaline concentrations at rest, and on exercise, and (3) the beat-to-beat variability of waking ambulatory blood pressure.

Subjects with diminished baroreflex sensitivity (1) achieved higher maximum mean arterial blood pressures during four different exercises, and greater absolute increases in blood pressure when bicycling, (2) tended ($P<0.06$) to have higher plasma noradrenaline concentrations when bicycling, and (3) exhibited greater variability of their waking mean arterial pressure. It was concluded that subjects with reduced baroreflex sensitivity were less able to buffer acute changes in blood pressure, and inhibit sympathetic efferent activity, particularly when somatic afferents were also activated, as in physical exercise.

The time course and extent of changes in baroreflex sensitivity, in relation to changes in the heart and (by inference from previous work) the peripheral vasculature, during the development and reversal of 2-kidney 1-clip Goldblatt hypertension was investigated in rats. A reduction in baroreflex sensitivity occurred within three days of renovascular hypertension, before the occurrence of cardiovascular

changes and resetting of the threshold for carotid sinus activation. Baroreflex sensitivity returned to normal one day after the reversal of renovascular hypertension, at a time when these structural changes were still present. It was concluded that 'non-structural', rather than 'structural' factors were responsible for the reduction in baroreflex sensitivity during the initial stages of renovascular hypertension.

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INTRODUCTION

CHAPTER 1

INTRODUCTION

The peripheral arterial baroreceptors are reset in hypertension to respond to the higher levels of mean arterial blood pressure (McCubbin, Green and Page, 1956; Aars, 1968; Nosaka and Wang, 1972; Angell-James, 1973; Sapru and Wang, 1976; Sleight, Robinson, Brooks and Rees, 1977; Peveler, 1980). The threshold for single and whole nerve firing is increased, and the individual receptors seem to be less sensitive to a given rise in blood pressure (Angell-James, 1973; Sapru and Wang, 1976). The mechanism of this resetting has been thought to be due to some form of structural change in the receptor regions, the receptor-wall element coupling, or possibly in the nerve endings themselves (Abraham, 1967; Hilgenberg, 1967; Aars, 1969; Angell-James, 1973; Brown, Saum and Tuley, 1976; Peveler, 1980).

As baroreceptor nerve firing cannot be recorded directly in conscious man, a number of alternative methods which examine the sensitivity of whole or part of the baroreflex arc have been employed. Carotid sinus massage (Galdston, Goldstein and Steele, 1943), or occlusion (Pickering, Kissin and Rothschild, 1936), carotid sinus nerve stimulation (Schwartz, Griffith, Neistadt and Hagfors, 1967) or blockade (Kezdi, 1953; Tuckman, Slater and Mendlowitz, 1965) all alter heart rate and blood pressure, but cannot be used to quantify the baroreceptor reflex. Tilting, lower body suction, or the Valsalva manoeuvre, which stimulate all of the peripheral arterial baroreceptors, rather than simply the carotid

sinus reflex, have additional effects on low pressure receptors as well.(Sharpey-Shafer, 1955; Abboud, 1979).

Smyth, Sleight and Pickering (1969) raised blood pressure transiently by the intravenous injection of angiotensin and recorded the reflex cardiac slowing. Blood pressure was measured directly from the brachial artery. A linear relationship between pulse interval and the preceding systolic blood pressure was observed over the course of the pressure rise, and plotted. The slope of this line was used as an index of baroreflex sensitivity (BRS). Individuals with more sensitive baroreflexes therefore exhibited a greater reflex bradycardia for a similar pressure rise.

A functional abnormality in the baroreflex regulation of heart rate in hypertension was apparent when this method was applied to man. Earlier work, based on carotid sinus occlusion, had suggested that the carotid baroreflex was intact in patients with high blood pressure (Pickering et al., 1936). Bristow, Honour, Pickering, Sleight and Smyth (1969) were able to show that baroreflex regulation of heart rate (BRS) was reduced, but still present. Age and mean arterial pressure act independently to lower baroreflex sensitivity (Gribbin, Pickering, Sleight and Peto, 1971). As both of these factors act to reduce the distensibility of the arterial wall (Wolinsky, 1972; Folkow, 1978) it seemed reasonable to suggest that the resetting of baroreceptors seen in hypertensive animals, and the reduction in baroreflex sensitivity observed in hypertensive man were based on similar 'structural' processes. Indeed, teenage males with borderline blood pressure elevation exhibit alterations in the resistance vessels of the hand (Sannerstedt, Sivertsson and Lundgren, 1976) and diminished baroreflex sensitivity (Takeshita, Tanaka, Koroiwa and Nakamura, 1975).

Reflex mechanisms, including the baroreceptor reflex, can be modulated or overriden by autonomic activation or blockade. Most human activity produces parallel, rather than inverse changes in blood pressure and heart rate. Therefore, it should not be surprising to find that baroreflex sensitivity can be altered acutely in a way that is not purely 'structural'. This has been noted with sleep (Smyth, Sleight and Pickering, 1969), exercise (Bristow, Brown, Cunningham, Howson, Strange Petersen, Pickering and Sleight, 1971), mental arithmetic (Sleight, Fox, Lopez and Brooks, 1978), and with drugs such as propranolol (Pickering, Gribbin, Strange Petersen, Cunningham and Sleight, 1972) or clonidine (Korner, Oliver, Sleight, Chalmers and Robinson, 1974). Although these changes in baroreflex sensitivity may be mediated by alterations in baroreflex afferent activity to a modest degree (Angell-James and Bobik, 1979; Coleridge, Coleridge, Kaufman and Dangel, 1981), for the most part they appear to be a consequence of summation or convergence of differing afferent input within the central nervous system (Korner, 1978, 1979; Abboud, 1979).

The reduction in baroreflex sensitivity in hypertension is generally believed to be due to the structural vascular changes that follow and are a consequence of the elevated blood pressure (Downing, 1979), but there is empirical evidence to suggest that a 'non-structural' or 'autonomic' component may be contributory. If the peripheral arterial baroreceptors were active in the early stages of hypertension, for instance, before these structural changes develop, the increase in blood pressure should be opposed by a reflex fall in cardiac output and slowing of the heart rate. This does not occur, which would imply that during this initial

period baroreceptor function must be altered or overcome in some way that is evidently not 'structural' in origin. Similarly, the reversal of renovascular hypertension leads to a rapid fall in blood pressure, despite the persistence of these vascular changes; heart rate and cardiac output are not altered initially (Lundgren, 1974b; Hallback-Nordlander, Noresson and Lundgren, 1979).

The time course of blood pressure changes, and of the development of left ventricular hypertrophy and structural vascular adaptation in the peripheral vasculature during the evolution of 2-kidney 1-clip Goldblatt hypertension, has been accurately documented by Lundgren, Hallback, Weiss and Folkow (1974). Changes in blood pressure, left ventricular weight, and structural vascular design during the reversal of short-term 2-kidney 1-clip Goldblatt hypertension have also been studied (Lundgren, 1974a,b). The time course of changes in the threshold for carotid sinus activation in this rat model parallels the development of structural vascular adaptations (Jones, 1977). However, the changes in baroreflex sensitivity during the development and reversal of hypertension, particularly in the initial stages of each process when 'non-structural' influences might be detected, has not been previously studied. One aim of this thesis, therefore, was to investigate the time course and extent of changes in baroreflex sensitivity in rats, in relation to changes in the heart and (by inference from previous work) peripheral vasculature, during the development and reversal of 2-kidney 1-clip Goldblatt hypertension.

Considerable attention has been paid to the reduction in baroreflex control of the heart in hypertension (Bristow, Honour, Pickering, Sleight and Smyth, 1969; Gribbin et al., 1971; Korner, 1978, 1979; Sleight, 1979),

owing to the lack of a method, at present, which can examine the effect on both heart rate and peripheral resistance of stimulating carotid and aortic baroreceptors simultaneously: techniques which change carotid sinus transmural pressure (Ernsting and Parry, 1957) give an incomplete picture of the total reflex response, as the changes which they evoke are modified by the persistent buffering activity of the aortic nerves.

One might also predict that the reduction in afferent baroreceptor input to the central nervous system would lead to a withdrawal of parasympathetic tone and a release of the tonic inhibition normally exerted over the sympathetic nervous system (Heymans and Neil, 1958; Angell-James, 1974a; Abboud, 1979). One consequence would be a decrease in the parasympathetic, and an increase in the sympathetic regulation of heart rate and cardiac output, as has been seen in some young subjects with borderline hypertension (Julius, Pascual and London, 1971).

Investigation of the sympathetic nervous system in essential hypertension has been hampered by the lack of a suitable direct measure of sympathetic nervous activity. Muscle nerve sympathetic discharge, which has been recorded by Wallin and his associates (Delius, Hagbarth, Hongell and Wallin, 1972a), is, not surprisingly, similar in normal and hypertensive man (Wallin and Sundlof, 1979). Discharge from the renal and splanchnic nerves, which would be of greater interest, is not accessible to this technique. Therefore, indirect indices of sympathetic nerve activity are more commonly studied.

The second aim of this thesis was to study whether reduced baroreflex sensitivity in hypertension is reflected in a withdrawal of

inhibition of sympathetic nervous activity. These investigations were conducted in man. Three indirect indices of sympathetic function were examined: the haemodynamic responses to mental and physical exercise, plasma noradrenaline concentrations at rest, and on exercise, and the variability of ambulatory blood pressure. I wished to see whether resting blood pressure, heart rate, or plasma noradrenaline concentration, or changes in these variables during activity were increased in the presence of reduced baroreflex sensitivity.

The Hospital Ethics Committee restricted these investigations to hypertensive patients. Thus, instead of comparing hypertensive to normal patients, multiple regression analysis, and partial correlation coefficients were used to study the independent influence of age, mean arterial pressure, and baroreflex sensitivity on the variables in question. The adoption of this method of analysis required the inclusion in this study of a sizeable number of subjects, with a broad range of ages and mean arterial pressures.

CHAPTER 2

BARORECEPTOR REFLEX REGULATION OF THE CIRCULATION

Review

Bernard (1851) found that sectioning the cervical sympathetic chain in the rabbit led to vasodilation of its facial blood vessels; stimulation of these fibres could induce vasoconstriction (Brown-Séquard, 1854). The importance of the nervous system in cardio-vascular regulation was revealed when Bernard (1858) produced profound hypotension by transection of the cervical spinal cord.

In 1859 Marey noted that an increase in blood pressure was followed by a fall in heart rate that could be prevented by vagal section (Marey, 1881). Cyon and Ludwig (1866) discovered that stimulation of the central end of the aortic nerve in the rabbit produced bradycardia and hypotension. Slowing of the heart rate could be abolished by atropine. They suggested that reflex 'inhibition' of neural centres of cardiovascular regulation might be occurring (Neil, 1962). Dittmar (1870, 1873) localised the site of the vasomotor centre in rabbits to the ventrolateral reticular formation near the region of the superior olivary and facial nuclei. Blood pressure fell dramatically when the brainstem was transected at a level 3 mm rostral to the obex.

Ludwig noted that section of both aortic nerves did not cause a rise in arterial pressure, and proposed that these nerves were not tonically active (Neil, 1962). An alternative explanation was afforded by Hering (1923). In 1866, Czermak had observed that bradycardia could be produced by applying firm pressure to the skin over the

carotid sinus. He believed that this was by direct stimulation of the vagus. Hering doubted whether direct mechanical stimulation could produce this cardiac slowing. Evidence for the existence of sensitive vasoactive areas in the region of the carotid sinus had accumulated during the nineteenth and early twentieth century (Cooper, 1836; Magendie, 1838; Bayliss, 1893; Siciliano, 1900; Pagano, 1900; Sollman and Brown, 1912), but the reflex nature of their activity was not fully appreciated until the discovery of the carotid sinus nerve (Hering, 1923). Stimulation of the central end of the cut nerve caused a bradycardia and hypotension which occurred through two separate pathways. The bradycardia, which occurred first, could be blocked by atropine or sectioning the vagi; the hypotension could not. Hering was able to demonstrate similar responses if the carotid sinus wall was stimulated mechanically with a small clip, by tension on the common carotid artery, or by stimulation of the internal wall. These responses were abolished by sectioning the ipsilateral sinus nerve. Denervation of both carotid sinus regions had several effects: it abolished the reflex responses to increases and decreases in sinus perfusion pressure, and led to systemic hypertension (Hering, 1924).

Koch (1931) studied the effect of changing endosinus pressure on the heart rate and systemic blood pressure in the rabbit, monkey, cat, dog and hare. He noted a sigmoid relationship between endosinus pressure and the reflex change in pulse interval, which he termed the "Blutdruck-Herzfrequenz-Charakteristic" curve. The reflex control of the heart and blood pressure exerted by the aortic nerves was documented by Heymans and Ladon (1924, 1925) and Anrep and Starling (1925).

Baroreceptor Afferent Fibres

Baroreceptors are activated by distortion or distension; they are sensitive to changes in both the mean and the rate of change of transmural pressure that produce this deformation (Bronk and Stella, 1932; Angell-James, 1971b). Reflex changes can be prevented if the carotid sinuses are embedded in plaster; experimental hypertension may also be produced by this method in the rabbit (Wakerlin, Crandall, Frank, Johnson, Pomper and Schmid, 1954; Burstyn, Horrobin and Lloyd, 1972). The baroreceptor consists of mechanical (i.e. the collagen elastin and smooth muscle of the vessel wall) and electrical (receptor, spike-initiating zone, axon) elements. The manner in which baroreceptor deformation leads to mechano-electrical transduction is poorly understood, as the receptor potentials are too small to be recorded directly. This process appears to be sensitive to changes in extracellular concentrations of sodium, potassium, and calcium ions (Brown, 1980). Bergel, Anand, Brooks, MacDermott, Peveler, Robinson and Sleight (1980) have proposed that baroreceptor endings are coupled mechanically in series to smooth muscle, such that its contraction will pull on and activate the receptor.

Action potentials were first recorded from aortic nerves by Koster and Tschermak (1902), who distended the isolated aorta with saline. Einthoven, Flohil and Battaerd (1908) and Adrian (1926) noted that activity in these nerves was synchronous with the pulse; similar discharge was recorded from the carotid sinus nerve.

Impulse frequency from single nerve fibres is greatest during the upstroke of the pressure wave, and tends to fall off after the peak systolic pressure is reached, although the sinus pressure remains

above the threshold for nerve firing. Increasing the systemic pressure leads to recruitment of baroreceptor units with differing thresholds; saturation of the receptor is usually reached at pressures near 200 mm Hg (Heymans and Neil, 1958). Single fibres exhibit a minimum frequency of firing at a static threshold pressure, a maximum frequency of firing above a saturation pressure or inflection point, and a linear increase of firing with blood pressure between these two points. Multifibre preparations exhibit a more sigmoid shaped pressure-response curve (over the range of 60-180 mm Hg in the dog) (Kirchheim, 1976). Single fibres adapt to static pressure changes (Landgren, 1952; Robinson and Sleight, 1980).

Pulsatile pressure augments these characteristics, lowering the pressure threshold for nerve firing and enhancing the reflex changes in heart rate and blood pressure. The aortic baroreceptors are thought to require a higher pressure threshold for their activation than the carotid (Ead, Green and Neil, 1952; Donald and Edis, 1971; Pelletier, Clement and Shepherd, 1972; Schmidt, Kumada and Sagawa, 1972). The steady state responses of unmyelinated baroreceptors have higher thresholds and lower maximum asymptotic discharges than myelinated receptors (Thorén, Saum and Brown, 1976).

Central integration

Myelinated and unmyelinated baroreceptor afferent fibres terminate mainly within the middle one-third of the nucleus tractus solitarius (NTS) where rhythmic discharge characteristic of baroreceptor firing may be detected (Seller and Illert, 1969; Jordan and Spyer, 1980). Input from aortic and carotid baroreceptor afferent nerves may terminate in different areas (Calaresu and

Ciriello, 1980). The primary neurotransmitter of these afferents may be l-glutamate, rather than a catecholamine (Reis, Tallman, Perrone, Doba and Kumada, 1980).

The NTS receives additional input from atrial and ventricular receptors (Lee, Kuo and Chai, 1972), chemoreceptors (Muira and Reis, 1972), the fifth and seventh cranial nerves (Sousa-Pinto, 1970), as well as higher centres, such as the hypothalamus and the A5 and A2 catecholaminergic cell groups (Korner, 1978, 1979; Loewy and McKellar, 1980; Talman, Alonso and Reis, 1980). Suprapontine influences can be interrupted by decerebration, but are not essential for baroreflex function (Katz, Kahn and Wang, 1967), which is abolished by bilateral NTS destruction (Humphrey, 1967; Nathan and Reis, 1977). Noradrenergic and adrenergic neurones participate in the central integration of the baroreflex (Chalmers and Reid, 1972; Chalmers, Petty and Reid, 1979). Selective noradrenergic denervation of the NTS with 6-hydroxydopamine (6-OHDA) impairs the baroreflex control of heart rate (Snyder, Nathan and Reis, 1978).

Efferent Baroreflex Activity

The efferent arc of the baroreflex is mediated through cardiac vagal and spinal preganglionic sympathetic fibres. The latter synapse with postganglionic neurones in the sympathetic ganglia. Baroreceptor projections to cardiac vagal efferents appear to diverge from those to sympathetic vasomotor neurones (Korner, 1978, 1979). Decussation of the fibres responsible for the vasomoter response occurs mainly in the cord; the vagal response to carotid sinus distention has only a small crossed component (Wang and Borison, 1947a).

At rest, tonic activity is present in both vagal and sympathetic efferent nerves. Cardiac vagal efferents exhibit pulse synchronous discharge when pulse intervals are greater than 350 ms. The vagal discharge usually begins in the falling phase of the aortic pressure wave. With shorter pulse intervals, peak discharge tends to occur later in the cardiac cycle (Kunze, 1972). Vagal discharge has a frequency of 1 Hz at normal resting blood pressure, and rises to a maximum of about 40 Hz when systemic blood pressure is increased (Kunze, 1972). The extent to which the cardiac cycle is prolonged by a single vagal volley depends on the phase of the cardiac cycle at which the stimulus is delivered (Brown and Eccles, 1934).

Vagal efferent discharge may be altered by respiration or chemoreceptor stimulation (Davidson, Goldner and McCloskey, 1976); this is probably trivial in the conscious animal (Kirchheim, 1976; Borst and Karemaker, 1980).

Discharge from preganglionic sympathetic fibres averages 1-2 Hz, and rises to about 15 to 30 Hz during maximum stimulation. The discharge rate of post-ganglionic fibres is slightly higher. This discharge also exhibits respiratory fluctuations, in conjunction with the rhythmic discharges of bulbar respiratory motor neurones (Korner, 1978, 1979).

Pulse synchronous discharges can be recorded from post-ganglionic multifibre preparations (Adrian, Bronk and Phillips, 1932; Taylor and Gebber, 1975). These oscillations have been recorded from muscle sympathetic nerves in man by Wallin and his associates (Delius, Hagbarth, Hongell and Wallin, 1972a,b,c).

The baroreflex regulation of heart rate and peripheral resistance

The elevation of blood pressure in the carotid sinus causes a reflex activation of cardiac vagal fibres and a reduction of impulse activity in cardiac, cervical and splanchnic sympathetic nerves (Bronk, Ferguson, Margaria and Solandt, 1936; Spickler, Kezdi and Geller, 1967; Ninomiya, Nisimaru and Irisawa, 1971). Bilateral lesions in the ventromedial NTS about 1.5 mm anterior to the obex retain the bradycardia but abolish the hypotension following carotid sinus nerve stimulation in the cat (Humphrey, 1967). More caudal lesions abolish both reflexes (Miura and Reis, 1969).

By synchronising sinoatrial node activity with vagal efferent bursts, the baroreceptor reflex exerts a beat-to-beat control over heart rate (Jewett, 1964; Scher and Young, 1970). The latency between the start of an abrupt pressure change and reflex vagal efferent activity is about 100ms (Jewett, 1964). The inhibition of sympathetic activity requires a longer period - about 260ms from the start of the aortic pressure pulse, or 170ms from the stimulation of the carotid sinus nerve (Korner, 1978, 1979).

An abrupt rise in blood pressure evokes immediate changes in heart rate. The vagal component may contribute to between 50 and 70% of the overall response, depending on the resting pulse interval (Robinson, Epstein, Beiser and Braunwald, 1966; Korner, Shaw, West and Oliver, 1972; Levy and Martin, 1979). Vagal efferent excitation can be seen within one second; inhibition of cardiac sympathetic activity does not occur for 10 to 30 seconds, i.e. the time required for noradrenaline to be taken up into nerve terminals, or washed away by the coronary circulation. As the hydrolysis of acetylcholine is more rapid, the effect of heart rate of vagal withdrawal is seen

before that of sympathetic nerve activity, which has a more delayed and gradual onset (Wang and Borison, 1947b; Glick and Braunwald, 1965; Katona, Barnett and Jackson, 1967; Warner and Russell, 1969; Scher and Young, 1970; Thames and Kontos, 1970; Kardon, Peterson and Bishop, 1974; Levy and Martin, 1979).

If the carotid sinus nerve is stimulated repeatedly, at regular frequencies, the heart rate and blood pressure responses adapt; sympathetic nerve discharge, initially inhibited, resumes in less than a minute, but at reduced strength (Wallin, Sundlof and Delius, 1975; Kirchheim, 1976). The limitation for frequency transmission appears to lie in the NTS (Seller and Illert, 1969).

Carotid sinus occlusion increases both cardiac output and femoral blood flow (Delanois and Bernard, 1967). Schmidt, Kumada and Sagawa (1971) studied the reflex effects of 25 mm Hg stepwise changes in carotid sinus perfusion pressure on cardiac output and systemic vascular resistance in mongrel dogs, anaesthetised with chloralose and urethane. Stepwise incresaes in carotid sinus pressure had little effect on heart rate; the fall in mean arterial pressure was mediated by a decrease in stroke volume, peripheral resistance, or both.

Sympathetic neural activity to various vascular beds is not uniform. In animals, baroreflex effects on vascular resistance are more marked in the skeletal muscle bed than in the skin or kidney. This may be due to the greater number of nerve fibres to muscle beds, rather than due to any differences in baroreflex curves relating carotid sinus pressure to renal, muscular and intestinal responses (Vatner, Franklin, Van Citters and Braunwald, 1970; Kendrick, Oberg and Wennergren, 1972; Cox and Bagshaw, 1975). At high carotid

sinus pressures, reflex vasodilatation in muscle beds may be mediated by the excitation of cholinergic sympathetic vasodilator fibres, as well as by inhibition of sympathetic constrictor fibres (Takeuchi and Manning, 1971).

Methods used to test the baroreflex arc in conscious animals and man

The integrity of the baroreflex arc in conscious animals and man may be tested by methods which stimulate or inhibit sinus nerve firing: carotid sinus massage (Czermak, 1866; Galdston, Goldstein and Steele, 1943) or occlusion (Pickering, Kissin and Rothschild, 1936) or direct electrical stimulation of the sinus nerve (Schwartz, Griffith, Neistadt and Hagfors, 1967; Epstein, Beiser, Goldstein, Redwood, Rosing, Glick, Wechsler, Stampfer, Cohen, Reis, Braunwald and Braunwald, 1969). Unilateral or bilateral application of local anaesthetic to these nerves induces blood pressure elevation, tachycardia and increased cardiac output in both normal and hypertensive subjects. The blood pressure rose to 320/180 mm Hg in one instance (Kezdi, 1953; Tuckman, Slater and Mendlowitz, 1965). Hypertension may also be produced by blockade of both glossopharyngeal nerves at the base of the skull (Guz, Noble, Widdicombe, Trenchard, Mushin and Makey, 1966).

Although Beiser, Zelis, Epstein, Mason and Braunwald (1970) found that stimulation of the carotid sinus baroreceptors with neck suction led to a reflex reduction in skin and muscle vascular resistance, Abboud, Eckberg, Johannsen and Mark (1979) have suggested that the influence of the cardiopulmonary reflex over the muscle resistance vessels may predominate, with the principal role of the carotid sinus reflex being the regulation of heart rate and the

splanchnic vascular resistance. Each of these techniques may be used to demonstrate that the carotid sinus baroreflex retains its tonic activity in hypertension, but they do not allow for its quantification. Baroreflex sensitivity may be quantified by stimuli such as tilting, lower body suction and the Valsalva manoeuvre (Sharpey-Schafer, 1955; Abboud, 1979). However, these manoeuvres also activate cardiopulmonary receptors. The assessment of baroreflex function in man is hampered by our inability to use the isolation and blocking techniques developed in animal studies in order to distinguish between primary evoked responses to a stimulus, and secondary responses from additional groups of receptors.

Blood pressure may be altered by vasoactive drugs (Smyth, Sleight and Pickering, 1969) or cuffs inserted around the great vessels (Scher and Young, 1970; Korner, Shaw, West and Oliver, 1972). These methods only allow the cardiac response to acute changes in blood pressure to be quantified. On the other hand, the blood pressure and heart rate responses evoked by neck suction or pressure (Ernsting and Parry, 1957) are modified by the persistent buffering activity of the aortic nerves. Each method, therefore, has its limitation in the quantification of its evoked responses. Moreover, vascular cuffs are restricted to animal experiments, and the other two methods necessitate indwelling arterial cannulae unless the cardiac response alone is the subject of investigation.

Methods employing vasoactive drugs

Smyth, Sleight and Pickering (1969) raised blood pressure transiently by the intravenous injection of angiotensin, and recorded the reflex cardiac slowing. A relationship between pulse interval and the

preceding systolic pressure, measured directly from the brachial artery, was observed over the course of the pressure rise, and plotted. The least squares regression equation was used to fit a linear regression line through these points, and the slope of this line was used as an index of baroreflex sensitivity (BRS). Individuals with more sensitive baroreflexes exhibited a steeper slope, i.e. a greater reflex bradycardia for a similar pressure rise. If the slope of the regression line remained the same, but its y-intercept shifted, such that larger or shorter pulse intervals were now observed at identical arterial pressures, the reflex was said to have "reset" (Pickering, 1970). Changes in the baroreceptor regulation of heart rate, defined in this fashion, should be distinguished from the "resetting" of nerve firing observed in recordings from baroreceptor afferent fibres in hypertensive animals. Smyth (1967) noted that the reflex bradycardia produced by angiotensin was often followed later by a tachycardia; this was subsequently shown to be due to the central actions of angiotensin and to a direct cardiac effect (Koch-Weser, 1965; Severs and Daniels-Severs, 1973). Phenylephrine, an alpha adrenergic agonist (Beck, Barnard and Schrire, 1969) was substituted for angiotensin in subsequent investigations. This linear beat-to-beat relationship between pulse interval and systolic pressure appeared to be reproduceable and independent of either resting heart rate or systemic pressure in five individuals, who were studied twice, up to fifteen months apart (Gribbin, Pickering, Sleight and Peto, 1971). The response to a fall in blood pressure was shown to be less than that to rising pressure (Pickering, Gribbin and Sleight, 1972).

Using this method, Pickering and Davies (1973) estimated the time delay of the baroreceptor heart rate reflex to be about 475ms in man. This 'ramp' method of assessing BRS was used in the present series of investigations.

Korner and his colleagues developed a 'steady state' technique to examine the reflex during more sustained changes in blood pressure. Here arterial pressure is again altered with vasoactive drugs, and maintained constant for a 30-second period. The pulse interval, which is reexamined near the end of this time, is usually less than when the ramp method is employed. Korner (Korner, West, Shaw and Uther, 1974; Korner, 1978, 1979) states that 60-70% of this steady state response is due to vagal efferent activity.

Methods employing changes in neck pressure

Angell-James (1971a) using an open chest operation in rabbits found that changes in transmural pressure were as effective stimuli to aortic baroreceptor firing as were changes in intraluminal pressure. Neck chambers apply this principle to man (Ernsting and Parry, 1957; Bevegard and Shepherd, 1966; Thron, Brechmann, Wagner and Keller, 1967; Eckberg, Cavanaugh, Mark and Abboud, 1975; Ludbrook, Mancia, Ferrari and Zanchetti, 1976). A plastic or metal collar, extending from the chin to the shoulders, is placed around the neck and sealed with double layers of rubber flaps. Positive and negative pressures are generated by a vacuum motor attached to an exhaust. Most of the positive pressure or negative suction applied to the neck is transmitted to the tissues surrounding the carotid sinus and perceived by the baroreceptors as a change in the sinus transmural pressure (Ludbrook et al., 1976).

Negative pressure, which increases transmural pressure, is perceived as a rise in intra-arterial pressure. Eckberg (1977) used this technique to examine the cardiac response to short pulses of negative suction, synchronised with the electrocardiogram. He altered resting vagal tone by applying progressive amounts of negative suction to the neck and then added incremental suction onto this steady-state level. The heart rate response to the increasing suction (i.e. -10 mm Hg) was similar, regardless of the pre-existing steady state. This would imply that the baroreflex regulation of heart rate is independent of resting vagal tone.

Bevegard and Shepherd (1966) found that their normal subjects responded to an increase in transmural pressure with substantial falls in blood pressure and smaller changes in heart rate and cardiac output. Some dilatation of the resistance vessels also occurred. In contrast, Mancia, Ferrari, Gregorini, Valentini, Ludbrook and Zanchetti (1977) stated that a normal subject responds to an increase in transmural pressure with a small decrease in mean arterial pressure, and to positive neck pressure with larger absolute increases in blood pressure. Stephenson and Donald (1980) have exposed the vascularly isolated carotid sinuses of conscious dogs to static pressures between 50 and 240 mm Hg. With the aortic baroreceptors intact, the hypotension in response to an increase in carotid sinus pressure was considerably greater than the hypertension in response to a fall in sinus perfusion pressure. Stephenson and Donald (1980) were unable to explain the discrepancy between their animal data, that of Bevegard and Shepherd (1966) on the one hand, and that of Mancia et al. (1977), but commented that their own animals showed no signs of arousal or discomfort. Anxiety on

the part of the human subjects, who are quite aware of the sensation of suction or pressure about their neck, might have blunted the reflex hypotension and bradycardia and accentuated the reflex hypertension in Mancia's group, who were not as well acquainted with the experimental procedure. Differences between the animal and human results may also be due to the varying interaction of carotid and extracarotid baroreceptors in these two species. When Stephenson and Donald (1980) interrupted the cardiopulmonary and aortic afferent fibres by vagotomy, the resultant rise in arterial pressure could not be completely inhibited by maximum activation of the carotid baroreceptors. Data from anaesthetised dogs supports the view that the extracarotid baroreceptors appear to buffer hypertension better than hypotension (Edis, 1971; Pelletier, Clement and Shepherd, 1972). The threshold for activation of the aortic arch receptors of rabbits (50 mm Hg) is lower than that in dogs (95 mm Hg) (Aars, 1968; Angell-James, 1971; Pelletier, Clement and Shepherd, 1972) and may be set at a different level in man. Thus caution must be used in applying conclusions derived from neck suction studies to hypotheses concerning the control of heart rate and peripheral resistance by the reflex integration of input from the entire vascular tree.

Is the baroreflex regulation of heart rate and blood pressure similar in resting conscious animals and man?

The difficulty in obtaining direct evidence to address this question can be inferred from the previous discussion. Schmidt, Kumada and Sagawa (1971) noted that stepwise increases in carotid sinus perfusion pressure led to a fall in cardiac output and

peripheral resistance, but as one or the other tended to predominate in a particular animal, these changes were inversely related. However, it is difficult to relate the changes observed in anaesthetised animal preparations to conscious animals or man in view of the vagolytic effect of most anaesthetics (Stephenson and Donald, 1980).

Faris, Iannos, Jamieson and Ludbrook (1980) encapsulated one carotid sinus of a rabbit in a fluid-filled reservoir whose internal pressure could be increased or decreased in a square wave fashion. When the aortic baroreceptors and the other carotid sinus were denervated, the characteristic of the blood pressure and heart rate response to these stimuli were similar; there was a significant association between both the gain and the range of the heart rate and blood pressure response in each animal. Nonetheless, the authors underlined the weakness of this relationship, which might have been improved if dynamic, rather than static, pressure stimuli were used and the other baroreceptor areas remained intact. They noted that denervation of the opposite carotid sinus led blunted reflex slowing by two to three fold. This might be expected on the basis of the facilitative effect that two intact carotid sinus nerves exert upon the cardiac response when stimulated simultaneously (Wang and Borison, 1947a).

There is good evidence for a relationship between the control of blood pressure and heart rate by the carotid sinus baroreceptors in resting conscious man (Bevegard and Shepherd, 1966). Stepwise increases in negative neck pressure led to decreases in heart rate and blood pressure of a similar proportion and degree. Mancia et al. (1977) did not show as clear a relationship. This may have been due to the reasons discussed earlier, or perhaps due to their

use of heart rate, rather than pulse interval in relating the reflex cardiac changes to an increase in arterial pressure (Bristow, Brown, Cunningham, Howson, Strange Petersen, Pickering, Sleight, 1971).

A direct relationship between changes in heart rate and blood pressure might only exist when baroreceptors are stimulated by rising, rather than falling, blood pressure. Stephenson and Donald (1980) noted that the immediate fall in blood pressure following an increase in carotid sinus pressure was mediated by a vagally-induced decrease in heart rate and cardiac output, whereas sinus hypotension did not increase the animals' heart rates.

Acute changes in baroreflex sensitivity

Acute changes in baroreflex sensitivity may occur as a result of alterations in one or more of baroreceptor afferent input, central integration of information, or baroreflex regulation of efferent parasympathetic and sympathetic nervous activity. These mechanisms may be 'structural' or 'non-structural' in origin.

Changes in afferent input may be secondary to or independent of the viscoelastic properties of the arterial wall. Kunze has shown that a reduction in extracellular sodium, or an increase in calcium and magnesium concentrations, within the physiological range, will reset baroreceptor firing and reduce the depressor response to increased carotid sinus pressure (Kunze, Saum and Brown, 1977; Kunze and Brown, 1978; Kunze, 1979).

Rees (1967) and Reis and Fuxe (1968) have demonstrated catecholamine containing sympathetic nerve endings in the carotid sinus regions, but the way in which sympathetic neural activity may influence baroreflex function and its significance in the conscious animal is

not fully understood. Sampson and Mills (1970) found that stimulation of the sympathetic supply to the carotid sinus of the cat modulated baroreceptor activity, as did Koizumi and Sato (1969) in the opossum. Sampson and Mills (1970) suggested that this might occur if sinus wall tension had been altered at a constant endosinus pressure, or if the sinus was sensitive to the release of noradrenaline from nerve endings. Bagshaw and Peterson (1972) showed that stimulation of the sympathetic nerve supply to the carotid sinus could reduce both its diameter and its elastic modulus in a frequency dependent fashion.

Peveler, Bergel, Gupta, Sleight and Worley (1980) stimulated the vago-sympathetic trunk in anaesthetised dogs and noted a reduction in carotid sinus diameter (measured ultrasonically) at each static pressure level. Firing frequency was reduced at low pressures and increased at high pressures; the sensitivity of single baroreceptor units to static and pulsatile pressures was increased at all pressures when related to diameter.

Similar changes were seen by this group when noradrenaline was perfused through the carotid sinus. Earlier workers had reported that drugs such as noradrenaline or adrenaline when applied to the carotid sinus in high doses increased, rather than decreased, sinus nerve discharge. The converse was found with substances that decreased arterial tone, such as tolazoline, papaverine, potassium chloride or sodium nitrate (Heymans and Van den Heuvel-Heymans, 1950; Landgren, Neil and Zotterman, 1952). The means by which a decrease in vessel radius at constant intrasinus pressure (which should in fact decrease wall tension and consequently strain) in fact stimulates sinus nerve activity is imperfectly understood.

However, the concentration of catecholamine applied topically in these studies may have been excessive. Bergel et al. (1980) found that noradrenaline (1 µg/ml) could activate carotid sinus smooth muscle and constrict the sinus. A decrease in firing at low pressures with an increase in firing at high pressures with a crossover was again observed. Nerve discharge was increased by noradrenaline at a constant wall radius.

Angell-James and Bobik (1979) found that propranolol shifted the aortic baroreceptor pressure response curve to the left, such that nerve firing was increased by about 11% at resting pressures. This may be due to the unopposed alpha-adrenergic effect of noradrenaline on the aortic vasculature; only a modest change was seen with labetolol, a partial alpha- and non-selective beta-adrenoceptor blocking agent (Angell-James and Peters, 1980).

Short-term resetting of baroreceptor pressure firing occurs when aortic pressure is either increased or decreased and held for 20 minutes. This has been recently (since the completion of this experimental work) demonstrated by Coleridge, Coleridge, Kaufman and Dangel (1981). This phenomenon is similar to the hysteresis observed when pressure-firing curves are constructed from stepwise increases and decreases in pressure, and can probably be explained by the viscoelastic behaviour of the wall element-receptor coupling in series (Bergel et al., 1980). With an increase in wall distending pressure a progressive lengthening, or creep, of the viscous elements in the wall occurs (i.e. elastin, collagen, smooth muscle) during which the force transmitted to the receptor may be reduced.

The central integration of baroreceptor afferent input may be affected acutely by input to the NTS from other centres within the

central nervous system, or the simultaneous activation of several groups of sensory afferents, with synergistic or opposing effects, resulting in an inhibition or enhancement of the baroreceptor reflex. Smyth, Sleight and Pickering (1969) suggested that the sensitivity of the baroreflex arc was increased during sleep; it was subsequently felt that the regression line between pulse interval and systolic pressure had "reset" to the lower levels of blood pressure during sleep, but that the sensitivity of the reflex was on the whole the same (Bristow, Honour, Pickering and Sleight, 1969). Korner (1978, 1979) has suggested that these changes in autonomic tone reset the baroreflex when independent inputs to autonomic motor neurones are summated, whereas sensitivity may be affected if input converges onto common sites within the CNS.

In man, hypoxia, hypercapnia (Bristow, Brown, Cunningham, Goode, Howson and Sleight, 1971) and halothane and nitrous oxide anaesthesia (Bristow, Prys-Roberts, Fisher, Pickering and Sleight, 1969) reset the reflex whereas thiopental diminishes baroreflex sensitivity.

Stimulation of the hypothalamic defence area leads to hypertension and tachycardia, as the vagus is inhibited and sympathetic activity to the heart and venous circulation increased. Hilton (1963, 1966) demonstrated that the baroreceptor heart rate reflex could be suppressed by stimulation of this area. Lisander (1970) felt that the reflex modulation of resistance is minimally suppressed by stimulation of the defence centre; enhancement of the vasoconstrictor effects have been observed by others (Djojosugito, Folkow, Kylstra, Lisander and Tuttle, 1970; Gebber and Snyder, 1970; Humphreys and Joels, 1972; Kumada, Schramm, Altmansberger and Sagawa, 1975). A possible explanation for this discrepancy was offered by Coote,

Hilton and Perez-Gonzalez (1979) who showed that both the bradycardia and sympatho-inhibitory effects of carotid baroreceptor or sinus nerve stimulation could be suppressed by stimulation within the hypothalamic defence area, whereas hypothalamic stimulation close to but outside the defence area increased arterial pressure and sympathetic activity to a smaller degree, and abolished the baro-reflex mediated bradycardia, not the hypotension. Stimulation of the amygdala, hippocampus, inferior olivary, and fastigial nuclei can also produce excitation or inhibition of the control of heart rate (Smith and Nathan, 1966; Hockman, Talesnik and Livingston, 1969; Gebber and Klevans, 1972). Not surprisingly, mental arithmetic, which increases heart rate and blood pressure by evoking an alerting response and anxiety in man (Brod, Fenel, Hejl and Jirka, 1959) also reduces the baroreflex regulation of heart rate (Sleight, Fox, Lopez and Brooks, 1978).

Input from central catecholaminergic areas also modulates the gain of the baroreflex - the regulation of heart rate can be blunted by selective destruction of the noradrenergic innervation to the NTS by 6-OHDA. This is not inconsistent with the demonstration that clonidine, a centrally acting drug which reduces sympathetic nervous activity, can improve baroreflex sensitivity (Korner, Oliver, Sleight, Chalmers and Robinson, 1974), as catecholaminergic neurons may have facilitatory or inhibitory functions at differing locations within the CNS (Chalmers et al., 1979).

The baroreflex may be modulated by input from receptors in the carotid bodies, upper airways and lungs (Wennergren and Oberg, 1980; Angell-James, de Burgh Daly and Taton, 1980). Right heart failure (Higgins, Vatner, Eckberg and Braunwald, 1972) and left ventricular

hypertrophy (Mark, Abboud, Schmid and Heistadt, 1973) blunt the baroreflex. The integration of baroreceptor, cardiopulmonary, chemoreceptor and somatic reflexes has been reviewed by Abboud (1979). Recently, Malliani, Pagani and Bergamaschi (1979) have shown that stimulation of spinal sympathetic afferents by inflation of a cuff inside the aorta of conscious dogs reduces the bradycardia following phenylephrine injection.

It is not clear as to whether volume loading blunts the baroreflex. Cardiopulmonary receptors are stimulated by rapid infusions of saline in dogs (Vatner, Boettcher, Heyndricks and McRitchie, 1975) and man (Anlauf, 1979), leading to a reduction in baroreflex sensitivity that may be related to increases in right atrial pressure. On the other hand, alterations in plasma volume in patients with renal failure did not affect BRS, but did increase blood pressure (Tomiyama, Shiigai, Ideura, Tomita, Mito, Shinohara and Takeuchi, 1980). Ludbrook, Faris and Jamieson (1981), using a surgically implanted capsule in conscious rabbits, found that neither the heart rate nor the blood pressure response to a sine wave stimulus was significantly affected by physiological changes in plasma volume.

Baroreflex sensitivity appears to be independent of heart rate or vagal tone in conscious resting man (Gribbin, Pickering, Sleight and Peto, 1971; Eckberg, 1977).

Baroreceptor efferent responses may be altered selectively in experimental situations, as can be seen during the infusion of small doses of angiotensin into the vertebral artery. This has an inhibitory action on vagal efferent activity probably mediated through the area

postrema (Joy and Lowe, 1970; Lumbers, McCloskey and Potter, 1979). It is possible that renovascular and neurogenic hypertension may be linked in this fashion (Dickinson, 1981). A similar dissociation between the heart rate and blood pressure responses to baroreflex stimulation occurs during exercise in conscious animals and man.

Effect of dynamic exercise on the baroreflex regulation of heart rate and blood pressure

If phenylephrine is injected intravenously into exercising subjects the reflex bradycardia in response to the induced hypertension diminishes as the workload increases (Bristow, Brown, Cunningham, Howson, Strange Petersen, Pickering and Sleight, 1971). On the other hand, Bevegard and Shepherd (1966) who used neck suction, and Robinson, Epstein, Beiser and Braunwald (1966) who used phenylephrine to raise blood pressure during milder exercise found similar changes in heart rate at rest and during exercise. Bristow and his colleagues explained this discrepancy by the inverse relationship between pulse interval and heart rate, as changes in pulse interval would be correspondingly less for similar absolute changes in heart rate at the higher levels seen during physical exercise.

Peripheral resistance falls during exercise, due to vasodilation in active muscle. A neurogenic vasoconstriction occurs in inactive vascular regions, and sympathetic discharge to the venous capacitance system increases (Shepherd, 1966; Krasney, Levitsky and Koehler, 1974). Exercise can increase cardiac output up to fourfold in man (Astrand, Cuddy, Saltin and Stenberg, 1964); this is normally mediated by an increase in heart rate (Vatner and Pagani, 1976).

There is good evidence to suggest that some baroreceptor regulation of blood pressure persists during exercise, even though the cardiovagal response is markedly diminished. If systemic vascular resistance is kept constant by a cuff placed around the aorta, exercise tachycardia can be prevented (Warner and Topham, 1967). Carotid sinus stimulation continues to inhibit sympathetic tone during exercise in conscious dogs (Vatner et al., 1970). Bevegard and Shepherd (1966), who observed similar reductions of blood pressure at rest and during exercise when the carotid sinus baroreceptors were stimulated by negative suction, concluded that the baroreflex continued to oppose the rise in blood pressure and heart rate during exercise.

In contrast, Donald, Rowlands and Ferguson (1970) were unable to detect a difference in the vasodilatation between limbs with and without innervation in exercising dogs. Moreover, other authors found that the baroreceptors were not essential for a normal haemodynamic response to exercise (Van Houtte, LaCroix and Leusen, 1966; Krasney et al., 1974; McRitchie, Vatner, Boettcher, Heyndrick, Patrick and Braunwald, 1976), although the increases in cardiac output and heart rate were in fact attenuated in Krasney's study, and a marked fall in blood pressure in the baroreceptor denervated dog was noted by Ardell, Scher and Rowell (1980) during exercise.

On the whole, the evidence is in favour of a retention of baroreflex control of blood pressure during exercise. Recently, Geis and Wurster (1980) have convincingly demonstrated that the reflex blood pressure responses to carotid sinus occlusion and hypertension are retained in exercising dogs, although the response to the latter was not as great. They suggested that this was necessary

to maintain arterial pressure at a level needed to support tissue perfusion in the exercising animal.

"Central command" and afferent input from exercising muscle may interact to modulate the baroreflex arc at the initiation of exercise. The rapid rise in heart rate, within 0.5 s of the initiation of voluntary movement, is likely due to direct activation of autonomic pathways in the CNS (Freyschuss, 1970a,b; Petro, Hollander and Bouman, 1970). The stimulation of somatic muscle afferents by exercise may contribute to increased blood pressure and heart rate (Coote, Hilton and Perez-Gonzales, 1971; McCloskey and Mitchell, 1972). Electrical stimulation of Group III and IV afferents from muscle lowers the gain of the baroreflex and causes a reflex vasoconstriction in muscle, an increase in blood pressure, and heart rate (Quest and Gebber, 1972; Kumada, Nogami and Sagawa, 1975; Abboud, 1979). The magnitude of this response can be enhanced if the carotid sinus reflex is inhibited by low perfusion pressures, and blunted when endosinus pressure is high. Abboud (1979) has suggested that the reduced baroreflex sensitivity in hypertension may be associated with an increased sympathetic outflow to blood vessels when these somatic afferents are activated, as in exercise.

Effect of isometric exercise on the baroreflex regulation of heart rate and blood pressure

Lind, Taylor, Humphreys, Kennelly and Donald (1964), and Freyschuss (1970a,b) observed the large changes in blood pressure occurring during isometric exercise and suggested that the baroreflex was suppressed. Cunningham, Strange Petersen, Peto, Pickering and Sleight (1972) noted that the baroreflex control of pulse interval

was reduced by sustained handgrip at 30% of maximal voluntary contractile force. The reduction in BRS, which was greater than that seen during bicycle exercise at similar heart rates, persisted after the cessation of handgrip, for reasons that were not explained.

"Central command" and somatic afferent input from exercising muscle may inhibit the baroreflex regulation of heart rate, but not of blood pressure during isometric exercise. The heart rate response seems to be affected more by negative than by positive neck pressure (Ludbrook, Faris, Iannos, Jamieson and Russell, 1978; Mancia, Iannos, Jamieson, Lawrence, Sharman and Ludbrook, 1978).

Goodwin, McCloskey and Mitchell (1972) noted that blood pressure, heart rate, and respiratory minute volume could be altered by vibratory stimulation of muscle spindle afferents during prolonged isometric contraction; in a later study in the anaesthetised dog these authors concluded that these afferents did not interfere with or inhibit the baroreceptor reflex (Streatfield, Davidson and McCloskey, 1977). Delius, Hagbarth, Hongell and Wallin (1972b) recorded muscle nerve sympathetic activity during handgrip. Sympathetic discharge increased in parallel with blood pressure, and yet the normal rhythmic inverse relationship between sympathetic bursts and variations in systolic blood pressure could still be observed. These authors therefore concluded that the baroreflex continued to operate during isometric exercise.

The Arterial Baroreflex in Hypertension

Developmental changes in baroreflex sensitivity with age

Mild increases in blood pressure associated with aging lead to a vascular response similar to that seen with hypertension, but to a lesser degree, with an increase in vascular elastin and collagen and a decrease in wall distensibility (Roach and Burton, 1959; Wolinsky, 1972). Aortic baroreceptors in normotensive rats are less sensitive to strain at 20 weeks of age than at 10 weeks of age. This resetting may be required as the aorta becomes larger and more distensible over this period (Andresen, Krauhs and Brown, 1978). In adult man, BRS declines with age (Gribbin, Pickering, Sleight and Peto, 1971), as does the fall in mean arterial pressure and peripheral resistance on carotid sinus stimulation with neck suction (Lindblad, 1977).

The baroreceptor reflex in experimental cardiovascular disease

Experimental atherosclerosis in rabbits leads to mildly elevated arterial pressure, vascular changes, degeneration of aortic baroreceptor nerve endings and a diminution in baroreceptor impulse frequency (Angell-James, 1974a) that is related to the duration of disease. This was not as severe as the reduction in impulse frequency noted in rabbits with renal hypertension (Angell-James, 1973) or medial sclerosis (Angell-James, 1974b) who exhibited similar findings but to a more pronounced degree. Hysteresis was increased in these preparations suggesting that the viscoelastic properties of the aortic arch had altered. The baroreceptor firing threshold was reset to a higher level in experimental atherosclerosis and hypertension but was in fact lower in calciferol treated animals.

This may have been because plaques of calcium were preventing the arterial walls from collapsing at these lower pressures. Angell-James (1974a) proposed that the mild hypertension observed may occur reflexly through an increase in sympathetic nervous activity and vascular resistance resulting from a reduced baroreceptor population, activity, and reduced distensibility of the aortic wall following the development of atherosclerosis. A similar phenomenon may occur in man (Sleight, 1979).

Vascular changes in hypertension

The vascular consequences of hypertension, among them medial and left ventricular hypertrophy, had been observed by Johnson (1868). Pickering (1945) suspected that these changes had a role to play in the maintenance of elevated peripheral resistance in rabbits with renovascular hypertension following the first week or so of hypertension. These changes might affect neural control of blood pressure if they lead to decreased distensibility of the arterial wall and hence diminished baroreceptor nerve firing (Volhard, 1948). The nature, extent and consequences of these changes have been documented by Folkow and his coworkers in a series of experiments in which the isolated hindquarters of hypertensive rats and matched normotensive control rats have been infused in parallel under constant flow. Maximal dilatation was established with papaverine and the resistance (proportional to pressure) then measured. Next, noradrenaline (NA) was infused in a stepwise fashion from subthreshold up to supra-maximal concentrations. This allowed the NA threshold, the steepness of the resistance curve, and the maximal pressor response to supra-maximal amounts of NA to be calculated (Folkow, Hallback, Lundgren

and Weiss, 1970). The increased resistance at maximal dilatation, steeper slope of the resistance curve, and increased maximal pressor response to noradrenaline which were observed strongly suggested the presence of an increased medial thickness, a reduced lumen, and an increased wall /lumen ratio, even at maximal dilatation. Neither increased smooth muscle sensitivity to noradrenaline, nor water-logging of the vasculature could fully explain these findings (Folkow, 1978). These predictions have been confirmed in morphological and physiological studies on small resistance vessels in the mesenteric beds of spontaneously hypertensive rats and Wistar Kyoto rats (Mulvany, Hansen and Aalkjaer, 1978). These changes do not occur in a part of the circulation that is protected from hypertension; moreover, the resistance to flow at maximal dilatation, and the pressor response to noradrenaline may be correspondingly reduced in an area of vasculature exposed to sustained hypotension (Weiss and Hallback, 1974).

This structural adaptation is present throughout the peripheral vasculature, involving the baroreceptor regions as well. The distensibility of the carotid arteries and sinus is reduced in greyhounds with renovascular hypertension, while the elastic modulus of the wall material, relative to strain, is not changed. This implies that the change in distensibility is due to the increased wall thickness alone, rather than to any altered properties of the wall material, such as by 'waterlogging' (Peveler, 1980). Similar changes in the distensibility of the aortic arch baroreceptor regions have been described in experimental hypertension, and are also associated with diminished baroreflex sensitivity (Aars, 1969; Angell-James, 1973; Peveler, 1980).

The consequences of these vascular alterations in hypertension would be twofold: higher peripheral resistance at maximal dilatation, whether achieved pharmacologically, through vasoactive metabolites, or maximum inhibition by baroreceptor stimulation of sympathetic influence on blood vessels, and increased changes in flow resistance in these vessels for any degree of smooth muscle shortening or lengthening (Folkow, 1978). Teenage subjects with mild blood pressure elevation have been shown to exhibit increased resistance at maximal dilatation in the vascular bed of the hand and markedly greater resistance changes when NA was infused into the artery proximal to these vessels than age-matched normal subjects. This was not due to increased smooth muscle sensitivity to NA, as the threshold concentration of NA was similar in the hypertensive subjects and controls (Sivertsson, 1970; Sannerstedt, Sivertsson and Lundgren, 1976). Conway (1963) found that resistance to blood flow in the forearm was increased, both at rest and during reactive hyperaemia, in hypertension.

Resetting of baroreceptors in hypertension

McCubbin, Green and Page (1956) compared sinus nerve activity in normal dogs and dogs with renovascular hypertension. At 'normal' pressures the afferent nerve discharge, pulsatile in the controls, was absent in the hypertensive animals. At higher pressures, nerve activity was continuous in the normotensive animals and pulsatile in the experimental dogs. The baroreflex remained tonically active, but at a higher level of pressure (Matton, 1957). Resetting of the baroreceptors in hypertension has been confirmed in dogs and other species (Aars, 1968; Nosaka and Wang, 1972; Angell-James, 1973; Sapru

and Wang, 1976; Jones, 1977; Sleight, Robinson, Brooks and Rees, 1977; Peveler, 1980), although this may not be as complete for baroreceptors with unmyelinated fibres (Jones and Thorén, 1977; Thorén and Jones, 1977). The threshold for single and whole nerve firing is reset in hypertensive animals, and the individual receptors seem to be less sensitive to a given rise in pressure (Angell-James, 1973; Sapru and Wang, 1976).

Baroreceptor resetting may be effected in several ways - through adaptation of the receptors to the rising pressure (McCubbin, Green and Page, 1956), altered distensibility of the arterial wall (Aars, 1969; Angell-James, 1973), changes in the receptor-wall element coupling (Brown, Saum and Tuley, 1976; Peveler, 1980), or degeneration of the receptor endings (Abraham, 1967; Hilgenberg, 1967; Angell-James, 1973), although this latter finding has been disputed (Rees, Sleight, Robinson, Bonchek and Doctor, 1978). In man, these changes are possibly enhanced by atherosclerotic plaques in the regions innervated by mechanoreceptors (Sleight, 1979).

These changes could reduce the gain of the baroreflex by altering the coupling of receptors to wall elements and making the recruitment of additional baroreceptor units more difficult. Angell-James (1973) concluded that the impairment in gain of the overall baroreceptor heart rate reflex in renal hypertensive rabbits could be accounted for by changes in the receptors.

Resetting was not observed in carotid sinuses that had been protected from hypertension by an arteriovenous fistula (Kezdi, 1967).

There is some evidence to suggest that baroreceptors may be reset acutely in hypertension, before adaptive changes in peripheral vessels can occur. Six hours after the aorta was constricted in

rats, a marked bradycardia was present. This eased by 48 hours, at which point resetting of the threshold for aortic baroreceptor firing was seen in almost all of the animals (Krieger, 1970). Adaptation to the rising pressure may have occurred through altered viscoelastic properties of the wall, as discussed earlier (Coleridge et al., 1981).

Brown, Saum and Tuley (1976) reported an increase in the threshold for steady state discharge, a reduced slope of the impulse frequency-pressure relationship, and a higher pressure of maximum firing of aortic baroreceptors in 4 to 6 month old SHR. They stated that these changes occurred independently of alterations in arterial distensibility, but at the same time noted that the pressure volume relationship of the SHR showed an increased stiffness of about 15%.

Change in baroreflex control of blood pressure and heart rate in hypertension

The demonstration, by Hering (1924), that carotid sinus baroreceptor denervation led to hypertension, promoted a search for similar pathology in human hypertension. Regniers (1930) and Mies (1932) occluded the carotid arteries, digitally, below the level of the sinus and failed to observe a rise in systemic pressure. Although a fall in pressure and a bradycardia was noted when the carotid sinuses of hypertensive patients were compressed, these authors concluded that the baroreceptors were inactive in high blood pressure. Pickering et al. (1936) did not feel that adequate occlusion of the sinus had occurred in these experiments. When repeated, digital obliteration of one carotid artery below the sinus produced rises in blood pressure and heart rate, whereas pressure on the sinus caused a fall in pulse

rate and blood pressure. The percentage fall appeared to be greater in the elderly and in hypertensive patients. These observations suggested that the carotid sinus reflex was indeed functionally intact in hypertension, but could not explain the normal heart rates in these patients.

It was not until a method for testing the sensitivity of the baroreflex arc in man was developed that a functional abnormality in the baroreceptor reflex in hypertension became apparent. Bristow, Honour, Pickering, Sleight and Smyth (1969) demonstrated a reduction in baroreflex sensitivity in patients with hypertension, prompting Pickering (1968) to write: "This diminished sensitivity could represent the fault for which we have searched for long" (p.202). Gribbin, Pickering, Sleight and Peto (1971) investigated 81 subjects and found that increasing age and mean arterial pressure were independently correlated with diminishing baroreflex sensitivity. Diminished BRS has been demonstrated in teenage males with borderline hypertension when the baroreceptors are stimulated by phenylephrine (Takeshita, Tanaka, Koroiwa and Nakamura, 1975) or by neck suction (Eckberg, 1979). Takeshita, Tanaka and Nakamura (1978) studied the effect of intravenous propranolol on baroreflex sensitivity in young subjects with borderline hypertension, and age-matched normal controls. Baroreflex sensitivity improved in the hypertensive group, but did not return entirely to normal levels, suggesting that 'autonomic' or 'non-structural' factors may interact with changes in vascular design to reduce baroreflex sensitivity in the early stages of hypertension, as the improvement was more than might be expected purely on the basis of increased afferent nerve discharge (Angell-James and Bobik, 1979). Some young subjects with

borderline hypertension exhibit an increase in cardiac output and a decrease in parasympathetic control of the heart (Julius, Pascual and London, 1971; Julius, 1976) which may be a consequence of this interaction.

Reductions in BRS have been observed in renal hypertensive rabbits (Angell-James and George, 1976) and dogs (Peveler, 1980) when phenylephrine was used to raise blood pressure acutely. The linear portion of the pressure-pulse interval curve is also reduced when the "steady-state" method is employed, in proportion to the severity of the hypertension (Korner, West, Shaw and Uther, 1974).

Mancia, Ludbrook, Ferrari, Gregorini and Zanchetti (1978) studied the effect of neck suction, i.e. an increase in carotid sinus transmural pressure (CSTMP) on blood pressure in hypertensive patients. These individuals exhibited a larger reduction in mean arterial pressure than normal subjects, and yet only small changes in heart rate. A decrease in CSTMP produced a small increase in mean arterial pressure. These authors concluded that hypertensive patients were better able to buffer rises than falls in pressure, and that the sigmoid stimulus-response curve (Koch, 1931) in these patients had been reset in such a way that resting mean arterial pressure, which was close to the peak of the sigmoid curve in normal subjects (explaining the small response to an increase in CSTMP), shifted to the bottom of the curve in hypertension (where a rise along the linear portion of the curve could induce a greater response to a rise in pressure). This interpretation would suggest that a dissociation of heart rate and blood pressure responses had occurred in hypertensive subjects, i.e. that while the former had become less sensitive, the latter had become more so. This would seem to be

inconsistent with the demonstration of baroreceptor resetting and reduced afferent nerve discharge in hypertension (Angell-James, 1973; Sapru and Wang, 1976).

These findings are difficult to interpret, for several reasons: the buffering action of the aortic nerves cannot be quantified, and the effect of age on these responses was not controlled for. Furthermore, Mancia, Ludbrook, Ferrari, Gregorini and Zanchetti (1978) have presumed that stimulation of the baroreceptors is identical whether the pressure changes are intraluminal or extraluminal. This may be true with the aortic arch receptors in the normotensive rabbit (Angell-James,1971a), it may not be the case in aged or hypertensive humans, in whom receptor endings, situated at the medial-adventitial border, may be isolated from intraluminal pressure changes by increased wall thickness and atherosclerotic deposition. Externally applied suction might therefore have a different effect on the baroreceptor units than would similar changes in transmural pressure produced by vasoactive drugs. Angell-James and George (1980) observed similar responses to Mancia et al. (1978) in anaesthetised rabbits, but drew different conclusions from them. The maximum gains of the curves relating increases in carotid sinus pressure to changes in vascular resistance were in fact increased in both renal hypertensive and medial sclerotic rabbits when examined about their resting mean arterial pressures, whereas the maximum gain of curves relating carotid sinus pressure to heart rate were significantly reduced. They suggested that these observations were consistent with Folkow's arguments (Folkow, 1978), i.e. that withdrawal of efferent sympathetic tone would lead to larger changes in resistance and blood pressure in those animals with an increased wall to lumen ratio, as was seen in

fact in rabbits with renal hypertension and medial sclerosis. Thus, any changes in afferent baroreceptor input could be offset by a heightened dose:response curve at the efferent, vascular level.

There is good evidence to suggest that sympathetic efferent activity is also reset in hypertension. Thorén and Ricksten (1979) obtained single fibre recordings of renal and splanchnic sympathetic activity in normotensive (NCR) and spontaneously hypertensive rats (SHR). At rest, SHR had double the mean sympathetic activity of NCR. During noradrenaline infusion, the decrease in fibre activity/mm Hg rise of arterial pressure was less in the SHR than in the NCR when expressed as a percentage change from baseline.

Baroreflex modulation of vascular reactivity

The extent to which changes in vascular design alter the pressor response to hormonal or neural stimuli may be altered by the baroreflex arc. If carotid sinus perfusion pressure is kept constant in the experimental dog, and other baroreceptor areas denervated, the pressor effect of adrenaline and the depressor effect of acetyl-choline are markedly enhanced (Cuypers, 1935; Heymans, de Schaepdryver and King, 1956). This phenomenon was not commented on by McRitchie, Vatner, Boettcher, Hendrick, Patrick and Braunwald (1976) who used methoxamine, a vasoconstrictor, to raise the arterial pressure of intact and baroreceptor denervated conscious dogs. Similar pressure rises were obtained in the latter group with only 6% of the control dose.

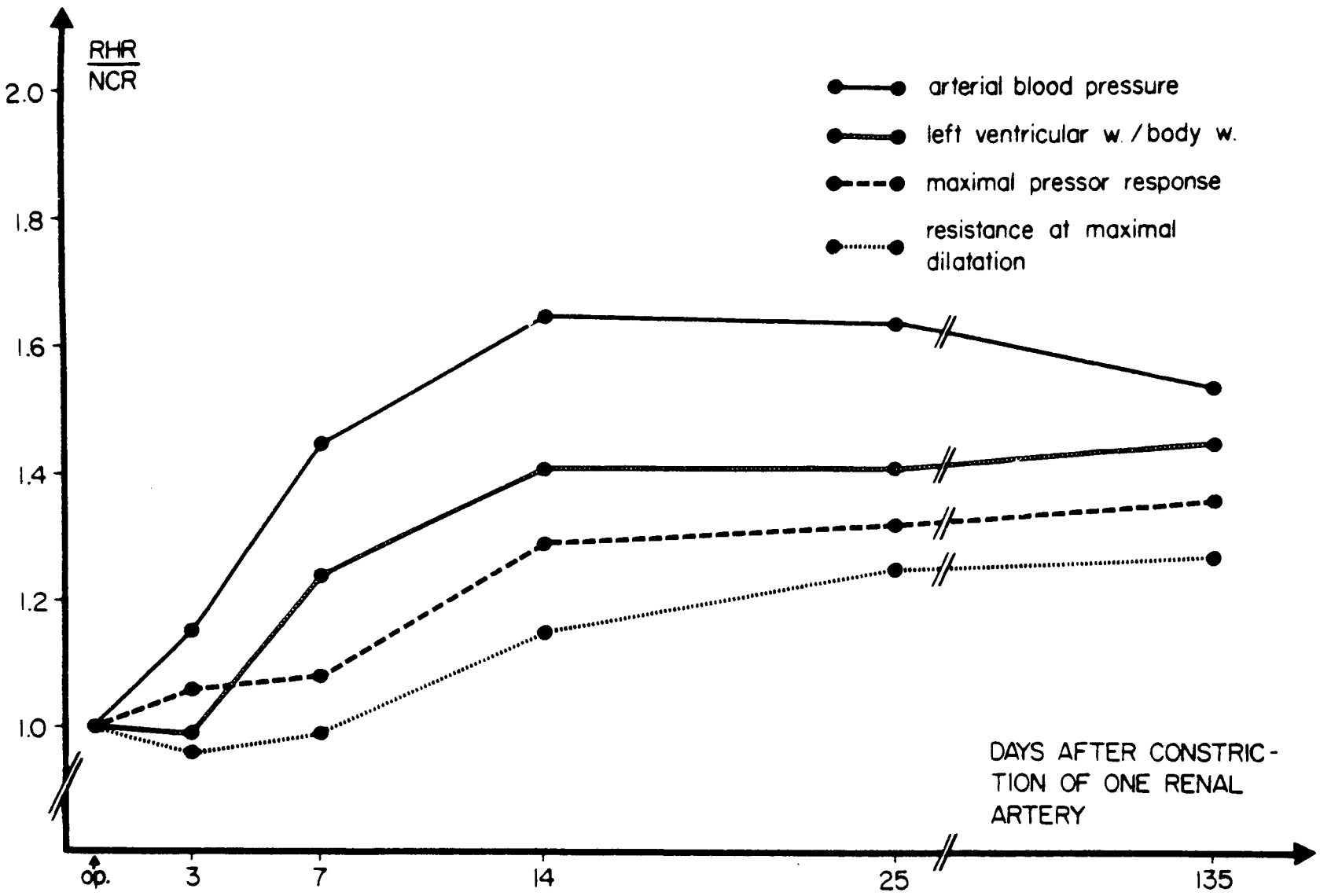

Fig. 2-1 The time course of changes in mean arterial pressure, left ventricular/body weight ratio, maximal prssure response to noradrenaline, and resistance to flow at maximal dilatation following constriction of one renal artery in the rat, from Lundgren (1974a). Values for renal hypertensive rates (RHR) are expressed as a ratio to values in control rats (NCR).

Time course of changes in blood pressure, baroreceptor function, and cardiovascular design following the development of renovascular hypertension

Long-term resetting of the mechanoreceptors is said to develop gradually following the induction of experimental hypertension in animals (McCubbin, 1958) but the exact time course of changes in arterial pressure, in the peripheral resistance and left ventricle, and in the properties of the baroreflex arc have not been documented as yet. Almost all studies of baroreceptor resetting have been in animals with established hypertension. Krieger (1970) noted resetting of aortic arch baroreceptors occurred about 48 hours after aortic constriction but did not compare this with changes in aortic distensibility. Angell-James and George (1976) noted that the reduction of baroreflex sensitivity in rabbits, as determined by the phenylephrine technique and by nerve fibre recordings, was better correlated with the duration of hypertension, and the distensibility of the isolated perfused aortic arch than with the level of mean arterial pressure, but did not examine the period of developing hypertension.

The time course and extent of changes in mean arterial pressure, the heart and the resistance vessels during the development of 2-kidney 1-clip Goldblatt hypertension have been documented, and are illustrated in Figure 2-1 (from Lundgren, 1974a). Left ventricular hypertrophy appeared by one week, changes in the resistance vessels by two weeks. The vascular sensitivity to NA was not altered; nor was the heart rate. These structural vascular alterations were fully established by 25 days; no further changes were noted after 135 days of renovascular hypertension.

The time course of changes in the threshold for carotid sinus activation, examined by Jones (1977) in the same rat model, was found to parallel the development of structural vascular adaptations.

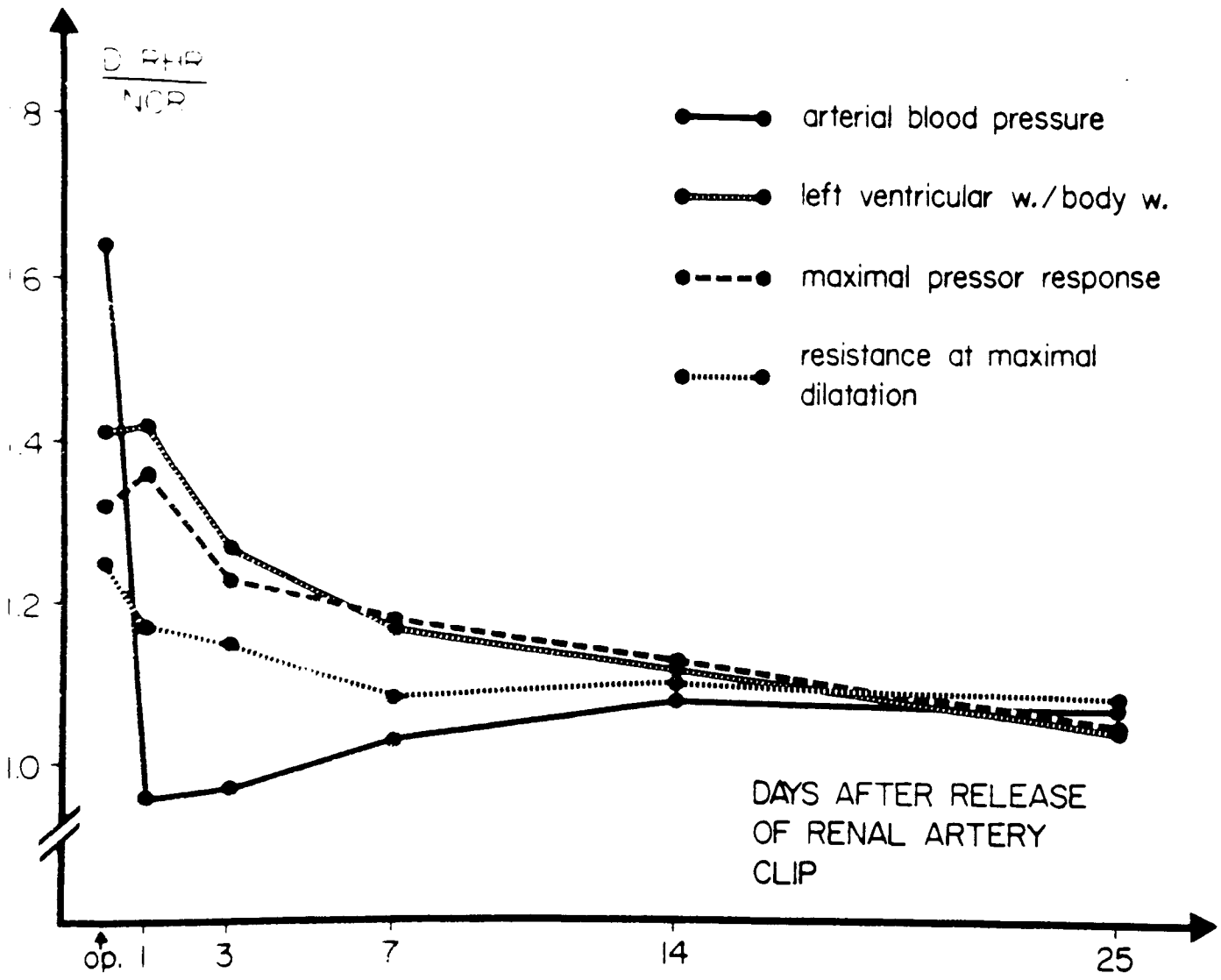

Fig. 2-2 The time course of changes in mean arterial pressure, left ventricular/body weight ratio, maximal pressor response to noradrenaline and resistance to flow at maximal dilatation following reversal of 25 days of 2-kidney 1-clip Goldblatt hypertension in the rat. From Lundgren (1974a). Values for declipped rats (D-RHR) are expressed as a ratio to values in control rats (NCR).

Baroreflex sensitivity was not studied in these animals, and the absence of reflex bradycardia during the initial period of hypertension could not be explained.

Time course of changes in blood pressure, baroreceptor function and cardiovascular design following the reversal of renovascular hypertension

Blood pressure falls to normal or subnormal levels within two hours of the reversal of short-term 2-kidney 1-clip renovascular hypertension, despite the presence of structural vascular changes (Lundgren, 1974a,b; Hallback-Norlander, Noresson and Lundgren, 1979; Thurston, Bing and Swales, 1980). This is due to a fall in total peripheral resistance, as cardiac output and heart rate remain unchanged. Cardiac output tends to rise on the following day, but total peripheral resistance remains reduced for at least a month (Hallback-Nordlander et al., 1979).

The time course and extent of the regression in these vascular alterations have been documented during the reversal of 25 days of renovascular hypertension by Lundgren (1974a,b). As illustrated in Figure 2-2 (from Lundgren, 1974a), the resistance to flow at maximal dilatation returns to normal by one week, the left ventricular weight/body weight ratio by two weeks, but the maximal pressor response to noradrenaline, which reflects the bulk of contractile tissue in the wall of the resistance vessels does not return to normal until three weeks have passed. This model also affords the opportunity to examine the time course of changes in baroreflex sensitivity during the reversal of renovascular hypertension.

When paired hindquarter perfusion studies are performed 8 weeks after the reversal of 135 days of 2-kidney 1-clip Goldblatt hypertension,

neither the mean arterial pressure nor the cardiovascular design revert entirely to normal (Lundgren and Weiss, 1979). It is likely that collagen has been added to the heart and blood vessels by this point (Wolinsky, 1972).

Salgado and Krieger (1973) found a rapid downward shift in the threshold pressure for aortic baroreceptor activation, and an arbitrarily defined pattern of 'normal neural firing' at 1 and 6 hours following removal of a renal artery clip from rats with 2 months of 2-kidney 1-clip Goldblatt hypertension. Resetting seemed to lag behind the fall in pressure. This change is difficult to interpret, as haemorrhage was used to alter the pressure in some of the animals, and may have altered the sympathoadrenal state of the rats. However, this would seem to precede the reversal of structural vascular alterations in baroreceptor regions.

To achieve a normal or subnormal peripheral resistance in the presence of increased flow resistance, tonic smooth muscle activity must also be subnormal in the unclipped rats. Hallback-Nordlander et al. (1979) postulate that this may be due to the release of vasodilators from the ischaemic kidney when the clip is removed, or the sudden withdrawal of a renal influence which exerts an excitatory action on central sympathetic activity. They suggest the latter hypothesis is more in keeping with the absence of a tachycardia; in addition, one might expect the fall in blood pressure to be opposed by an increase in heart rate if an agent which depressed baroreflex sensitivity in this fashion were removed by declipping. However, both reversal experiments (Lundgren, 1974b; Hallback-Nordlander et al., 1979) were performed under chloralose anaesthesia, which may have had a vagolytic effect on the baroreflex.

CHAPTER 3

THE ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN HYPERTENSION

Cardiovascular homeostasis is maintained through inhibitory parasympathetic and excitatory sympathetic efferent activity (Edis and Shepherd, 1970). The sympathetic nervous system innervates the heart and extracerebral vascular beds, where it provides extensive innervation to the resistance vessels (Burnstock, Gannon and Iwayama, 1970), regulates catecholamine secretion by the adrenal medulla (Perlman and Chalfie, 1977) and modulates renin release from the kidney (Davis and Freeman, 1976). The sympathetic nervous system therefore has the ability to raise blood pressure and heart rate acutely, and in the rare instance of phaeochromocytoma, permanently, but whether a chronic excess of sympathetic nervous discharge can induce essential hypertension is not known (Birkenhager and Schalekamp, 1976; de Champlain, 1977; Zanchetti and Bartorelli, 1977; Reid, Dean, Hamilton, Watson, Jones and Littler, 1978; Sever, 1978, 1980). There are several reasons for this. Sympathetic discharge is difficult to quantify, and can only be measured directly from a limited number of sites, but not the splanchnic and renal nerves. It has been suggested that sympathetic nerve activity might be assessed indirectly instead, i.e. by its effect on haemodynamics at rest, and during mental and physical exertion. Alternatively, the haemodynamic response to pharmacological blockade of the sympathetic nervous system, or the changes which occur during sleep, when sympathetic tone is reduced to low levels, may be examined. Secondly, as pointed out by Folkow (1978), sympathetic

nervous activity need not be continuously increased in order to exert a pathophysiological effect. Sympathetic activity may only be intermittently elevated, or possibly only elevated in the initial phase of the disorder, and not easily detected. An additional problem, namely interpreting changes in blood pressure or vascular resistance, in light of the structural changes in the walls of the resistance vessels, has been mentioned earlier.

Sensitive and specific assays for the measurement of plasma catecholamines have been developed recently (Engelman, Portnoy and Lovenberg, 1968; Henry, Starman, Johnson and Williams, 1975). Many authors now believe that plasma catecholamine concentrations provide a reasonable indirect index of sympathetic activity, but with certain reservations, for they may also reflect individual variations in production, release, reuptake and metabolism, in addition to overflow from sympathetic nerve discharge into the plasma (Reid, Jones, FitzGerald, Davis and Boobis, 1980).

The investigation of this question has therefore followed two lines: (1) can hypertension be induced experimentally, through stimulation of the sympathetic nervous system, and (2) is hypertension associated with direct or indirect evidence of increased sympathetic nervous activity? Clearly the presence of such evidence in hypertension would not imply a causal relationship, if other factors, responsible for its initiation, might themselves increase sympathetic tone. Angiotensin, for instance, may increase sympathetic outflow and peripheral resistance by facilitating the release, inhibiting the reuptake or increasing the synthesis of noradrenaline (Severs and Daniels-Severs, 1973). Diminished baroreflex input, for whatever reason, would also tend to remove the

normal tonic inhibition of sympathetic efferent outflow.

Experimental induction of hypertension

Chronic splanchnic nerve stimulation leads to acute hypertension in dogs, but this is not sustained once the stimulation ceases. The induction of tachycardia in these experiments suggests that the baroreflex regulation of heart rate is temporarily overridden (Kubicek, Kottke, Laker and Visscher, 1953).

Hypothalamic stimulation invokes a defence reaction, characterised by increases in heart rate and stroke volume due to enhanced sympathetic stimulation and reduced vagal tone, constriction of capacitance, renal, visceral and epidermal vessels, and vasodilation in the heart, brain and muscular beds, the latter possibly mediated by sympathetic cholinergic fibres. The baroreflex control of heart rate, and probably of vascular resistance, is abolished (Hilton, 1963; Djojosugito et al., 1970; Kylstra and Lisander, 1970; Coote et al., 1979). Stimulation of different hypothalamic areas can lead to selective secretion of adrenaline or of noradrenaline (Folkow and von Euler, 1954). Confrontation and fighting behaviour produces similar circulatory adjustments in unanaesthetised cats; milder forms of this defence response can occur whenever these animals are mildly alerted to their environment (Zanchetti and Bartorelli, 1977).

Long term intermittent stimulation of the hypothalamic defence area in the rat leads to an elevation in blood pressure which subsides once the stimulation ends (Folkow and Rubenstein, 1966). These observations suggested to the authors that intermittent environmental stimuli, which evoke a response similar to the defence reaction, could trigger chronic hypertension in animals, and possibly

in man, in whom the acute pressor reaction to mental arithmetic appeared to mimic this response (Brod, 1963). Thus, hypertension has been produced in squirrel monkeys subjected to a shock avoidance protocol (Herd, Morse, Kelleher and Jones, 1969) and in mice colonies, in which simulation of the conditions of present day life led to increased blood pressure and pathological damage in dominant animals (Henry, Meehan and Stephens, 1967).

Chronic 'neurogenic hypertension' may also develop if the baroreceptor reflex is ablated peripherally or interrupted centrally. Baroreceptor denervated dogs exhibit features of exaggerated sympathetic nervous tone: a tachycardia, marked fluctuations of arterial pressure while awake or on sleeping, and increased cardiac output (Heymans and Bouckaert, 1931; Bing, Thomas and Waples, 1945). It is generally agreed that these animals respond to routine stimuli with a greatly increased lability of arterial pressure; whether they go on to develop chronic hypertension is at present a subject of considerable controversy (Hering, 1924; Alexander and deCuir, 1966; Cowley, Liard and Guyton, 1973; Jones and Hallback, 1978; Chalmers, Petty and Reid, 1979; Ito and Scher, 1979, 1980, 1981; Cowley, Quillen and Barber, 1980). Sinoaortic denervation accelerates the development of Goldblatt hypertension in the dog over the first 48 hours, but does not affect the final level of blood pressure reached (Liard, Cowley, McCaa, McCaa and Guyton, 1974).

Hypertension in sinoaortic baroreceptor denervated rabbits can be prevented or abolished with intracisternal injections of 6-OHDA, suggesting to Chalmers and Reid (1972) that central noradrenergic neurones are responsible for its elevation (see also

Chalmers, Petty and Reid, 1979). Moreover, plasma noradrenaline concentrations at rest are increased in rats with sinoaortic baroreceptor denervation hypertension (Alexander and Velasquez, 1980).

Central interruption of the baroreflex by lesions to the nucleus tractus solitarius (NTS) also produces marked hypertension, sustained tachycardia and blood pressure variability (Nathan and Reis, 1977). The removal of the tonic inhibition that the baroreflex normally exerted over the sympathetic nervous system could be seen best during the day; at night, the lability of blood pressure returned to control levels.

Increases in sympathetic tone need not be associated with hypertension, however. Selective removal of the noradrenaline innervation of the NTS with 6-OHDA, in doses insufficient to elevate blood pressure, damage the NTS, or abolish the baroreflex, induces a chronic state of increased lability of blood pressure that is enhanced when these animals are stimulated. The increase in variability appears to be proportional to the loss of baroreflex sensitivity (Snyder, Nathan and Reis, 1978). Lesions in the A2 catecholamine region of the rat brain also increase the lability of arterial pressure and attenuates the baroreflex control of heart rate, but do not produce hypertension (Talman, Alonso and Reis, 1980). Angell-James (1974a,b) and Angell-James and George (1976) noted, in passing, that rabbits whose baroreceptor impulse frequency had diminished through experimental atherosclerosis, medial sclerosis, or renal hypertension also exhibited increased lability of blood pressure; however, labile blood pressure, of its own, need not invoke vascular adaptation and target organ damage in baroreceptor denervated animals (Jones and Hallback, 1978).

Induction of hypertension in man

The evidence for similar processes occurring in man is scant. The urbanisation or civilisation of populations which may invoke a greater range and number of new environmental stimuli of alerting reactions, without the psychological protection previously afforded by tradition and taboo, leads to hypertension, undoubtedly through a variety of pathways (Sever, Gordon, Peart and Beighton, 1980).

Graham (1945) reported that exposure to battle led to elevated cuff pressures in British soldiers in North Africa; blood pressure fell in almost all of these men after 2 months of rest.

Changes in affect may alter blood pressure acutely. Sokolow (1979) found that 'negative affect' was associated with rises in blood pressure and 'positive affect' with falls. The long term effect of repeated elevations in the subjects is not known, however, blood pressure was consistently lower when they were alone or engaged in pleasant activity, and higher at work or in the presence of strangers. The defence reaction need not occur with 'negative' events, however. Tachycardia and hypertension can occur acutely during participation in challenging and enjoyable pursuits.

The effect of the work environment on blood pressure has been reviewed by Mustacchi (1977) with inconclusive results; the long term effects of emotional tension or sublimated anger have yet to be explored.

Direct evidence of increased sympathetic nerve activity in experimental hypertension

In an elegant series of experiments, Judy and Farrell (1979) showed that the spontaneously hypertensive rat (SHR) exhibited

greater renal and splanchnic sympathetic nerve discharge than its related strain, the Wistar Kyoto rat (WKY), when this was measured from whole nerve recordings. This difference, already present at 5 weeks of age, increased with time. The ability of the arterial baroreceptor reflex, when stimulated by brief aortic occlusion, to maximally inhibit renal sympathetic nerve activity was similar in 5 and 10 week old groups of SHR and WKY, but diminished in the older SHR. This was a function of aortic, rather than carotid baroreceptor resetting. Maximal inhibition was sustained throughout the 40 weeks of study in the WKY, however. When the aortic baroreceptors were denervated and carotid sinuses occluded, renal sympathetic nerve discharge and mean arterial pressure increased markedly in both SHR and WKY, but these values were higher in the SHR at all ages, leading the authors to conclude that SHR exhibited increased sympathetic nerve activity, of central origin from birth, but that by 15 weeks of age this was accentuated by baroreflex resetting. The latter was not likely to be the cause of hypertension in this model, but enhanced an existing predisposition to increased sympathetic nerve activity, expressed even further when baroreceptor afferent input to the CNS was interrupted.

When blood pressure is elevated with phenylephrine, the duration of baroreflex induced silence in these renal sympathetic nerves is also shortened once the baroreceptors have reset (Coote and Sato, 1977).

The methodological problems in interpreting whole nerve recordings in anaesthetised animals have been pointed out by Thorén and Ricksten (1979) who showed that sympathetic nerve activity in single fibres of renal and splanchnic nerves of mature SHR was double that of normal control rats. Parallel changes in heart rate

and discharge from those nerves were seen when animals displayed the alerting response. Again, when baroreceptors were stimulated by the infusion of noradrenaline, the inhibition of sympathetic nerve activity was less in the SHR.

Direct evidence of increased sympathetic nerve activity in hypertensive man

Wallin and his colleagues have obtained brief recordings of muscle nerve sympathetic activity in resting recumbent subjects by inserting a tungsten microelectrode into fascicles of the peroneal or median nerve. Pulse synchronous bursts, which are well correlated to diastolic, rather than systolic blood pressure, occur most frequently during temporary reductions in blood pressure, with a latency of about 1.3s. They are followed, and inhibited, by a rise in blood pressure, suggesting that the baroreflex tends to protect against falls in pressure in this way. An increase in calf vascular resistance also occurs. Electrical stimulation of the carotid sinus nerve, or neck suction, reduces the number of these bursts (Wallin, Sundlof and Delius, 1975; Wallin, Sundlof and Lindblad, 1980). Sympathetic nerve activity decreases during mental arithmetic, but increases slightly during isometric exercise, when baroreflex mediated fluctuations with changes in blood pressure are still observed (Delius, Hagbarth, Hongell and Wallin, 1972b).

Neural activity varies greatly from individual to individual, but is relatively constant when subjects are restudied weeks or months later; activity tends to increase with age (Sundlof and Wallin, 1977, 1978). The diastolic pressure at which sympathetic

discharge is inhibited is reset to a higher level in hypertensive subjects, but there is no quantitative relationship between burst frequency and the level of arterial pressure (Wallin and Sundlof, 1979). In normotensive subjects, at rest, there is a significant linear correlation between sympathetic activity and plasma noradrenaline, suggesting that sympathetic outflow to muscles makes an important contribution to noradrenaline release at rest. The absence of correlation between sympathetic nerve activity and blood pressure, and between blood pressure and plasma noradrenaline in normal subjects, implies that the extent to which this neural activity regulates blood pressure is rather small. It further implies that plasma noradrenaline concentrations might be expected to increase with age in normal subjects (Wallin, Sundlof, Eriksson, Dominiak, Grobecker and Lindblad, 1981). A similar investigation in hypertensive patients has not yet been performed, but it might be predicted on this basis, that plasma noradrenaline would be similar in age-matched normotensive and hypertensive subjects.

Unfortunately, it is difficult to record sympathetic activity for prolonged periods or during vigorous activity. Even so, the response of the muscle sympathetic nerves might not be characteristic of the sympathetic discharge elsewhere, e.g., during alerting responses, an increase in splanchnic and renal nerve activity, inaccessible to this technique, might occur, whereas muscle nerve sympathetic activity should fall. A similar haemodynamic pattern might also occur during the early phases of essential hypertension.

Haemodynamic evidence of increased sympathetic tone in experimental hypertension

The spontaneously hypertensive trait in rats has been attributed to an enhanced neural drive of central origin, reflected in neurohumoral changes, e.g., increased activity of the ACTH-corticosteroid and TSH-thyroxine axes, as well as increased sympathetic nerve discharge from the first few weeks of life onward. Isolated SHR have a lower mean arterial pressure than animals reared together (Folkow and Hallback, 1977; Judy and Farrell, 1979). At rest, young SHR appear to have a 'hyperkinetic' circulation, as compared to controls, with vagal tone reduced, and sympathetic activity enhanced, as is also seen in some young borderline hypertensive subjects (Julius, Pascual and London, 1971; Hallback and Folkow, 1974). Cardiac output and heart rate contribute to the increased blood pressure; stroke volume remains unchanged.

SHR react to alerting stimuli, such as light, noise or vibration, at a lower threshold, and with greater changes in heart rate and blood pressure than either normal control rats (NCR) or renovascular hypertensive rats (RHR), i.e., the difference is not simply a consequence of altered vascular design. Folkow's group have suggested that repeated intermittent alerting stimuli may act to induce a neurogenic hypertension in both animals and man (Hallback and Folkow, 1974; Folkow and Hallback, 1977).

Haemodynamic evidence of increased sympathetic tone in essential hypertension:

(a) the variability of blood pressure

The first direct measure of arterial blood pressure was by

Stephen Hales (1733), who inserted into the carotid artery of a mare a brass pipe "and to that the Wind-Pipe of a Goose, to the other End of which a Glass Tube was fixed". During the course of his investigations he noted that blood pressure varied from beat to beat, often, but not always, in conjunction with respiration. He attributed these fluctuations to changes in the blood, or in the vascular resistance. With the development of the sphygmomanometric method of measuring blood pressure (Hill and Barnard, 1897) variations in arterial pressure during the course of daily activities were documented in man (Hill, 1898). When recorded over a 6 day period in 100 students, this variation in blood pressure was not related to its height (Diehl, 1929).

The clinical decision to treat patients on the basis of causal clinic or surgery blood pressure readings is made difficult by the variation in these measurements, particularly if they fluctuate from visit to visit about an arbitrary 'abnormal' level (e.g. 140/90 mm Hg). Individuals in whom clinic blood pressures have oscillated about this line have been called "labile hypertensives", probably erroneously, as similar fluctuations occur in normal and severely hypertensive subjects from day to day, but about different means. When various groups examined the haemodynamic characteristics of young "labile" hypertensive patients to see if they could be distinguished from either normal subjects or "fixed" hypertensives, some subjects exhibited increased cardiac outputs and an inappropriately elevated peripheral resistance. It was postulated that they might be "hyperreactors" to stressful stimuli (Eich, Peters, Cuddy, Smulyan and Lyons, 1962; Finkielman, Worcel and Agrest, 1965; Sannerstedt, 1966). In some of these patients, the increased cardiac output was due to stroke volume (Finkielman

et al., 1965; Miura, Kobayashi, Sakuma, Tomioka, Adachi and Yoshinaga, 1978) in others, heart rate (Sannerstedt, 1966; Lund-Johansen, 1967; Julius and Conway, 1968; Frohlich, Kozul, Tarazi and Dustan, 1970), suggesting that an impairment of the baroreflex control of heart rate might also be present. The increased heart rate seemed to be due to increased sympathetic drive and decreased parasympathetic inhibition, as cardiac output and heart rate fell more in these borderline hypertensive subjects than in age matched normals but remained consistently elevated when adequate beta blockade with propranolol was given. The administration of both propranolol and atropine led to cardiac output and heart rates that were similar to the controls (Julius, Pascual and London, 1971). Peripheral resistance remained inappropriately elevated following propranolol and atropine, but could be reduced by alpha-adrenoceptor blockade (Julius, Esler and Randall, 1975).

These patients were not "hyperkinetic" in that their oxygen consumption, relative to their cardiac output, was normal. Many went on to develop "fixed" hypertension, with normal cardiac output and elevated peripheral resistance (Eich, Cuddy, Smulyan and Lyons, 1966; Lund-Johansen, 1976). Nevertheless, the evidence for "hyperreactivity" and an "inappropriately" elevated cardiac output in borderline hypertension was not entirely convincing. Conway (1970) demonstrated a positive relationship between diastolic blood pressure and cardiac output in a large series of normal subjects, which extended to borderline or "labile" but not to moderate hypertensives, in whom cardiac output declined with increasing diastolic pressure. A single dose of propranolol i.v. resulted in a similar fall in cardiac output in borderline hypertensive patients and

normals, suggesting that their cardiac output was not inappropriately elevated by increased sympathetic nervous activity. The extent of the "lability" of these patients' blood pressures could not be estimated with methods existing at that time, nor was it certain that borderline hypertensive patients were indeed "hyper-reactors" to mental stress, tilt or exercise (Sannerstedt, 1966; Julius and Conway, 1968; Sannerstedt, Julius and Conway, 1970). Until this evidence was available, "borderline hypertensive" was proposed as a more reasonable descriptive term for these individuals.

Large numbers of observations are needed in order to accurately quantify and interpret the extent of fluctuations in blood pressure. This can be done conventionally through home blood pressure recording (Julius, Ellis, Pascual, Matice, Hansson, Hunyor and Sandler, 1974; Laughlin, Sherrard and Fisher, 1980), through semi-automatic (Sololow, Werdegar, Kain and Hinman, 1966) or automatic (Horan, Kennedy and Padgett, 1981) indirect blood pressure recorders, or through continuous ambulatory monitoring (Littler, Honour, Sleight and Stott, 1972). Various degrees of accuracy, continuity, freedom of movement and physician-patient interaction are afforded with these techniques. The first two methods have their obvious disadvantages in the calculation of blood pressure variability; only direct ambulatory monitoring allows the continuous record of blood pressure required to calculate the beat-to-beat variability of arterial pressure. Its use is limited to selective centres by its invasive nature.

Home blood pressure records have shown borderline hypertensive patients to have slightly increased lability of their systolic

(but not diastolic) blood pressure when compared to normal subjects (Julius et al., 1974). Moderate hypertension, in turn, may be associated with greater variations in diastolic pressure (Laughlin et al., 1980).

Richardson, Honour, Fenton, Stott and Pickering (1964) described a cuff plethysmographic method of measuring blood pressure discontinuously and indirectly, but automatically. The range of blood pressure was used as a rough index of blood pressure variability. This was similar in normal and hypertensive subjects, but seemed to increase with age. Sokolow et al. (1966) used a semi-automatic recorder with a microphone to pick up Korotkoff sounds in order to measure the range and extent of blood pressure in a large number of hypertensive patients. These authors found no significant relationship between the level of arterial pressure and its variability, or the overall severity of an individual's end-organ complications and his blood pressure variability. The Del Mar Avionics device, an automatic recorder, was recently used by Horan et al. (1981) to compare blood pressure variability in normal subjects and "borderline" and "fixed" hypertensives. Hypertension, per se, was associated with a slight increase of blood pressure variability; borderline hypertensives showed no greater lability than fixed hypertensives, but many of these latter individuals were taking anti-hypertensive drugs, which may have blunted their blood pressure variations (Watson, Stallard and Littler, 1979a). Moreover, the true extent of blood pressure variability in these patients cannot be assessed with indirect methods.

Clement (1977) demonstrated a linear relationship between blood pressure and its variability, using the Arteriosonde^{R}

ultrasonic technique (Kazamias, Gander, Franklin and Ross, 1971), and suggested that the coefficient of variation (i.e. the standard deviation/mean of measurements) rather than the standard deviation of all measurements per se, as used by others, should describe blood pressure variability (Clement, 1979). DeLeeuw and his colleagues (deLeeuw, Kho, Falke, Birkenhager and Wester, 1978) have also studied the variability of arterial pressure in 58 patients, using ultrasound; the variability of blood pressure in this series was derived from the range, rather than the variation of measurements (i.e., the difference between the maximum and the minimum value divided by the maximum, expressed as a percentage). Variability, in these terms, declined with age.

It should be emphasised that these are discontinuous records, taken mostly at rest, which cannot describe the diurnal range or variability of an individual's blood pressure. As they are indirect measurements, based on the Korotkoff sounds, they may differ substantially from simultaneous direct readings obtained from the same limb (Raftery and Ward, 1968). Cuff readings cannot predict or measure changes in blood pressure during routine activity, exercise, sleep, etc. These limitations are overcome by direct 24 hour ambulatory monitoring of blood pressure (Littler, Honour, Sleight and Stott, 1972).

At the same time this study was initiated, there were no published reports quantifying the beat-to-beat variability of arterial pressure in normal or hypertensive man. Pickering had noted anecdotally (Pickering and Stott, 1980) that the range and lability of blood pressure appeared to be similar in normal and hypertensive subjects when direct 24 hour records were scanned

by eye. Subsequently Watson, Stallard, Flinn and Littler (1980) studied 26 hypertensive patients under standardised conditions in hospital, and concluded that systolic pressure and its variability were related, but diastolic was not. The variability of systolic pressure increased with age, but seemed to be dependent on the increase in arterial pressure with age in these subjects. Mancia, Ferrari, Gregorini, Parati, Pomidossi, Bertinieri, Grassi and Zanchetti (1980) measured variability over small intervals of time (rather than beat to beat). With this approach, variability also increased with age and mean arterial pressure, but the colinearity of these two variables was not assessed. Pessina, Mormino, Semplicini, Palatini, Casiglia, Hlede and Dal Palu (1980) noted that the variability of arterial pressure over the waking and sleeping periods of the 24 hour record was greater in 8 "fixed" than in 8 "borderline" hypertensive patients; the ages of these individuals were not mentioned. This evidence is not consistent with the hypothesis that borderline hypertension is associated with increased lability of blood pressure. It does however suggest, as discussed in Chapter 1, that the loss of baro-reflex sensitivity with increasing age and mean arterial pressure may be related to an increasing inability to buffer these fluctuations.

(b) mental exercise

Two factors in hypertensive patients could lead to an increase in the pressor response to similar mental or physical stimuli -- an increase in resting or exercising sympathetic nerve activity, or a change in the characteristics of the resistance vessels, with an increased smooth muscle mass and a greater wall to lumen ratio,

such that similar activation of smooth muscle shortening would lead to greater encroachment on the arteriolar lumen, and a correspondingly larger increase in resistance and blood pressure for the same stimulus. The latter factor may not have any practical importance. Mental stress, for instance, produced pressor rises up to five times as intense in both young "pre-hypertensive" SHR and old SHR than it did in the control or renal hypertensive rats (RHR), in spite of demonstrable vascular hypertrophy in the latter group (Hallback and Folkow, 1974). Heightened activity of the sympathetic nervous system may therefore be of greater overall importance in determining the extent of haemodynamic change in these animals.

The alerting response in animals can be simulated in man by a test such as mental arithmetic: the heart rate and blood pressure rise, renal, epidermal and, by inference, splanchnic vascular resistance increase, and muscle bed vasodilatation occurs. Patients with hypertension had larger absolute (30 mm Hg v 20 mm Hg) but similar relative (20%) increases in blood pressure when stressed by a 4 minute subtraction test, but did not differ from normals in the means by which the rise in blood pressure was effected. Increases in cardiac output, peripheral resistance, or both occurred in both groups, but tended to persist for a longer time in those with higher pressures (Brod, Fencl, Hejl and Jlika, 1959).

A situation analogous to the genetic predisposition to 'hyperreact' to environmental stimuli in SHR may be observed in adolescent man. Falkner, Onesti, Angelakos, Fernandes and Langman (1979) studied the haemodynamic response to mental arithmetic in

three groups of normotensive adolescents. One group had blood pressures above the 95th percentile for their age, and at least one parent with hypertension ("labile" group). The other two, with ("genetic") and without ("control") family histories of hypertension, had blood pressure below the 90th percentile for their age. The "labile" group had significantly higher baseline blood pressure (123/75 mm Hg v. 107/71 mm Hg) and also higher heart rates (88±11 v. 79±25) than the controls. The "labile" and "genetic" groups exhibited significantly greater increases of systolic and diastolic pressure and heart rate, in absolute and relative terms, than did the "control" group after 10 minutes of mental arithmetic, and their post-stress values did not fall to baseline levels. The interesting possibility that some protective factor might prevent the blood pressure in the "genetic" group from rising above the 90th percentile for age is not discussed by these authors.

Hollenberg, Williams and Adams (1981) suggested that this genetic predisposition might be expressed as an abnormality of control of the renal circulation. A mild mental stimulus evoked significant falls in renal blood flow in both essential hypertensives and normal subjects with a positive family history for hypertension. This was associated with increases in plasma renin activity and angiotensin II concentration. The reverse occurred in normal subjects. Heart rate and blood pressure were hardly changed by this stimulus.

Most studies have used non-invasive techniques to examine blood pressure and heart rate during mental stresses. Larger absolute and relative changes in blood pressure were seen in hypertensive patients by Nestel (1969) ("labile") and Lorimer,

Macfarlane, Provan, Duffy and Lawrie (1971) ("heterogenous") but not by Hjemdahl and Eliasson (1979) ("latent hypertensives") during other forms of mental stress. The "labile" hypertensives selected by Nestel (1969) excreted a relatively greater quantity of urinary catecholamines when stressed; the heterogenous group of hypertensives studied by Lorimer et al. (1971) did not.

Obrist (1976) observed that the performance of a reaction time test, sufficiently difficult to keep the subjects' interest, led to larger increases in systolic pressure (23 mm Hg) and heart rate (22 bpm) but much smaller increases in diastolic pressure than either a cold pressor test, or viewing of a pornographic film. Although he did not perform haemodynamic measurements, Obrist suggested that this form of active coping led to blood pressure changes mediated by increases in cardiac output alone, and would therefore be useful in non-invasive psycho-physiological studies.

The pressor response to mental stimulation or alerting has often been discounted by investigators searching for evidence of persistent elevation of sympathetic nervous activity in hypertension. In primitive times, the defence reaction was usually followed by flight or fighting responses, i.e., the pressor response was relieved by muscular vasodilatation. This pattern of behaviour is rarely observed in civilised society. In this way, frequent alerting responses in daily life might increase the average pressure load on the circulation and act as a neurogenic trigger for the development of hypertension.

(c) isometric exercise

Dramatic increases in arterial pressure occur during lifting exercise, particularly if a Valsalva manoeuvre is inadvertently

performed at the same time (McCurdy, 1901). Similar rises in pressure are observed when the blood supply of an exercising muscle is impaired, either by an occluding cuff, or a high frequency of muscular contractions. Alam and Smirk (1937) postulated that the accumulation of metabolic products in muscle stimulated this increase.

Handgrip at 30% of the maximum power of a muscle group leads to modest increases in heart rate and cardiac output; stroke volume and peripheral resistance do not change in young healthy subjects (Stefadouros, Grossman, El Shahawy, and Witham, 1974; Laird, Fixler and Huffines, 1979). This level of exertion can be sustained about 5 minutes before fatigue occurs (Lind, 1970). The increase in blood pressure is independent of the size of the contracting muscle group. Systolic and diastolic pressure continue to increase, for the duration of isometric exercise, before plummeting to normal at its conclusion. There is little change in pulse pressure (Lind and McNicol, 1967).

These haemodynamic responses to isometric exercise have been attributed to a reflex arising from the exercising muscle, when blood flow is markedly impeded by the sustained muscular contractions (Donald, Lind, McNicol, Humphreys, Taylor and Staunton, 1967; McCloskey and Mitchell, 1972; Mitchell, Reardon and McCloskey, 1977), but the rapid onset of these changes also suggests that there may be a component of 'central command', stimulating the vasomotor centre to increase blood pressure and heart rate (Freyschuss, 1970a, b; McCloskey and Mitchell, 1972). Moreover, they can also occur in the absence of muscle sensory nerves; sensory input may only be important if mechanical occlusion of blood flow to the limb is applied at the same time as the muscle

exercise is performed (Duncan, Johnson and Lambie, 1981).

It might be expected that the rise in blood pressure during the first few seconds of isometric exercise would be buffered by the baroreceptors. However, an increase in heart rate, which can be duplicated simply by the intention to perform exercise, occurs within 0.5s of beginning handgrip, and peripheral resistance, in normal individuals, does not alter, implying that the baroreceptor reflex is rapidly overriden by this 'central command'. The initial change in heart rate, attributed to a withdrawal of vagal tone, can be blocked by atropine, but after 30s of sustained contraction, it cannot. Sympathetic stimulation, which can be blocked by propranolol, dominates by this time. The increase in cardiac output, but not in blood pressure, can be blocked by beta-adrenergic blockade (Freyschuss, 1970a,b; Petro, Hollander and Bouman, 1970; Martin, Shaver, Leon, Thompson, Reddy and Leonard, 1974). An augmented pressure rise, which may be mediated by alpha-adrenergic receptors has been described in some patients taking propranolol. The pressor reflex in this case can be abolished by phentolamine (McAllister, 1979).

Most studies have found similar haemodynamic changes during isometric exercise in normal subjects and patients with borderline, mild, or moderate hypertension (Alam and Smirk, 1938; Hoel, Lorentsen and Lund-Larsen, 1970; Sannerstedt and Julius, 1972; Chrysant, 1978; Brorson, Wasir and Sannerstedt, 1978; McAllister, 1979; Robertson, Shand, Hollifield, Nies, Frölich and Oates, 1979). However, Nyberg (1976) noted larger absolute but similar relative changes during handgrip in his hypertensive patients, and Lamid and Wolff (1973) found much greater relative increases in middle aged

men with moderate hypertension than in normal subjects. The nature of this pressure rise may differ in some patients, however: 5 of 15 hypertensive subjects studied by Ewing, Irving, Kerr and Kirby (1973) increased their peripheral vascular resistance rather than their cardiac output. As all 5 showed electrocardiographic or roentographic evidence of left ventricular enlargement, it was suggested that the pressor reflex might be mediated by sympathetic vasoconstriction in the presence of impaired ventricular function, rather than by vagal withdrawal. Similar observations have been made in men with angina, with or without congestive failure (Kivowitz, Parmley, Donoso, Marcus, Ganz and Swan, 1971), and in older subjects, including men with no evidence of cardiac disease (Donald et al., 1967; McDermott, Stekiel, Barboriak, Kloth and Smith, 1974; Kino, Lance, Shahamatpour and Spodick, 1975), but this was not seen by Petrofsky and Lind (1975). Maximal voluntary contraction increased heart rate by 50 bpm in young and middle aged men, but only 10 bpm or so in healthy older men and in men with ventricular hypertrophy or coronary artery disease (McDermott et al., 1974; Kino et al., 1975).

(d) dynamic exercise

In contrast to isometric, or static exercise, dynamic exercises, such as bicycling, increase the heart rate and cardiac output markedly; peripheral resistance tends to fall (Brod, 1963; Laird et al., 1979). The first direct arterial recording of blood pressure during exercise was by Eskildsen, Gotzsche and Tybjaerg Hansen (1950), who noted a rapid rise in systolic pressure on beginning exercise and an abrupt fall when it ended. These authors found greater absolute increases in blood pressure in their hypertensive subjects,

as did Varnauskas (1955), who also observed an increase in their diastolic pressure on exercise.

Borderline hypertensives have similar increases in blood pressure and heart rate to age matched controls during treadmill (Levy, Tabaken and Hanson, 1967) and bicycle exercise (Sannerstedt, 1966; Julius and Conway, 1968; Brorson et al., 1978; Henquet, Kho, Schols, Thijssen and Kahn, 1981). At rest, borderline subjects were distinguished from controls by a higher heart rate and cardiac output. On moderate exercise, this difference disappeared and the elevated pressure in the borderline hypertensives was maintained by an increased peripheral resistance, suggesting the presence of a structural vascular adaptation in the resistance vessels of the hypertensive group that was resistant to any vasodilating substances present (Amery, Julius, Whitlock and Conway, 1967).

Similar changes in blood pressure and heart rate occurred in borderline hypertensive and normotensive subjects when sitting (Julius, Pascual, Sannerstedt and Mitchell, 1971) or when tilted (Sannerstedt, Julius and Conway, 1971), leading these authors to conclude that borderline or mild hypertensives did not exhibit neurogenic hyperreactivity in their acute regulation of blood pressure.

Sannerstedt (1966) found that heart rate and blood pressure rose to a significantly greater extent in WHO Stage II (cardiac hypertrophy) or III (more severe end-organ damage) than in borderline hypertensives or controls (World Health Organization, 1962). This was not seen by Brorson et al. (1978) in their own Stage II group of hypertensive patients. In both these studies, however, WHO II and III class patients were significantly older than the normal, or borderline subjects.

Interestingly enough, isometric exercise for 4 minutes at 30% of maximum voluntary capacity (MVC) and 6-10 minutes of exercise on a bicycle ergometer to a heart rate of 150 bpm led to similar changes in mean arterial pressure in both the normal and the hypertensive subjects (Brorson, Wasir and Sannerstedt, 1978).

Influence of age on the haemodynamic response to exercise

With advancing age, resting cardiac output decreases, peripheral vascular resistance increases, and the impedance to left ventricular ejection is greater. Heart rate remains constant. With exercise, the maximal heart rate, stroke volume and the arterio-venous oxygen difference are all lower, and less exertion is tolerated by the subjects (Gerstenblith, Lakatta and Weisfeldt, 1976). The left ventricular ejection fraction decreases with age, although this is not evident at rest (Port, Cobb, Coleman and Jones, 1980). The changes in systolic pressure with exercise increase with age, and the systemic vascular resistance is greater at all levels of exertion (Julius, Amery, Whitlock and Conway, 1967).

Aging effects cardiac and vascular changes. Although circulating catecholamines on exercise are similar, or increased (McDermott et al., 1974; Palmer, Ziegler and Lake, 1978; Rowe and Troen, 1980), the ionotropic response to catecholamines is decreased in both rat (Lakatta, Gerstenblith, Angell, Shock and Weisfeldt, 1975) and man (Conway, Wheeler and Sannerstedt, 1971; Bertel, Bühler, Kiowski and Lutold, 1980). The elastic modulus of the aorta and other arteries increases with age, as the composition and thickness of the arterial wall change (Learoyd and

Taylor, 1966). This probably contributes to the decline in baroreflex sensitivity with age (Gribbin et al., 1971). Moreover, vasodilation in response to isoproterenol, but not nitrates, is diminished in the aortic wall of rabbits and rats (Fleisch and Hooker, 1976), suggesting a general post-synaptic decline in the response to beta-adrenergic stimulation (Lakatta, 1980).

These characteristics are enhanced in aging hypertensive subjects; the similarity of arterial wall pathology has been previously noted (Wolinsky, 1972). During exercise, the maximum heart rate is reduced and the capacity for exercise itself is limited. Although cardiac output is reduced, as compared to controls, in the youngest hypertensives, it is similar in older normal and hypertensive subjects; the latter have higher systemic vascular resistance at comparable workloads and exhibit greater increases in systolic blood pressure (Amery, Julius, Whitlock and Conway, 1967).

Plasma noradrenaline concentrations in normal and hypertensive subjects

Review

The pressor response that followed injections of adrenal extracts into animals was first noted by Oliver and Schaefer (1895). The active constituent in these extracts was isolated and identified as adrenaline by Abel and Crawford (1897). Its effects could be reproduced by stimulation of the splanchnic and other sympathetic nerves, suggesting that a substance resembling adrenaline was released from sympathetic nerve endings (Dreyer, 1898; Langley, 1901; Elliot, 1905). von Euler (1948) showed that noradrenaline was present in sympathetic nerve endings; its release when these nerves were stimulated was demonstrated by Peart (1949).

Noradrenaline may act as a central, or peripheral transmitter, or as a circulating hormone, as the enzymes capable of its biosynthesis are found in the brain, the sympathetic nerves and ganglia, and the adrenal medulla. The rate limiting step in this enzymatic sequence is the conversion of tyrosine to DOPA (Levitt, Spector, Sjoersdsma and Udenfriend, 1965). The synthesis of adrenaline, from noradrenaline, with S-adenosyl methionine acting as methyl donor, takes place in the brain and in the adrenal medulla, tissues which contain phenylethanolamine-N-methyl-transferase (PNMT) (Axelrod, 1962).

Noradrenaline, once synthesized in nerve terminals, is stored in granulated core vesicles about 50 nm in diameter, which protect it from degradation by monoamine oxidase (MAO). Uptake into these vesicles can be blocked by reserpine (von Euler and Lishajko, 1963).

Nerve stimulation causes these vesicles to fuse with the neuronal membrane and discharge their contents, including noradrenaline, into the synaptic cleft. Noradrenaline synthesis is activated almost immediately after exocytosis, with newly synthesized noradrenaline released preferentially (Kopin, 1977).

Activation of vascular post-synaptic $alpha_1$ receptors, or cardiac $beta_1$ adrenoceptors, mediate vasoconstriction, chronotropy and ionotropic responses. Most of the noradrenaline released is immediately taken up into the nerve endings by active transport ($uptake_1$) and stored again in vesicles. Some is metabolised by MAO within the nerve ending. Alternatively, extraneuronal uptake may occur ($uptake_2$), with subsequent O-methylation and deamination of catecholamines (Kopin, 1977). The products of catecholamine metabolism are vanillymandelic acid (VMA) in the periphery and 3'-methoxy-4'-hydroxy phenyl glycol (MMPG) in the brain. These are excreted in the urine, primarily as their sulphate conjugates (Ebert and Kopin, 1975).

The release of noradrenaline from nerve terminals is enhanced through pre-synaptic beta-adrenoceptors at low concentrations and inhibited through pre-synaptic $alpha_2$-adrenoceptors when its synaptic concentration is high. Thus noradrenaline, or an $alpha_2$ agonist, such as clonidine, inhibit noradrenaline release. Prolonged stimulation or blockade of these pre-synaptic receptors may affect the sensitivity with which they regulate neurotransmission. Sympathetic denervation, and drugs such as cocaine, which interfere with the reuptake of noradrenaline, therefore potentiate its action (Langer, Cavero and Massingham, 1980).

Only a small proportion of the noradrenaline released from nerve endings overflows into the systemic circulation, where it

can be detected in plasma. This is estimated by Reid, Jones, Fitzgerald, Davies and Boobis (1980) to be about 15-20% in normal subjects. Kuchel, Buu, Unger and Genest (1978) state that approximately 80% of the noradrenaline in plasma is conjugated with sulphuric acid.

The adrenal medulla is innervated by preganglionic sympathetic neurones, particularly those of the greater splanchnic nerve, which normally arises from T5 to T9. Stimulation of the splanchnic nerves and the release of acetylcholine leads to exocytosis of noradrenaline and adrenaline into the circulation where they are O-methylated in extraneuronal tissue (Perlman and Chalfie, 1977).

The ratio of noradrenaline:adrenaline in the adrenal medulla is about 15:85 (von Euler, Franksson and Hellstrom, 1954). Noradrenaline and adrenaline are stored in chromaffin granules. Conversion to adrenaline by PNMT takes place in the cytosol (Perlman and Chalfie, 1977). The activity of this enzyme can be modified by glucocorticoids (Axelrod, 1962).

Plasma noradrenaline is cleared by the liver (Jones, Allison, Hamilton and Reid, 1980) and possibly by the lung (Vane, 1969; Sole, Drobac, Schwartz, Hussain, Vaughan-Neil, 1979) although this is disputed (Watson, Page, Littler, Jones and Reid, 1979). Vecht, Gordon and Sever (1981) obtained identical plasma noradrenaline concentrations from 91 paired samples taken from the pulmonary artery and the left ventricle in patients undergoing cardiac catheterization. As they found similar concentrations from other venous and arterial sites, these authors concluded that the sampling site itself was not critical for the assessment of circulating catecholamines.

The clearance of noradrenaline from the circulation in normal subjects (5) was reported by Reid et al. (1980). A three to four-fold inter-individual variation in the noradrenaline clearance and endogenous noradrenaline production was observed following short term and long term noradrenaline infusions. Noradrenaline clearance may be reduced in hypertensive subjects, but again, this was a small study, and the reduction observed was far less than the variation observed in normals (Ghione, Palombo, Pellegrini, Fommei, Pilo and Donato, 1978). The difficulty in interpreting plasma noradrenaline concentrations in light of the intra-individual variation in noradrenaline kinetics has been underlined by Reid et al. (1980).

Plasma noradrenaline as an index of sympathetic nerve activity

Manoeuvres which increase the activity of the sympathetic nervous system lead to the release of noradrenaline and adrenaline from nerve terminals and the adrenal medulla. Urinary excretion of these catecholamines can be stimulated by postural change, stress and hypoglycaemia. Elevated catecholamine concentrations are also present in patients with phaeochromocytoma (Engel and von Euler, 1950; von Euler and Luft, 1952; Elmadjian, Hoper and Lamson, 1953, 1958). However, as an index of sympathetic nervous activity, urinary catecholamines have not proved to be useful in the investigation of essential hypertension. Kopin (1977) has suggested that bursts of sympathetic activity which may be haemodynamically significant could be obscured when collections are taken over a long period of time, whereas Reid et al. (1980) point out that the metabolism of catecholamines may differ widely from

subject to subject, and therefore the measurement of free noradrenaline and adrenaline alone, along with specific metabolites, may only give a partial, and variable indication of the extent of catecholamine released. They recommend the measurement of the catecholamines and all of their metabolites and conjugates in timed collections, instead.

The accurate measurement of plasma catecholamine concentrations, which might overcome these difficulties, awaited the development of sensitive and specific assays. Earlier methods, such as bioassays, were sensitive, but lacked specificity for individual catecholamines. Colorimetric techniques were not sufficiently sensitive for the measurement of catecholamines in plasma. Fluorometric techniques, useful for the quantification of noradrenaline and adrenaline in urine, are probably not sensitive enough to detect basal levels of these catecholamines in plasma. Radioimmunoassays are not sufficiently specific at present (Clare and Sever, 1981).

Axelrod and Tomchick (1958) used catechol-O-methyl transferase (COMT) in the presence of radioactive S-adenosyl methionine (SAM), a methyl donor, to measure the concentration of catecholamines as a whole in plasma, without differentiating between them. Engelman et al. (1968) later developed a double isotope assay which measured both adrenaline and noradrenaline. In the method of Henry et al. (1975) the catecholamines are adsorbed onto alumina. Noradrenaline, specifically, is converted to radiolabelled adrenaline by PNMT purified from bovine adrenal with tritiated SAM as a methyl donor. This assay, described in fuller detail in Chapter 4, has achieved general acceptance on account of its specificity, sensitivity (25 to 50 pg/ml of noradrenaline) and reproducibility. This method only measures noradrenaline, but may give values that

are 50 to 100% higher than the COMT method (Sever 1978; Goldstein, 1981). Other radioenzymatic techniques have been developed (deChamplain, Farley, Cousineau and van Ameringen, 1976; da Prada and Zurcher, 1976).

Gas chromatography, combined with mass spectrometry, or high performance liquid chromatography, are able to measure catecholamines and their metabolites directly, but at greater cost (Clare and Sever, 1981).

The range of inter-individual variation in noradrenaline synthesis, release, metabolism and clearance has not deterred most authors from assuming that plasma noradrenaline concentrations (PNA) could be used as an indirect index of sympathetic nervous activity. Kopin (1977) wrote: "Because of the rapid turnover rates of the plasma catecholamines, their levels are rapidly responsive to changes in the rate of their entry into the circulation and thus provide a sensitive index of sympatho-adrenal medullary discharge."

Similar basal catecholamine concentrations have been noted by differing groups, using the radioenzymatic technique (COMT) (Engelman, Portnoy and Sjoerdsma, 1970; de Quattro and Chan, 1972; Louis, Doyle and Anavekar, 1973; de Champlain et al., 1976; Lutold, Buhler and da Prada, 1976; Lake, Ziegler and Kopin, 1976). These levels are reproducible and do not vary from week to week if taken from the same individual under identical circumstances (de Champlain et al., 1976; Lake, Ziegler and Kopin, 1976).

There is little doubt that many physical and emotional stimuli which increase blood pressure and heart rate acutely are associated with increases in PNA (Lake, Ziegler and Kopin, 1976; Lutold, Buhler and da Prada, 1976; Watson, Hamilton, Reid and

Littler, 1979; Robertson, Johnson, Robertson, Nies, Shand and Oates, 1979), and PNA concentrations have been shown recently to correlate well with muscle nerve sympathetic discharge in resting subjects (Wallin et al., 1981).

Antihypertensive agents, such as clonidine, which reduces central sympathetic outflow (Wing, Reid, Hamilton, Sever, Davies and Dollery, 1977) and peripheral ganglion blockers, such as hexomethonium (Louis et al., 1973) or pentolinium (Louis, Doyle, Anavekar, Johnston, Geffen and Rush, 1974) reduce plasma noradrenaline concentrations. Interestingly, the converting enzyme inhibitors, which are effective at reducing blood pressure do not alter PNA (Morganti, Pickering, Lopez-Oyejero and Laragh, 1979).

Hypothyroidism, diabetes with autonomic dysfunction (Christensen, 1972a,b), quadriplegia (Mathias, Christensen, Corbett, Frankel and Spalding, 1976), and primary orthostatic hypotension (Ziegler, Lake and Kopin, 1977) are also associated with reduced PNA. In familial dysautonomia, PNA is normal when subjects are supine, but does not increase on standing or exercise (Ziegler, Lake and Kopin, 1976a).

Therefore blockade, inhibition or dysfunction of the sympathetic nervous system, as well as its stimulation, can be reflected in changes in plasma noradrenaline concentrations.

However, the sympathetic nervous system is capable of discriminant activity, and as an index of transmitter overflow, plasma noradrenaline concentrations may not be sufficiently sensitive to perceive discharge to the heart or splanchnic resistance vessels, although the latter may exert considerable haemodynamic effect. The inter-individual variations in noradrenaline release and clearance may make the interpretation of subtle changes in this

context, difficult. Alternatively, the measurement itself may be of little benefit in predicting the physiological response to noradrenaline or adrenaline, as the number of post-synaptic receptors, or their responsiveness, may differ from one individual to the next, or possibly in the same individual at different points in time.

These conceptual difficulties have not deterred numerous groups from investigating plasma catecholamine concentration in normal and hypertensive subjects, at rest, and during a variety of physical and mental exercises, but they, as well as differences in methodology and experimental design, may help to explain the great inconsistencies in the present literature.

The interpretation of earlier experiments is coloured by several influences which are now clear. Most earlier studies relied on laboratory personnel for their control groups. However, plasma noradrenaline concentrations in normal hospital outpatients are significantly higher than those obtained from laboratory personnel matched for age and blood pressure (Jones, Hamilton and Reid, 1978). The PNMT assay may give basal concentrations of PNA that are 50-100% higher than the COMT method (Sever, 1978; Goldstein, 1981). Finally, it is now generally accepted that patients should be withdrawn from anti-hypertensive medication for at least a month before inclusion in studies along with previously untreated patients (Campese, Myers and de Quattro, 1977).

Certain aspects of experimental design are now generally agreed upon. Venepuncture should not give higher levels of PNA than withdrawing blood from an indwelling catheter (Campese, Myers and de Quattro, 1977; Jones et al., 1978; Robertson, Johnson, Robertson,

Nies, Shand and Oates, 1979). The site from which blood is obtained is not critical (Watson, Page, Littler, Jones and Reid, 1979; Vecht, Gordon and Sever, 1981). As diurnal rhythms may affect plasma noradrenaline concentrations, experiments should be performed at similar times of day (Sever, 1978). Blood should be drawn under conditions of quiet rest, in the absence of stimulants which increase PNA, such as smoking (Cryer, Haymond, Santiago and Shah, 1976) coffee or tea (Levi, 1967; Robertson, Frohlich, Carr, Watson, Hollifield, Shand and Oates, 1978), although the influence of caffeine may not be as great if this is ingested habitually (Jung, Shetty, Jones, Barrand and Callingham, 1981).

There do not appear to be any racial differences in PNA (Jones et al., 1978; Sever, Peart, Meade, Davies and Gordon, 1979; Sever, Peart, Davies, Tunbridge and Gordon, 1979). Finally, it is generally agreed that there is no relationship between resting plasma noradrenaline concentrations and either systolic, mean, or diastolic blood pressure, or heart rate, in normotensive subjects (Brecht and Schoeppe, 1978; Jones et al., 1978; Sever, 1978, 1980). This did not surprise Reid's group, who later reported that intravenous infusions of noradrenaline must increase plasma concentrations several fold in order to alter systolic blood pressure over the short term, in normal volunteers, or over a longer period of time in conscious dogs (Reid et al., 1980).

Differing views persist in several areas, however. The duration of rest required to achieve basal concentrations of PNA is said to be 15 minutes by Sever (1980) whereas Brecht and Schoeppe (1978) do not obtain basal values in their subjects until 4 hours of quiet rest. Sever (1978) and Brecht and Schoeppe (1978) describe a logarithmic distribution of plasma noradrenaline concentrations in

normal and hypertensive populations they studied; Hofman, Boomsma, Schalekamp and Valkenburg (1979) describe a normal distribution, but in a smaller series. Males and females have similar plasma noradrenaline concentrations when age-matched, according to Ziegler, Lake and Kopin (1976b), Sever (1978), Brecht and Schoeppe (1978), and Ibsen, Christensen, Hollnagel, Leth, Kappelgaard and Giese (1979), whereas Jones, Hamilton and Reid (1978) found higher values in both black and white females. It should also be noted that most British, Scandinavian and American investigators have adopted the radioenzymatic technique, either using COMT to measure all catecholamines in plasma, or PNMT to measure noradrenaline exclusively. Some, e.g., de Champlain's group (Cousineau, de Champlain and Lapointe, 1978) calculate plasma adrenaline by performing both assays on the same blood sample, and calculating the difference between the latter and the former, although this is probably not a valid approximation of PA. Continental and Japanese researchers on the whole continue with refinements of the fluorometric method, i.e., Brecht et al. (1978), Miura et al. (1978). These differences should be borne in mind in the comparison of data from these different centres.

The principle dispute between centres is to whether PNA increases with age in normal subjects, as asserted by some authors (Pedersen and Christensen, 1975; Ziegler et al., 1976b; Sever, Birch, Osikowska and Tunbridge, 1977; Franco-Morselli, Elghozi, Joly, Di Giulio and Meyer, 1977; Miura et al., 1978; Kiowski, Van Brummelen and Buhler, 1979; Bertel et al., 1980; Esler, Skews, Lenard, Jackman, Bobik and Korner, 1981) but denied by others (de Quattro and Chan, 1972; de Champlain and Cousineau, 1977; Brecht and Schoeppe, 1978).

Jones, Hamilton and Reid (1978) found this to be the case with white men only. Sever (1978) felt that the lack of older subjects in some of the earlier studies may have influenced their authors' conclusions; it is generally agreed that there is a relationship between noradrenaline and age in normal subjects when a broader range of individuals are examined (Goldstein, 1981).

Esler et al. (1981) examined the rate at which tritiated noradrenaline spilled over into plasma, and was cleared. This spillover rate remained fairly constant in subjects between the ages of 20 and 70; the increase in PNA that they observed with age was therefore due to diminished clearance of noradrenaline.

Plasma noradrenaline concentrations in hypertension

Plasma noradrenaline concentrations are increased in most models of experimental hypertension in the rat: SHR (Grobecker, Roizen, Weise, Saavedra and Kopin, 1975), DOCA-salt (Reid, Zivin and Kopin, 1975), 1-kidney 1-clip Goldblatt hypertension (Dargie, Franklin and Reid, 1977) and baroreceptor denervated rats (Alexander and Velasquez, 1980), but not in 2-kidney 1-clip Goldblatt hypertensive rats (Dargie, Davies, Dean, Dollery, Maling and Reid, 1977).

Elevated PNA coincides with other evidence of increased sympathetic nervous activity in some of these models, i.e., an increased turnover of noradrenaline in the peripheral nerves, but in association with a significant decrease in noradrenaline turnover in the brainstem (Chalmers, 1975). In the DOCA salt model, noradrenaline turnover increases in the heart and internal organs of the rat before the development of hypertension, and returns to normal on salt restriction (de Champlain, Krakoff and Axelrod,

1967, 1968).

Pretreatment with 6-hydroxydopamine, which depletes central noradrenergic neurones, prevents the development of DOCA-salt and 1-kidney 1-clip Goldblatt hypertension, but not 2-kidney 1-clip Goldblatt hypertension in the rat (Reid et al., 1975; Dargie, Davies, Dean, Dollery, Maling and Reid, 1977; Dargie, Franklin and Reid, 1977), and inhibition of the activity of PNMT lowers the arterial pressure of SHR and DOCA-salt hypertensive rats (Saavedra, Grobecker and Axelrod, 1975). However, the action of noradrenaline and adrenaline peripherally should be considered separately from their functions as central neurotransmitters, because of the variety of roles, both facilitatory and inhibitory, they subserve in the latter capacity.

The problem with experimental design, and the interpretation of data discussed in the previous section apply, as might be expected, to any consideration of plasma noradrenaline concentrations in essential hypertension. Engelman et al. (1970), de Quattro and Chan (1972), Geffen, Rush, Louis and Doyle (1973), Louis et al. (1973), de Champlain, Farley, Cousineau and de Ameringen (1976) and Lutold et al. (1976) reported that total plasma catecholamines, or plasma noradrenaline, assessed with the COMT method, were increased in essential hypertension. Furthermore, Louis, Doyle and Anaveker (1973) reported a significant correlation between diastolic blood pressure and PNA, as well as a correlation between the decrease in blood pressure and circulating noradrenaline after ganglion blockade with pentolinium, or after treatment with clonidine (Louis, Doyle and Jarrott, 1975).

These studies were criticised for the use of laboratory controls and the absence of age matched normal subjects (Sever,

1978) although several of their authors denied the necessity of the latter (de Quattro and Chan, 1972; de Cousineau et al., 1977). A study suggesting that plasma noradrenaline concentrations were similar in normal and hypertensive subjects when adjusted for age (Lake, Ziegler, Coleman and Kopin, 1977a) was itself criticised for having insufficient age-matched controls (Campese, Myers and de Quattro, 1977). Furthermore, age and PNA were unrelated in the hypertensive group, a finding that was confirmed by Sever, Osikowska, Birch and Tunbridge (1977), Miura et al. (1978) and Bertel et al. (1980). PNA increased with age in their normotensive groups exclusively. Brecht and Schoeppe (1978) reported the converse. Ibsen, Christensen, Hollnagel, Leth, Kappelgaard and Giese (1979) chose to circumvent this controversy by restricting their study to 40 year old Danes. Resting plasma noradrenaline concentrations were the same in 'labile' and 'sustained' hypertensives with mild essential hypertension, as well as normal subjects; stimulation of the sympathetic nervous system with frusemide and ambulation failed to elicit any difference between these three groups. Kiowski, Buhler, van Brummelen and Amann (1981) again found no difference in PNA between a normotensive and hypertensive population of similar age (43 years); both groups of authors concluded that resting plasma noradrenaline concentrations were not increased in essential hypertension when patients were compared to a properly matched control group.

Nevertheless, the different disposition of PNA with respect to age within normal and hypertensive subjects led Sever et al. (1977) to infer that some of their younger hypertensive patients may have had elevated PNA with respect to age matched normals; they suggested that stimulation of the sympathetic nervous system

with challenges such as tilt might be a way of enhancing this difference. Miura et al. (1978), in a study of younger subjects with uncomplicated hypertension (mean age 35) found PNA to be significantly greater in borderline and persistent hypertension than in age matched subjects. Hofman et al. (1979) studied the blood pressure and PNA of 13-23 year old hypertensive and age matched normal youths identified as part of a screening survey, and followed up for 2 to 4 years. Plasma noradrenaline concentrations were significantly greater in the hypertensive group, particularly when those subjects whose systolic pressure fell on subsequent examinations were excluded. Again, there was no relationship between PNA and age in the hypertensive group, because of higher values in the younger subjects. Interestingly, there was a significant correlation between PNA and systolic blood pressure in the hypertensive population.

The hypothesis that this may represent a 'neurogenic phase' in the development of hypertension, associated with decreased baroreflex inhibition of the sympathetic nervous system is attractive. Esler, Julius, Zweifler, Randall, Harburg, Gardiner and de Quattro (1977) and Chobanian, Gavras, Melby, Gavras and Jick (1978) have suggested that such a 'neurogenic hypertension' may be characterised by high PNA and high plasma renin activity, but this has not been confirmed (Taylor, Pool, Lake, Ziegler, Rosen, Rollins and Mitchell, 1978). Furthermore, Henquet, Kho, Schols, Thijssen and Rahn (1981), who examined a slightly older group (ages 18-30) of 25 normotensive subjects and 25 borderline hypertensive patients, found similar concentrations of noradrenaline and adrenaline in plasma.

The inconsistencies in these studies were examined by Goldstein

(1981), in a review of the literature restricted to papers published in English, since 1973, devoted specifically to the comparison of PNA determined in resting supine hypertensive and age matched normal subjects, assayed with fluorometric, radioenzymatic or chromatographic techniques. Of the 32 studies fulfilling these criteria, only 41% reported a statistically significant increase in their hypertensive group ("positive studies"). All 7 studies using the fluorometric technique reported a significant increase, as opposed to 6 (25%) of those using the radioenzymatic techniques. "Positive studies" were also differentiated from "negative" ones by having lower plasma noradrenaline concentrations in their normotensive group, not by higher PNA in their hypertensive subjects; they were also differentiated by their inclusion of younger subjects. PNA tended to increase with age overall in the controls, but not in the hypertensive population. There was little evidence for the existence of a 'hyperadrenergic' group, with significantly elevated resting plasma noradrenaline concentrations (de Champlain, 1977) in this survey.

Louis, Doyle and Anavekar (1973), Brecht and Schoeppe (1978) Kiowski et al. (1981) (and also Bertel et al., 1980, but probably on the same group of patients) report a significant relationship between plasma noradrenaline and blood pressure in their hypertensive subjects. This relationship was not evident in the age-matched controls studied by Kiowski et al. (1981). Moreover, they did not find that PNA was increased in their hypertensive patients. A further distinction between normal and hypertensive individuals was seen when forearm blood flow was measured before and after beta-adrenoceptor blockade with propranolol and alpha-adrenoceptor

blockade with intra-arterial phentolamine. The increase in fore-arm blood flow under these conditions was directly related to resting plasma noradrenaline concentrations and mean arterial pressure in the hypertensive group only. Age did not affect these observations. Curiously, these authors argued that these observations could not be explained by structural changes in the resistance vessels, despite an increased resistance to fore-arm blood flow at rest and at maximal dilatation, and a greater decrease in resistance after phentolamine. Instead they proposed that the sympathetic nervous system might be more important in the determination of blood pressure in hypertensives than in normal subjects; this may be through a corresponding decrease in beta-adrenoceptor mediated functions, such as vasodilatation, noted to occur with increasing age or sympathetic nervous activity in animals (Fleisch and Hooker, 1976) and man (Bertel et al., 1980; van Brummelen, Buhler, Kiowski and Amann, 1981).

It would therefore appear that overall differences in resting PNA between hypertensive and normotensive age matched subjects are not pronounced, but the possibility that an increase in sympathetic nervous activity, concealed under resting conditions, might be revealed by mental or physical manoeuvres which stimulate the sympathetic nervous system and thus make this distinction clearer, should not be discounted. In this way, hypertensive man might be analogous to the spontaneously hypertensive rat, which exhibits a lower arterial pressure when raised in quiet isolation, but reacts vigorously to minimal stimulation (Folkow and Hallback, 1977).

Plasma noradrenaline concentrations during activation of the sympathetic nervous system in normal and hypertensive man

Plasma noradrenaline concentrations are increased by most manoeuvres that activate the sympathetic nervous system, such as standing, tilting or exercise. This observation added support to the contention that this measurement could be of use as an index of sympathetic nervous activity, and possibly preferable to basal concentrations, as individual differences in uptake, clearance and metabolism of noradrenaline might be minimized by sudden overwhelming increases in neurotransmitter release and overflow into plasma (Lake, Ziegler and Kopin, 1976; Rosenthal, Birch, Osikowska and Sever, 1976; de Leeuw et al., 1978, Robertson, Johnson, Robertson, Nies, Shand and Oates, 1979).

The rise in plasma noradrenaline during stimulation of the sympathetic nerves in pithed rats is directly proportional to the the rate of stimulation. The rise is gradual, reaching a steady state after 3-4 minutes, but the increase in blood pressure is immediate, proportional to the increase in PNA, and completely blocked by bretylium, which prevents the release of NA from sympathetic nerve endings. Under these conditions, the catecholamines released from the adrenal medulla have little effect on blood pressure. Kopin, McCarty and Yamaguchi (1980) concluded that the noradrenaline released from sympathetic nerve endings, not the circulating catecholamines, mediated the increase in blood pressure when sympathetic nerve activity was increased.

Changes in plasma noradrenaline are not observed on postural stimulation in subjects with autonomic deficiencies (Osikowska

and Sever, 1976; Ziegler, Lake and Kopin, 1977). Resting levels of plasma noradrenaline are low in Shy-Drager's syndrome, and do not increase with tilt (Bannister, Sever and Gross, 1977).

Robertson and his colleagues (Robertson, Johnson, Robertson, Nies, Shand and Oates, 1979) assessed the relative potency of a variety of stimuli to noradrenaline and adrenaline release in 15 normal subjects. Treadmill exercise had the greatest effect on PNA, increasing it 327% from supine and 143% from standing concentrations, followed by standing (111%), caffeine (75%), a cold pressor test (67%), sodium restriction (37%) and handgrip exercise (27% increase from resting concentrations). PNA was not affected by the Valsalva manoeuvre or by venepuncture. Plasma adrenaline was increased most by caffeine (147%), followed by treadmill exercise (131% from standing PNA), cold (112%), handgrip (68%) and the Valsalva manoeuvre (50% from resting PA concentrations). The authors concluded that differential activation of adrenal and neuronal release of catecholamines could be provoked with different stimuli.

Not surprisingly, qualitatively similar changes in PNA are observed in patients with hypertension. Watson, Hamilton, Reid and Littler (1979) recorded PNA, heart rate and intra-arterial blood pressure in 8 hypertensive subjects while they slept, lay quietly, awoke, stood, walked, and bicycled. A positive linear relationship between the log of PNA and systolic blood pressure was observed during these activities. The authors calculated that 66% of the variance in plasma noradrenaline concentrations was associated with changes in blood pressure and heart rate, and concluded that one could demonstrate a quantitative relationship between PNA and sympathetic nervous activity in hypertension.

Two points should therefore be considered: whether this relationship applies to all manoeuvres which activate the sympathetic nervous system, and whether increases in plasma noradrenaline are relatively greater when the sympathetic nervous system is stimulated in hypertensive subjects.

The influence of age again arises. Ziegler et al. (1976b) noted that older normal subjects not only had greater resting plasma noradrenaline concentrations, but the absolute increase in PNA when they stood up, or performed isometric exercise was significantly greater. Bertel et al. (1980) noted higher PNA concentrations with increasing age in hypertensive subjects while recumbent, sitting, and at all levels of bicycle exercise, and the absolute and relative increases from the recumbent or the standing figures were greater in his older subjects during exercise to 75% of their maximum capacity.

(a) orthostasis

Sever et al (1977) suggested that standing might reveal an underlying predisposition to increased sympathetic nervous tone, not apparent under basal, recumbent conditions, and reported a greater increase in PNA in young hypertensive patients following orthostasis. This same group (Sever, Peart, Meade, Davies and Gordon, 1979) later reported that this occurred in white, and not black subjects, and over a wider age distribution; this was confirmed by Bertel et al. (1980). Both studies included WHO Stage I and II subjects in their hypertensive group. However, this was not seen by others in young subjects (Miura et al., 1978; Hjemdahl and Eliasson, 1979).

de Champlain (1977) noted that the range of plasma catecholamines

was greater in his hypertensive patients than in his normal group, and suggested that the former could be subdivided into 'normo-adrenergic' or 'hyperadrenergic' subgroups, depending on whether or not their plasma catecholamines (PCA) lay above or within the 'normal' range. The 'hyperadrenergic' subgroup was said to have a higher heart rate and a greater adrenaline:noradrenaline ratio, but blood pressures were similar; standing in fact provoked smaller relative increases in PCA in both 'normoadrenergic' and 'hyperadrenergic' subgroups. This distinction is considered to be dubious by Sever (1978) and Goldstein (1981).

(b) neck pressure

According to Mancia and his colleagues (Mancia, Leonetti, Picotti, Ferrari, Galva, Gregorini, Parati, Pomidossi, Ravazzani, Sala and Zanchetti, 1979) positive neck pressure, which decreases carotid sinus transmural pressure and activates the sympathetic nervous system, leads to an increase in systemic arterial pressure and heart rate without altering plasma noradrenaline concentrations.

(c) mental exercise

Nestel (1969) found that a mental exercise could increase urinary excretion of catecholamines significantly in labile hypertensives, but this was not confirmed by Lorimer et al. (1971) who instead studied a broader range of patients.

Januszewicz, Sznajderman, Wocial, Feltynowski and Klonowicz (1979) reported a 30% increase in PNA, measured fluorometrically, in their hypertensive subjects, but a 46% increase in their normal control group, following a 30 minute written calculation test accompanied by background noise. Falkner et al. (1979) reported that PCA at the end of their mental arithmetic test was

similar in the "labile" and "genetic" (whose blood pressure was not elevated) subjects; both values were significantly higher than seen in the control group. Unfortunately, no baseline measurements were drawn, and plasma noradrenaline and adrenaline were not determined separately.

Hjemdahl and Eliasson (1979) asked 7 "latent" hypertensives (not defined) and 7 normal controls to perform a 30 minute mental exercise, rest, then stand for 10 minutes. Although changes in blood pressure and heart rate were more pronounced during mental arithmetic, only orthostasis increased PNA, and this was to a similar degree in both normotensive and hypertensive patients (78% v. 51%, n.s.). Plasma adrenaline was not affected by either manoeuvre. The authors therefore rejected the concept of a generalised increase in sympatho-adrenal activity, or adrenergic receptor supersensitivity in hypertension.

(d) isometric exercise

The haemodynamic response to isometric exercise is usually determined by asking a subject to sustain 3 to 6 minutes of hand-grip at 30% of his maximum voluntary contractile force (MVC). Considerable variation in PNA has been reported by different groups following a similar protocol. Kozlowski, Brzezinska, Nazar, Kowalski and Franczyk (1973) noted a threefold increase in PNA in 8 healthy normal subjects after 5 minutes of isometric exercise, compared to a 15% increase after 15 minutes of bicycling at 75 watts (i.e. the level of exertion in this study). PNA was measured using a fluorometric technique. It is not clear from the text whether these were the same 8 subjects. This group (Kozlowski, Nazar, Taton, Chwalbinska-Moneta and Zukowska, 1976) later reported significantly smaller absolute increases

in PNA in an older group of hypertensive subjects, but did not give baseline figures or mean ages. In contrast, McDermott et al. (1974), also using a fluorometric technique, did not see a significant change in PNA, either in young and middle aged healthy subjects following handgrip, but noted a significant increase in plasma adrenaline in the older group.

Between these two extremes were increases of 70%, 37% and 27%, following 5,3, and 3 minutes of handgrip reported by Lake, Ziegler, Coleman and Kopin (1977b), Vecht, Graham and Sever (1978) and Robertson, Johnson, Robertson, Nies, Shand and Oates (1979) respectively, using the radioenzymatic technique. Lake et al. (1977b) had their subjects perform handgrip while standing; the latter studies were performed in the recumbent position. Normotensive subjects were the material in all of these studies, but the data obtained by Vecht et al. (1978) may have been affected by the inclusion of patients with impaired left ventricular function (Hansen, Christensen and Hesse, 1978; Vecht, Gordon and Sever, 1981).

Watson, Littler and Eriksson (1980) described a smaller change in PNA after 3 minutes of handgrip, again at 30% of MVC. In 11 subjects, which included a small number with normal blood pressures, they found that PNA increased by 17%, which was significant. A larger increase in plasma adrenaline (27% in the resting arm, 97% in the exercising arm) was observed. There was no obvious qualitative or quantitative difference in the sympathoadrenal response of the hypertensive and normal subjects.

Marked changes in mean arterial pressure and heart rate were noted during exercise in all of these studies.

(e) dynamic exercise

Neither plasma noradrenaline nor adrenaline are said to be increased by mild (42% to 47% VO_2 max) exercise. Noradrenaline is elevated with moderate exercise (75% VO_2 max) and both catecholamines are increased at maximum workloads in normal subjects. Plasma noradrenaline and adrenaline increase in proportion to the duration of both bicycle and isometric exercise (Kotchen, Hartley, Rice, Moughey, Jones and Mason, 1971; Kozlowski et al., 1973; Chodakowska, Nazar, Wocial, Jarecki and Skorka, 1975;Galbo, Holst and Christensen, 1975).

Christensen and Brandsborg (1973) and Lutold, Buhler and da Prada (1976) noted a strong positive relationship between the increase in heart rate and in PNA during bicycle exercise. Sympathetic discharge to the heart, as well as the kidneys, increases markedly during exercise, but the noradrenaline released from these organs, although similarly increased, does not contribute greatly to plasma catecholamines (Hansen, Christensen and Hesse, 1978; Manhem, Lecerof and Hokfelt, 1978).

Bicycle exercise has provoked larger relative increases in PNA in hypertensive subjects in some studies (Chodakowska et al., 1975; Philipp, Distler and Cordes, 1978; Bertel et al., 1980) but not in others (Lutold et al., 1976; Henquet et al., 1981). The latter two groups used the radioenzymatic technique to measure PNA. Chodakowska et al (1975) claimed that hypertensive patients also increased their plasma adrenaline on light exercise, whereas their normal subjects did not. In the first four studies, a heterogeneous group of hypertensive subjects was exercised. In young (age 18-30) normal subjects and patients with borderline hypertension, Henquet

et al. (1981) found identical plasma noradrenaline and adrenaline concentrations at rest, and after 10 minutes of bicycle exercise up to 75% of each individual's maximum workload. In a smaller study, however (Robertson, Shand, Hollifield, Nies, Frolich and Oates, 1979), young borderline hypertensives, who had similar PNA to normal controls at rest, showed larger increases on sodium deprivation and treadmill exercise. Interestingly, Bertel et al. (1980) obtained larger absolute and relative increases in their young normal group than their hypertensive subjects, also exercised to 75% of the maximal capacity; the opposite effect was seen in their oldest age group. They do not comment upon this in their discussion, however; moreover, the statistical significance of their data may be diluted by subset selection.

Vascular reactivity to noradrenaline

The physiological response to similar plasma noradrenaline concentrations may differ from individual to individual if alterations in structural design have occurred such that a greater smooth muscle bulk leads to a more pronounced encroachment on the vascular lumen when the muscle is stimulated to contract by noradrenaline release, or if the number or sensitivity of the post-synaptic receptors differ. Philipp et al. (1978) suggested that the inconsistencies in resting and exercising studies in normal and hypertensive subjects may have been due to altered reactivity to noradrenaline in a varying proportion of the hypertensive subjects included in each case. They measured PNA at rest, and after bicycling, using a fluorometric assay, in subjects with normal and elevated blood pressure. The pressor response,

i.e., "reactivity" to noradrenaline infusions, was also determined in these individuals. A hyperbolic relation between resting or exercising noradrenaline concentrations, and the reactivity to noradrenaline infusions was found in normal subjects. In those with hypertension, this relationship was shifted; subjects with similar reactivity to noradrenaline had higher blood pressure, which were related, in turn, to higher concentrations of noradrenaline. Low concentrations of noradrenaline could exert profound effects in subjects with a great deal of vascular reactivity, i.e., a similar effect to that seen when pressor agents were infused into baroreceptor denervated animals, as described in Chapter 2.

Resting mean arterial pressure could be predicted, according to these authors, by a regression formula which included reactivity and exercising plasma noradrenaline concentrations as independent variables. Unfortunately, the confidence limits for this equation are not described. A similar relationship, relating vascular responsiveness to angiotensin, could not be constructed, suggesting that structural alterations in the vasculature alone could not account for these findings. Philipp et al. (1978) therefore concluded that the sympathetic nervous system and the pressor response to noradrenaline combined to determine the level of blood pressure in hypertension.

The observation that exercising, rather than resting, noradrenaline concentrations are useful predictors of resting mean arterial pressure suggests that elevated sympathetic activity in hypertension might only be detected in conditions such as exercise, when transmitter overflow is increased.

METHODS

In December I laid a common Field Gate on the Ground, with some Straw on it, on which a White Mare was cast on her right side, and in that Posture bound fast to the Gate....Then laying bare the left Carotid Artery, I fixed to it towards the Heart the Brass Pipe, and to that the Wind-Pipe of a Goose; to the other End of which a Glass Tube was fixed, which was twelve Feet nine Inches long. The Design of using the Wind-Pipe was by its Pliancy to prevent the Inconveniencies that might happen when the Mare struggled....The Blood rose in the Tube... till it reached to nine Feet six Inches Height. I then took away the Tube from the Artery, and let out by Measure sixty cubick Inches of Blood, and then immediately replaced the Tube to see how high the blood would rise in it after each Evacuation; this was repeated several times, till the Mare expired.

- Experiment III
Stephen Hales (1733)

CHAPTER 4

MATERIALS AND METHODS

Studies in man

Subjects

The sixty-two subjects who participated in these investigations were referred to the Hypertension or Cardiac Clinics for the assessment of newly diagnosed, untreated hypertension. Their personal details are listed in Table 4-1. Eighteen were women; two (E.D. and B.T.) were black. Subjects ranged in age from 16 to 69 years (45.8±11.4).

Blood pressure was measured with patients recumbent, using standard mercury sphygmomanometers (Accoson). Phase V of the Korotkoff sounds was used to record diastolic blood pressure. Hypertension was diagnosed if cuff pressures, obtained on three or more separate occasions, over one week apart, were 140/90 mm Hg or greater in subjects under 40 years of age, and 160/95 mm Hg or greater in subjects over 40 years of age. Additional readings below these points were obtained in some subjects. The mean of all cuff readings thus obtained appears in Table 4-1. Systolic pressures ranged from 137 to 216 mm Hg (173.2±19.6), and diastolic pressures ranged from 80 to 137 mm Hg (107.3±9.6).

The assessment of all patients included a history and physical examination, electrocardiogram and chest radiograph, urinanalysis, blood count, electrolytes, renal and hepatic function tests, and

Table 4-1

Subjects

Initials	Sex	Age	Mean Cuff Pressure[+]	Fundi[‡]	CXR[++]	ECG[‡‡]
1. P.B.	F	44	200/118	0	0	0
2. T.W.	M	62	216/107	0	0	0
3. B.B.	F	57	203/115	0	0	0
4. D.K.	M	27	139/80	0	0	0
5. J.R.	M	45	174/116	1	0	0
6. L.D.	M	42	171/96	2	0	0
7. H.D.	M	60	213/120	2	+	3
8. A.L.	M	40	174/92	0	0	0
9. N.H.	M	43	166/110	0	+	1
10. H.F.	M	66	199/101	2	+	0
11. J.H.	M	57	155/98	0	0	0
12. R.D.	M	41	160/102	1	0	0
13. G.P.	M	16	165/101	0	0	0
14. P.A.	F	58	185/100	0	0	0
15. G.L.	M	54	160/105	0	0	1
16. G.A.	F	38	152/104	2	0	0
17. S.F.	F	32	185/117	1	0	1
18. N.P.	M	33	165/106	2	0	0
19. L.L.	F	53	167/97	0	0	0
20. A.L.	M	41	147/112	2	0	0
21. W.S.	F	55	210/114	2	0	2
22. P.M.	M	44	213/137	2	+	2
23. T.T.	F	52	180/118	0	+	0
24. D.G.	M	51	188/112	0	0	0
25. J.S.	F	42	180/113	0	0	0
26. J.W.	F	28	179/114	0	+	0
27. L.H.	M	63	192/113	0	+	0
28. P.W.	M	34	159/112	0	0	0
29. J.C.	M	61	207/127	2	0	2
30. R.T.	M	61	188/97	2	+	0
31. G.D.	M	69	185/113	0	0	0
32. N.H.	M	42	172/113	2	0	1
33. M.P.	F	58	195/111	0	0	0
34. I.W.	F	54	157/113	0	+	0
35. S.R.	M	32	163/103	0	0	0
36. J.N.	M	19	167/97	0	0	0

Table 4-1 continued

Initials	Sex	Age	Mean Cuff Pressure[+]	Fundi[‡‡]	CXR[++]	ECG[++‡]
37. B.W.	M	30	162/110	1	+	1
38. E.D.	F	38	161/106	0	0	0
39. B.H.	M	42	155/118	0	0	0
40. C.L.	M	50	155/105	0	0	0
41. M.M.	M	35	140/96	0	0	0
42. M.S.	M	41	180/122	1	+	0
43. A.W.	M	52	151/100	0	0	0
44. E.F.	F	37	147/101	1	0	0
45. R.D.	M	46	148/102	0	0	0
46. J.B.	M	38	137/93	0	0	0
47. R.H.	M	51	155/95	2	0	0
48. V.P.	M	46	158/105	2	0	2
49. B.P.	M	40	164/98	0	0	0
50. M.T.	F	63	179/106	1	0	0
51. J.S.	M	50	168/109	2	0	0
52. M.H.	F	42	197/102	0	0	2
53. M.M.	F	29	170/109	0	0	0
54. M.A.	F	53	182/109	0	0	0
55. F.K.	M	56	180/101	1	0	0
56. J.D.	M	54	175/115	0	0	0
57. B.D.	M	47	150/100	0	0	0
58. J.G.	M	42	186/103	1	0	0
59. S.L.	M	52	187/107	2	+	0
60. A.A.	M	48	155/100	0	0	0
61. B.T.	M	48	176/127	0	+	0
62. W.J.	M	37	188/110	0	0	0

[+] Mean cuff pressure: arithmetical mean of supine cuff readings obtained on clinic visits.

[‡‡] Fundal changes: 0, normal; 1, diminished A/V ratio; 2, A/V ratio further diminished, plus focal spasm, and A/V nicking.

[++] Radiographic changes: 0, within normal limits; +, cardiothoracic ratio greater than 50%.

[++‡] ECG changes: 0, within normal limits; 1, suggestive of left ventricular hypertrophy (LVH); 2, LVH on voltage or axis criteria; 3, LVH with strain pattern.

serum cholesterol and triglycerides. Urine was collected over a 24-hour period for 3-methoxy-4-hydroxy-mandelic acid (HMMA) and an intravenous pyelogram was obtained. Where suggested by clinical evidence, renal arteriography was also performed.

No patient had greater than Grade 2 fundal changes (Keith Wagener and Barker, 1939). In 20, the chest radiograph or the electrocardiogram showed changes suggestive of left ventricular hypertrophy (Ungerlieder and Gubner, 1942; McPhie, 1958). None of the patients were in left ventricular or renal failure. Two (L.D. and P.A.) had past histories of exertional angina, and a third (N.H.) appeared, by his electrocardiogram, to have sustained an unsuspected anteroseptal myocardial infarction. These three patients were free of chest pain during these investigations. One patient (L.H.) had a history of bilateral intermittent claudication. Another (H.D.) was found to have significant renal artery stenosis. No other forms of secondary hypertension were detected.

Two subjects were on other medication at the time of these investigations: T.W. (digoxin, 0.125 mg daily, for paroxysmal atrial fibrillation), and I.W. (salazopyrine 0.5 g qds, for Crohn's disease).

The purpose and the nature of the protocol were explained on the clinic visits, and again on the first morning of the study, at which time informed written consent was obtained. Permission for these investigations was granted by the Hospital Ethics Committee.

Protocol

Subjects arrived at 9.30 a.m. They were permitted a light breakfast at home, but were instructed to avoid tea, coffee, or cigarettes. There were no other dietary restrictions.

The patients emptied their bladders, then removed their shirts or blouses and lay comfortably on the bed in the laboratory. The anterior surface of the left arm and forearm was cleaned with povidone-iodine scrub (Videne, Beta, Runcom, 0.75% iodine). Local anaesthetic (lignocaine hydrochloride, 1%) was injected into the skin and perivascular tissues, and two small incisions (2-3 mm) were made in the antecubital fossa with a scalpel blade. Through one incision (approximately 3 cm above the elbow crease), a flexible teflon cannula, 11 cm long, with an external diameter of 1.0 mm and an internal diameter of 0.6 mm (Seldicath 3856.10, Grandjean Plastimed, Saint-Leu-La-Forêt) was inserted into the brachial artery (Seldinger, 1953).

This cannula was connected, via a 200 cm manometer line (Portex, Hythe, 200/490/200, internal volume 4 ml) to a strain gauge transducer (initially a Statham P23 Gb, later a P23 1D, Gould-Statham, Hato Rey, Puerto Rico), which had been sterilized overnight with Cidex (activated glutaraldehyde solution). The line was flushed intermittently with a solution of sodium heparin 2000IU/L (Burgess, Hayes), in dextrose 5.0% (Travenol, Thetford), hung in a bag pressurised to 200-250 mm Hg and connected to the transducer by a blood administration set (A15, Avon Medicals, Birmingham). The base of the cannula, and part of the manometer line, were taped to the patient's skin.

Another cannula (Medicut, Argyle, Sherwood, o.d. 1.3 mm) was

inserted into an antecubital vein, through the second incision, and connected by a second 200 cm manometer line to two three-way stopcocks secured by tape to a moveable trolley. Dextrose 5% could be flushed into one of these stopcocks, through a blood administration set, from a second bag. One tap was used to inject phenylephrine into the manometer line, the second was used to flush the drug into the patient's vein, with a small amount of dextrose. A third three-way tap, used for the withdrawal of venous blood, was positioned between the Medicut cannula, and the manometer line. The venous cannula, stopcock, and part of the manometer line were then taped to the forearm. Free arm movement was now possible. The arterial pressure transducer was positioned at the level of the patient's aortic root, and calibrated for 0 and 200 mm Hg using a mercury column (Accoson). Calibrations were repeated each time the patient changed position, and at the end of the experiment. Five such calibrations were performed during each study. Transduction of pressure by this system was linear between 0 and 250 mm Hg.

Three pre-gelled disposable silver/silver chloride ECG electrodes (Bard Biomedical, Westmont, Illinois) were placed on the patient's chest, one on the right infra-clavicular region, and the other two at the level of the fifth intercostal space, in the mid-clavicular line, on both right and left sides. A lead II configuration was obtained.

The ECG and blood pressure transducer were connected to a pre-amplifier and amplifier system (SE 4000), displayed on a 44 cm oscilloscope screen (Lan-Scope, Lan-Electronics, Slough) and recorded on ultra-violet light sensitive paper (SE u.v. recorder 3006)

at paper speeds varying between 100 mm/min and 50 mm/sec, as required.

The frequency response of the recording system (Seldicath cannula, 200 cm manometer line, Statham transducer, SE amplifier, and u.v. recorder, with dextrose 5%) was measured by applying a sinusoidal pressure generated by a function generator (TWG 501, Feedback Amplified, Peldrive MK 1) and input to the cannula from a mechanical oscillator (Vibrator Type VI, Advance, Hainhault). The amplitude of the output was within 5% of the input up to 4 Hz and tended to increase at higher frequencies. Maximum resonance occurred at 12 Hz. Pickering (1970) obtained a similar frequency response with this system. This is adequate for the reproduction of systolic and diastolic blood pressure at rest, but may not reproduce the pressure wave form accurately at higher heart rates, as in exercise, when the values for mean arterial pressure are more reliable (McDonald, 1974).

The frequency response could be improved with a shorter manometer line, but this restricted the subjects' mobility and made exercise and movement, especially from the bed to the bicycle, awkward.

The output from the reference transducer, without the manometer line, was within 5% of the input amplitude up to 35 Hz.

The pressure and heart rate record were simultaneously transferred to magnetic tape (Scotch 215, 3M or Ampex 20/20+) through a FM recorder (Racal Thermionic Store-4), until the facility for on-line computer analysis of the blood pressure signal was developed.

Blood pressure and heart rate during mental and physical exercise

After approximately 15 minutes' quiet rest, in the supine position, baseline blood pressure and heart rate were obtained. The patients then performed four exercises in the same sequence: mental arithmetic, a reaction time test, isometric exercise, and bicycling. After a baseline recording (1 minute 30 seconds), the nature of the test was explained to the patient. There was a 30-second period of relaxation between the explanation and the exercise. At the end of each test, the patient was asked to relax until the blood pressure and heart rate returned to baseline levels. Mental arithmetic and the reaction time test were performed with the patient lying on the bed; the isometric and bicycle exercise were performed with the patient seated. Venous blood for the measurement of plasma noradrenaline concentration was obtained before, during and after mental arithmetic (10 patients), isometric exercise (52 patients), and bicycling (52 patients). These three samples were drawn after 15 minutes of quiet rest (i.e. before the test was explained), in the last minute of exercise, and three minutes after its completion.

Mental arithmetic consisted of subtracting 7's serially from 300. As the patient called out each answer in turn, he was urged to increase his speed of calculation and criticised for any errors.

A timer counter (RACAL Instruments, 9835) was converted to a reaction time testing apparatus by obscuring the last 5 numbers on the digital display with a card. Only the first number could be seen. The subject was shown two buttons marked "start" and "stop". When the start button was pressed, the number on the digital display changed sequentially. When the stop button was pressed, this number was frozen. The subject was instructed to press the start button

and wait until the investigator called out a number at random. He was to freeze this number the instant it appeared by pressing the stop button, and then immediately restart the timer. For the first 2 minutes and 30 seconds the numbers changed each second (slow), and for the last 2 minutes and 30 seconds changed at a faster speed (10 numbers per second). When the blood pressure and heart rate returned to baseline, the patient was asked to sit at the bedside until the next test.

The apparatus used for the isometric exercise was a syphgmomanometer bulb attached to an air pressure gauge, which displayed the patient's grip strength in lbs/in^2. The patient was asked to grip the bulb with the non-cannulated hand, squeeze it maximally for 30 seconds, then to release his grip slowly to 30% of his maximum voluntary contraction (usually 3-5 lbs/in^2). This level of pressure was sustained for as long as possible, up to 4 minutes 30 seconds. Subjects were instructed to avoid performing a valsalva manoeuvre by breathing naturally or counting under their breath during handgrip.

The patient then sat on a bicycle ergometer (Tunturi) whose work load (calibrated for a speed of 18 kph (50 rpm)) could be controlled by adjusting a brake. Exercise consisted of 5 minutes of bicycling at a load of 50 watts (300 kpm) followed immediately by another 5 minutes of bicycling at a load of 75 watts (450 kpm). In order to minimize any isometric component to this exercise, the patient was instructed to lay the backs of his hands upon the handle bars rather than grip them. Almost all subjects could perform this submaximal exercise test for the full 10 minutes. When blood pressure and heart rate returned to baseline values at

the end of the bicycling exercise, the subjects lay quietly on the bed for 10 to 15 minutes before proceeding to the next stage.

Measurement of baroreflex sensitivity

Phenylephrine hydrochloride 1% (Boots, Nottingham) solution was diluted in dextrose 5% to give a concentration of 100 µg/ml. The patient rested for a 1 minute 30 second baseline period. Phenylephrine was then administered in doses of 30 µg to 140 µg by bolus intravenous injection from a 1 ml "tuberculin" syringe and flushed into the vein with 6 ml of dextrose, over a 5-second period. The dose was adjusted to increase systolic pressure by 20 to 30 mm Hg in each patient. The start and the end of the dextrose flush were recorded on tape. The blood pressure and heart rate usually returned to baseline levels within a minute of the injection; five minutes were allowed between injections and between 5 and 8 injections were given to each subject. The patient was unaware of the start or the end of the injection as the stopcocks were not visible by him. A few patients experienced a cold sensation in the arm as the solution was injected. One remarked on a dryness in the throat and an urge to cough at the time that blood pressure began to rise.

Ambulatory monitoring of blood pressure

The venous cannula was removed. A fine autoclavable nylon tube (Portex 800/205/150, 1.02 mm o.d., 0.62 mm i.d.) about 1 meter in length connected the arterial cannula to the 24-hour ambulatory monitoring apparatus. This consisted of an Oxford Mark II portable blood pressure transducer unit (Selig, London) (Miller-Craig, Hawes

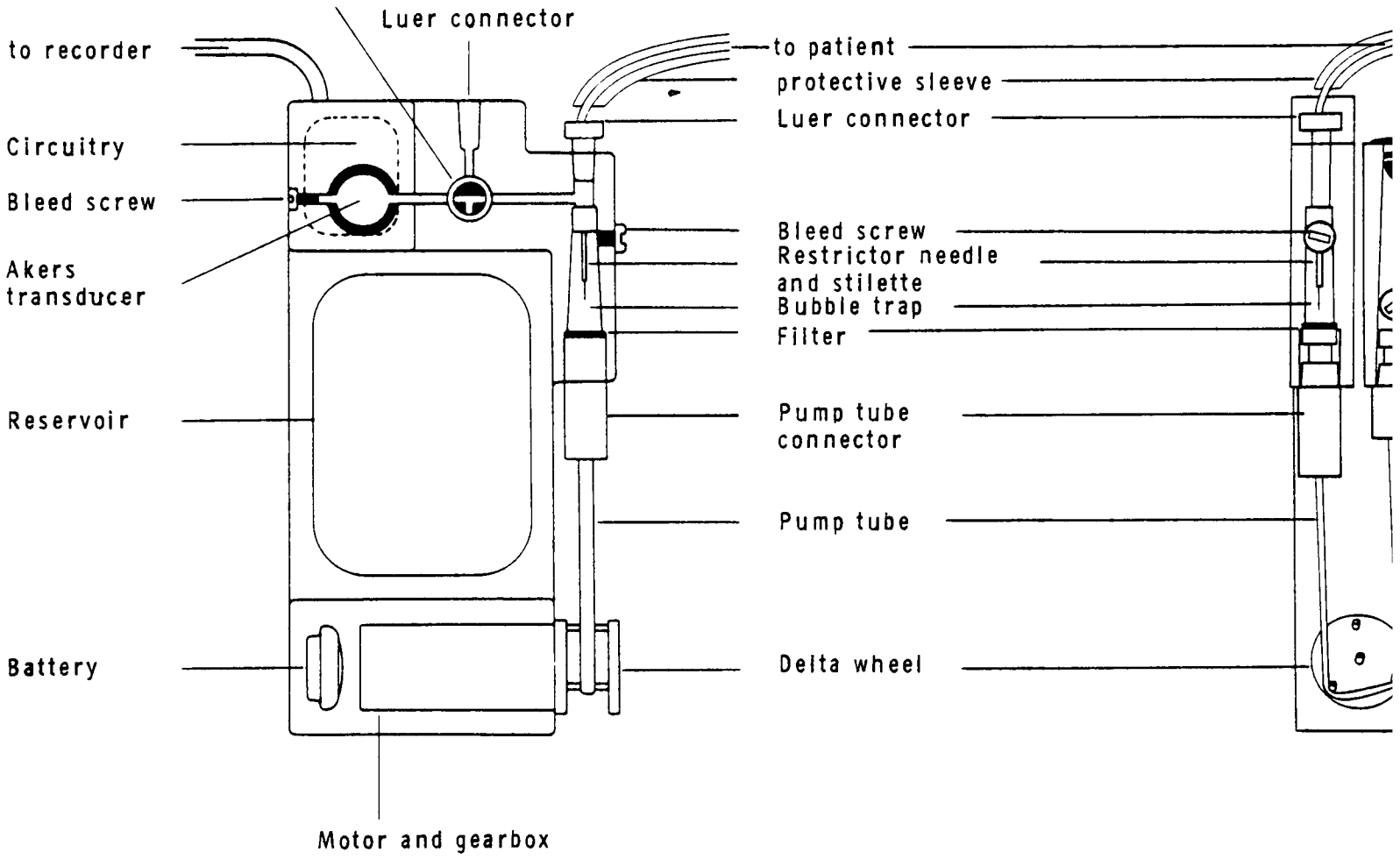

Fig. 4-1 The Oxford Mark II portable blood pressure transducer unit.

and Whittington, 1978; Stott, 1979), linked to a Medilog 4 channel analogue recorder (Oxford Instruments) which held a standard 120-minute cassette tape (AD-C120, TDK; Standard C-120, Philips). As can be seen in Fig. 4-1, the blood pressure unit has three parts: a semiconductor strain gauge pressure transducer (Akers Type 831B), a fluid reservoir filled with heparin (100U/ml) in sterile water (38 ml), and a peristaltic pump (Delta-Wheel), driven by a miniature electric motor (Escap 050/004), powered by a single 1.35V mercury button cell battery. The maximum pressure developed by the pump is 500 mm Hg and perfusion is independent of arterial pressure up to about 300 mm Hg (Stott, 1979). The perfusion rate can be adjusted between 1.2 to 2.4 ml/hour by altering the length of the silastic tubing, or can be halved if the voltage to the motor is decreased by a diode inserted in series. At lower rates of perfusion, clotting of the cannula tip and consequent damping of the pressure wave occurs more readily.

The perfusion unit was sterilized overnight with Cidex. The tape recorder turned on for 2 hours prior to its use in order to allow its batteries to stabilize. The transducer was calibrated with 50, 150 and 250 mm Hg, then connected to the arterial cannula. Blood pressure was recorded on one channel of the Medilog system, and the lead II of the electrocardiogram on a second. A crystal clock on a third channel provided a time signal. The two units, each about the size of a double pack of playing cards, were worn across the chest in a comfortable pouch. Patients were supplied with a digital watch (Texas Instruments) and a voice recorder (Philips 0095) and asked to keep an accurate record of their activities during the day.

A pressure bandage was wrapped around the site of the cannulation, and radial pulses were reassessed before the patients left the hospital. They usually returned in the evening for about 15 minutes. At that time the reservoir was refilled, the transducer recalibrated, the line flushed, and the patient's pulses and arm checked. Bathing the arm was prohibited. The patient was otherwise unrestricted and encouraged to be as active as possible. The cannula was removed the following afternoon and final calibrations were performed. Transient median nerve palsies (Littler, 1976) were avoided by careful attention to haemostasis at this point in the procedure. A pressure bandage was then applied to the puncture site and the pulses rechecked before the patient was discharged. The entire procedure was well tolerated. One patient suffered a small haematoma which resolved over the next few days. Bruising was noted by a few individuals; this again resolved in all instances. There were no long-term complications.

The dynamic characteristics of the transducer system, catheter, and connecting tube alone were found to be nearly constant (±2db) up to 15 Hz, with a slight (±2db) resonance at between 10-14 Hz, when tested by Millar-Craig et al. (1978). However, the frequency resonance of the entire system (including the Medilog 4 channel recorder and the replay system) is described as -3db at about 8 Hz, -6db at 10 Hz, and falling off very rapidly above 10 Hz (Stott, 1979). It is comparable to the system used in the laboratory. Simultaneous recordings of systolic and diastolic pressure, made with the Oxford system, and with a Millar catheter-tip transducer introduced into the aorta of an atrially paced dog were found to have a good correlation ($r=0.998$); the Oxford system consistently underestimated blood pressure by about 3% (Millar-Craig et al., 1978).

Analysis of blood pressure and heart rate during mental and physical exerci

A suite of multi-tasking real time FORTRAN IV blood pressure analysis programmes was developed for our laboratory Data General Eclipse S-200 computer (32K words core and two 5 mega-bite discs).

The SE 4000 amplifier output was input to the Racal Thermionic Store 4 FM recorder, and to an analogue-digital (a/d) converter. The latter sampled the blood pressure signal at a frequency of 100 Hz. A second channel of the converter was utilized for an event marker - a simple on/off switch, which marked periods of rest, exercise, etc. These marks appear along the bottom line of Figs. 4-2 to 4-5.

Calibrations of 0 and 200 mm Hg were recorded and the gain of the a/d unit adjusted for the patient's blood pressure. A resolution of 0.1 to 0.2 mm Hg (i.e. much greater than that of the input signal) was obtained.

The computer program sought troughs of pressure waves, using first derivatives of consecutive samples. If these troughs were followed by a trough to peak amplitude which exceeded a certain threshold value (in this case, the standard deviation of the 250 samples appearing in each 2.5 second time interval) then the absolute minimum (or trough - corresponding to the diastolic blood pressure), absolute maximum (or peak of the pressure wave - corresponding to the systolic blood pressure) and reference points (which are half-way between the trough and peak, along the upstroke) were determined. The time between two sequential reference points was used to calculate the pulse interval. Mean arterial pressure (corresponding to the area under the pressure wave between two sequential reference points, divided by the sample number) was

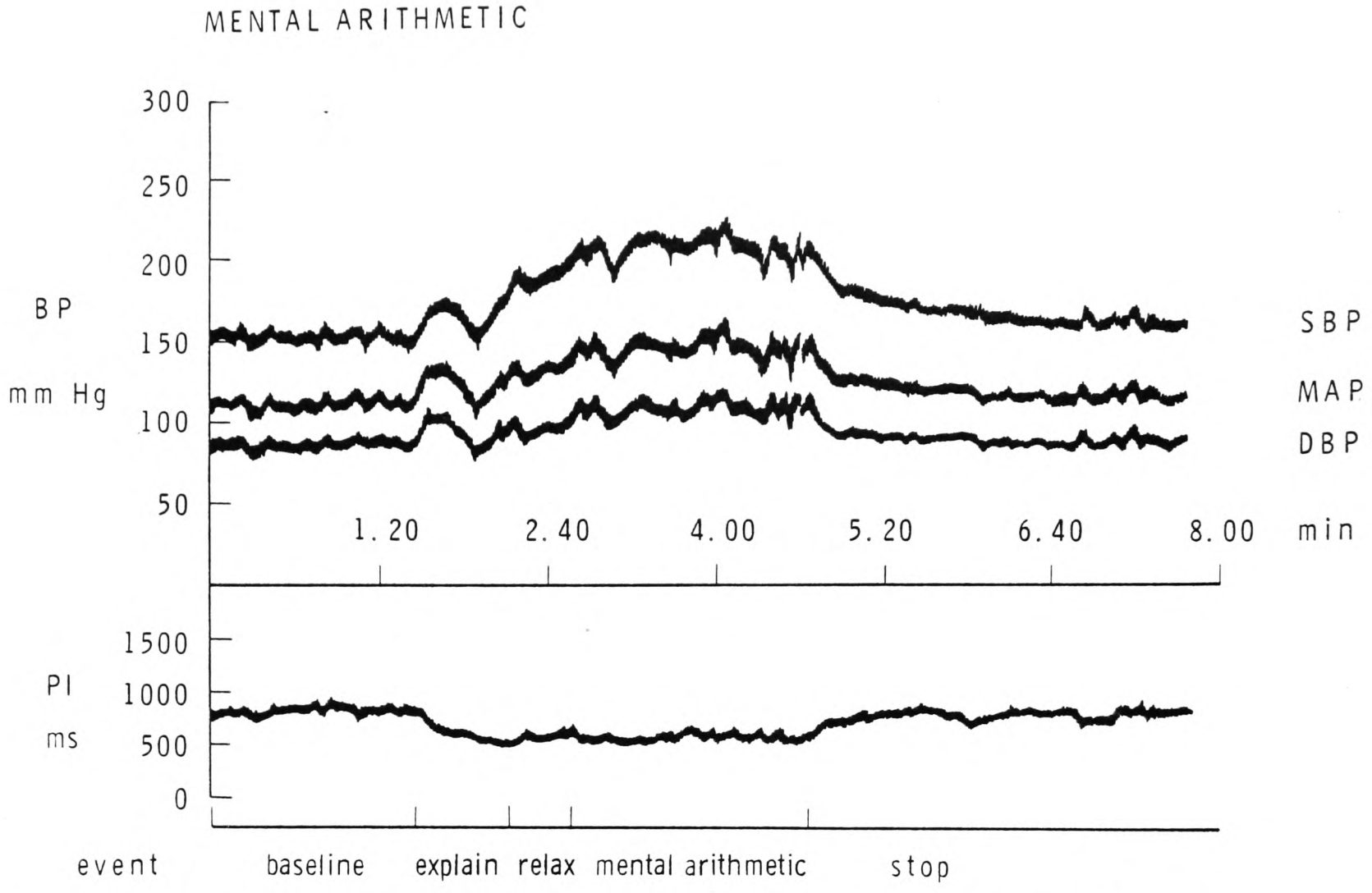

Fig. 4-2 Systolic (SBP), mean (MAP) and diastolic (DBP) blood pressure and pulse interval (PI) during a mental arithmetic stress test.

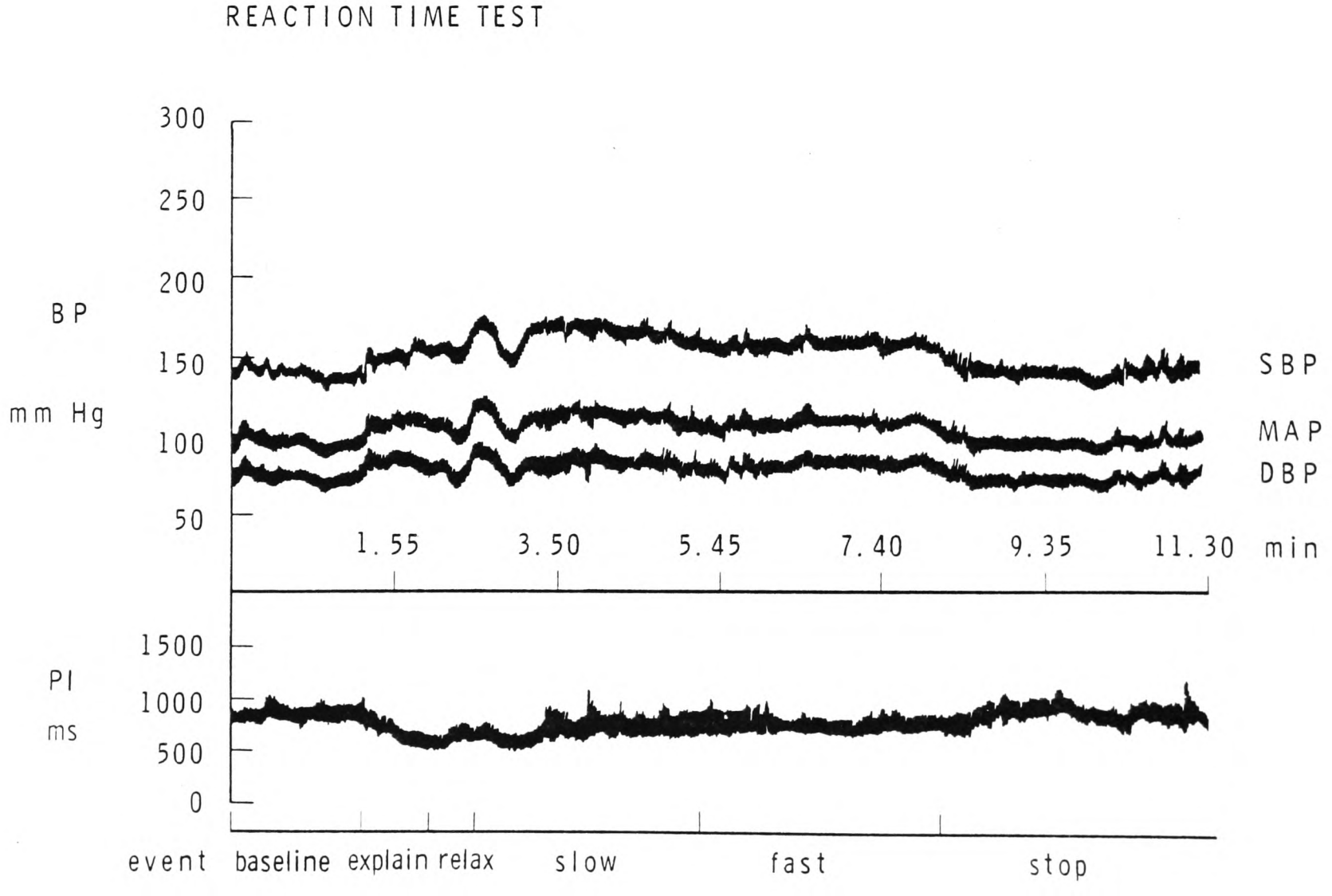

Fig. 4-3 Systolic (SBP), mean (MAP) and diastolic (DBP) blood pressure and pulse interval (PI) during a reaction time test.

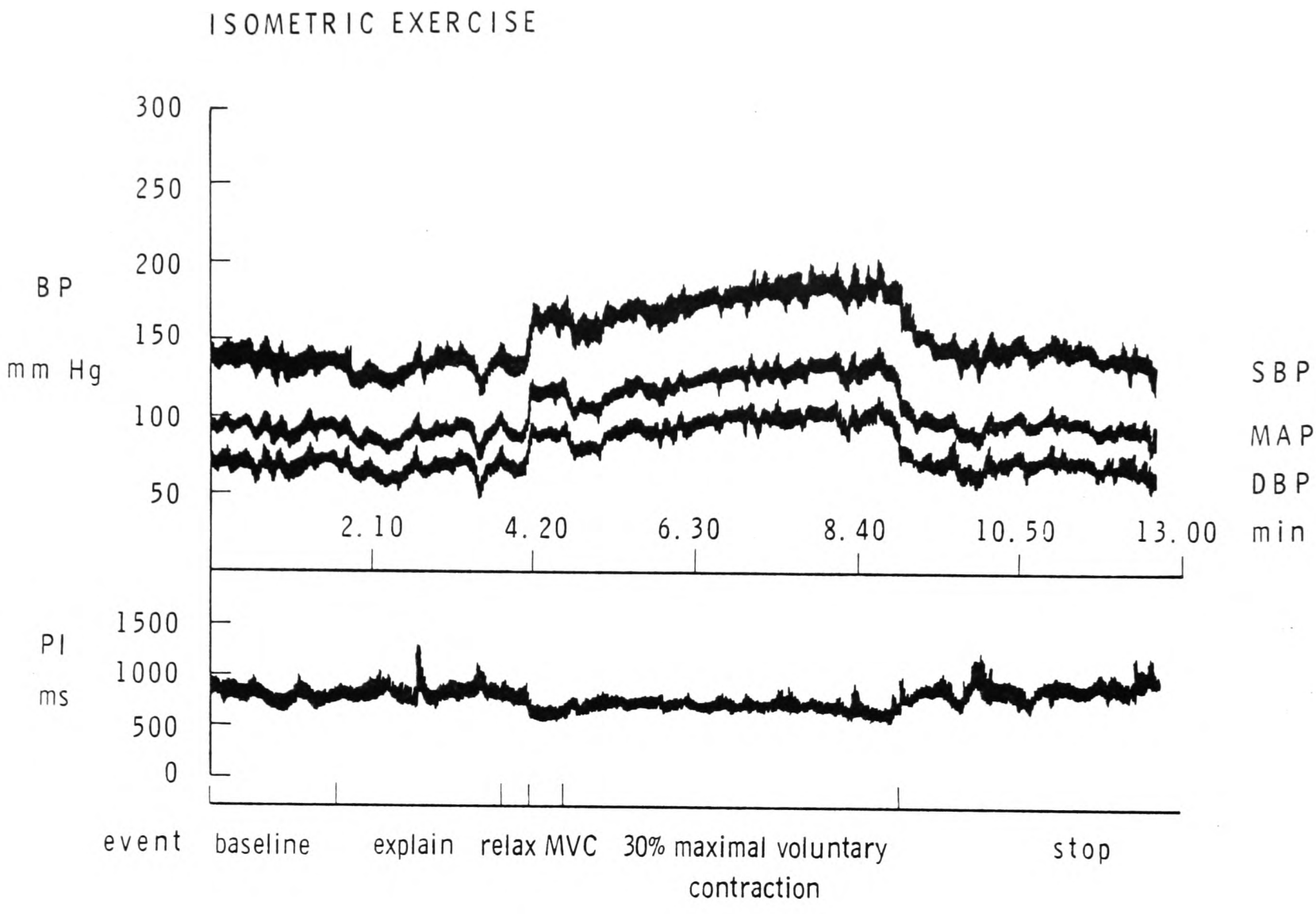

Fig. 4-4 Systolic (SBP), mean (MAP) and diastolic (DBP) blood pressure and pulse interval (PI) during isometric exercise.

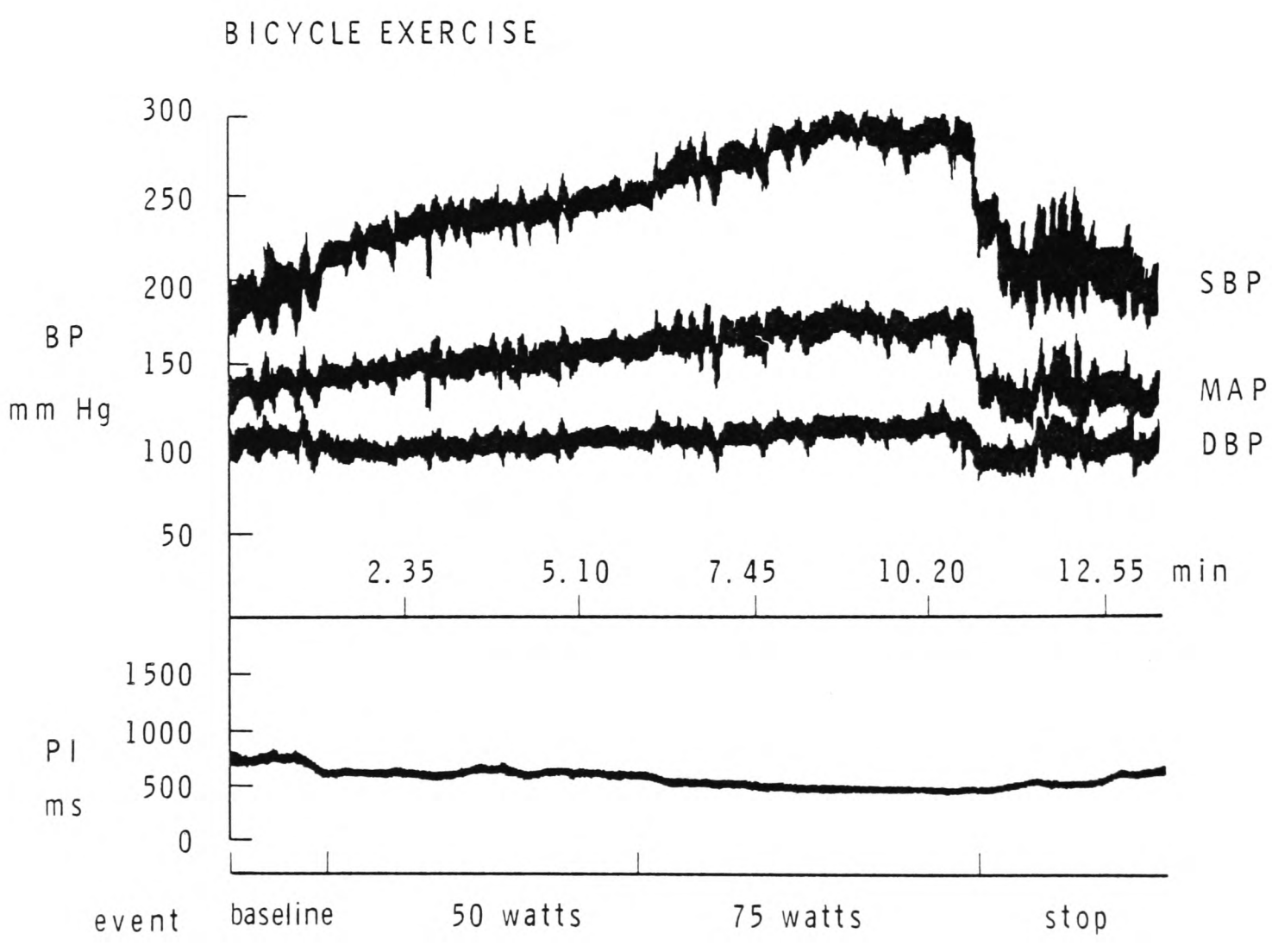

Fig. 4-5 Systolic (SBP), mean (MAP) and diastolic (DBP) blood pressure and pulse interval (PI) during bicycle exercise.

calculated arithmetically. Systolic, mean, and diastolic blood pressure, as well as pulse interval, and the event mark, appeared in expanding page format on a visual display unit (Tektronix 4006-1, Beaverton, Oregon). There was a delay of about 3 seconds between the occurrence of an event and its appearance on the VDU screen. Thirty seconds of time were displayed initially; if the particular exercise was longer, this time was automatically doubled, then redoubled on the VDU screen, as long as required, and all of the preceding information retained. One could therefore see the changes in blood pressure and pulse interval throughout the entire exercise, and know when baseline pressures had been reached at the cessation of each exercise period.

Figs. 4-2 to 4-5 are copies of this VDU display (Tektronix 4631 Hard copy unit). These four figures illustrate the changes in blood pressure and pulse interval obtained in each of the tests.

At the end of the exercise one could: (1) edit out pulse artefact, i.e. coughing, damped pulses, catheter movement; (2) insert additional event markings; and (3) perform statistical computations on the data.(Fig. 4-6). Systolic, mean, and diastolic pressures, and their standard deviations and the pulse interval, and its standard deviation, were calculated for each 15-second epoch throughout the period of the recording. At the end of each event, e.g. baseline (Fig. 4-2), the mean of each of these values, the minimum and maximum value obtained and the number of cardiac cycles included in each event were also printed. The latter were then printed out for permanent record by a deck writer (Digital Decwriter III, Rair, London). The data were then stored on computer disc.

Fig. 4-6 Decwriter print-out of blood pressures (mm Hg) and pulse intervals (ms) during a mental arithmetic test in one subject. Data are computed over 15 second epochs and for each part of the test.

MENTAL ARITHMETIC

RUN NO-- 2

Baseline

TYPE	DISTOLIC M	DISTOLIC SD	MEAN M	MEAN SD	SYSTOLIC M	SYSTOLIC SD	R---R M	R---R S
EPOCH	86.3	1.9	112.1	2.4	154.6	3.1	798.9	28
EPOCH	83.1	3.3	108.8	4.2	151.8	3.9	763.2	35
EPOCH	83.9	1.8	108.8	2.0	151.2	1.9	824.2	17
EPOCH	84.9	2.9	110.1	3.3	152.1	3.8	845.3	40
EPOCH	87.0	2.9	112.3	3.3	152.6	3.3	819.5	34
EPOCH	86.9	2.1	112.1	2.5	152.4	3.1	810.6	29
EPOCH	83.8	1.4	108.9	2.1	149.9	3.1	827.5	23
MAX	91.7		117.6		159.4		910.0	
MIN	78.3		102.3		143.9		710.0	
TOTAL	85.2	2.9	110.6	3.3	152.2	3.3	810.9	37

Explain

EPOCH	97.5	6.7	123.4	7.7	160.8	6.9	731.7	56
EPOCH	98.3	3.7	128.4	3.4	168.7	3.0	609.6	19
EPOCH	85.0	3.8	113.7	4.6	157.3	4.8	539.6	24
EPOCH	92.4	2.3	122.9	2.6	171.6	3.4	487.7	6
MAX	106.4		134.2		177.1		810.0	
MIN	77.9		104.6		146.5		480.0	
TOTAL	92.3	7.2	121.4	7.7	163.8	7.3	582.6	81

Relax

EPOCH	95.9	4.0	130.4	3.7	185.9	4.3	533.7	43
EPOCH	93.5	2.6	128.8	3.2	185.3	3.3	553.3	16
EPOCH	97.1	2.8	133.7	3.0	192.1	2.9	595.6	30
MAX	101.6		138.2		198.3		640.0	
MIN	88.7		123.1		178.9		490.0	
TOTAL	94.9	3.4	130.2	3.7	186.7	4.3	554.6	33

Mental Arithmetic

EPOCH	106.3	4.7	142.5	4.7	201.2	4.4	558.3	41
EPOCH	104.8	5.1	140.7	6.5	199.8	8.6	524.3	23
EPOCH	108.8	2.9	145.9	3.7	207.2	5.0	516.2	12
EPOCH	105.7	2.4	143.8	3.3	208.4	3.6	565.6	27
EPOCH	108.5	4.3	146.7	5.1	209.5	5.3	580.4	28
EPOCH	111.0	4.2	150.2	5.6	211.7	6.5	555.2	25
EPOCH	105.8	4.7	140.9	6.5	200.9	9.0	554.4	31
EPOCH	107.3	5.4	141.8	7.2	198.7	8.5	530.0	26
MAX	116.3		160.8		223.8		660.0	
MIN	96.0		126.2		182.3		480.0	
TOTAL	107.3	4.6	144.2	6.2	204.9	8.1	547.5	32

Stop

EPOCH	110.1	3.7	147.2	3.0	204.8	2.4	540.0	16
EPOCH	96.1	6.5	132.2	7.9	190.4	9.3	656.5	37
EPOCH	91.6	1.4	124.1	1.8	178.7	2.5	721.5	34
EPOCH	89.6	1.3	121.0	1.7	172.7	2.2	768.0	22
EPOCH	88.2	1.6	118.2	2.1	168.2	2.4	802.6	23
EPOCH	89.4	1.0	119.5	1.7	167.4	1.9	749.0	33
EPOCH	85.9	2.2	114.8	2.5	163.4	2.5	722.5	29
EPOCH	85.7	1.2	114.4	1.6	161.3	2.0	784.7	29
EPOCH	85.9	1.5	114.2	2.0	159.7	1.9	794.2	14
EPOCH	86.6	2.9	114.8	3.4	160.3	4.0	755.0	54
EPOCH	85.9	2.6	113.7	3.1	159.0	3.0	734.3	52
EPOCH	89.4	3.3	117.9	3.9	161.4	4.9	797.2	38
EPOCH	86.1	1.6	113.7	1.8	157.4	1.8	805.8	27
EPOCH	88.9	0.9	116.5	0.1	159.9	0.0	820.0	10
MAX	114.1		151.0		208.2		870.0	
MIN	82.6		110.0		153.4		520.0	
TOTAL	88.8	4.9	118.9	7.3	167.6	11.4	752.5	40

Definitions:

"Baseline" blood pressures, pulse intervals or heart rate are the mean value recorded over the resting period (usually 1:30 min), before the explanation or initiation of an exercise. "Maximum" blood pressures, pulse intervals or heart rate values represent the highest (or lowest, in the case of pulse interval) value recorded for a 15 second epoch during an exercise, not the absolute peak obtained during an exercise. "Recovery" values refer to the 15 second epoch which occurs at the third minute after the end of exercise.

Statistics:

Statistical analysis on these data was performed with the assistance of the Oxford University 1906A computer (ICL). The Statistical Package for the Social Sciences programme (SPSS) was utilized (Nie, Hull, Jenkins, Steinbrenner and Bent, 1975). The Bonferroni method (Wallenstein, Zucker and Fleiss, 1980) was used to calculate a modified t-statistic whenever simultaneous multiple comparisons were performed, e.g. when mean values from the four exercises were compared with each of the others, in turn. A more conservative P value (P/m, where m is the number of within group comparisons made) is required in order to attain statistical significance with the Bonferroni transformation.

The multiple regression analysis in the SPSS uses stepwise inclusion of the independent variables in the regression equation, starting with the one that is most highly correlated with the dependent variable under study. Variables which, when added, do not significantly improve the regression equation are

omitted. Two independent variables may be highly correlated with a dependent variable, but not necessarily significant when tested in a multiple regression equation if a high degree of colinearity exists between them. Therefore, partial correlation coefficients were also calculated in order to determine the relationship between two variables while excluding the effect of other variables on their correlation.

Analysis of ambulatory monitoring data

The 24 hour record was replayed from the cassette (Oxford Instruments Replay Unit) at 25 times real time into the a/d converter. The 60 Hz crystal time marker on one channel on the Medilog unit was implemented at replay to ensure tape speed accuracy. Off tape calibrations established the appropriate a/d span.

In this instance raw blood pressure was sampled at a frequency of 16 KHz (or 64 Hz real time). These data were dumped onto 8 hour disc buffers.

The ambulatory monitoring programme also sought pressure wave troughs. If these troughs were followed by a trough-to-peak amplitude which exceeded a pre-set (normally 32 mm Hg) yet manually adjustable threshold (if required, i.e. during sleep), the absolute minimum, maximum and reference points were determined as described earlier. Automatic editing facilities discarded heart rates of less than 25 and more than 256 beats/min. The percentage of time thus edited was recorded.

Display and interaction facilities allowed the operator to control and validate the input. Raw data were displayed out of the computer onto an oscilliscope. Bright-up points showed the computed systolic and diastolic pressures. The disc buffer could be

interrogated by operator interaction at variable speeds, i.e. a 4 second frame mode, variable speed roll-back and roll-forward, and fixed forward speeds of 20 and 30 times real time. This allowed flexible data verification, analysis and operator comments. In addition, it allowed for rapid blood pressure analysis when the 24 hour record was clean.

Commonly occurring artefacts, i.e., damping of the pressure wave, or catheter whip, could be noted by the observer, edited or marked and excluded from subsequent data analysis. Threshold limits could be adjusted when required. Retained data were stored onto a secondary disc, in beat format. Hourly frequency histograms were calculated, as was the percentage of the record that had been edited or marked. These hourly data could be summated, to give larger histograms, depending upon the time period (i.e., waking, sleeping) which one wished to examine. Hours that were marred by damping or pulse wave artefact could be excluded from these histograms. Examples of waking and sleeping pressure and pulse interval histograms are found in Figs. 4-7, 4-8 and 4-9. On the whole, these histograms are normally distributed.

FORTRAN programs were used to compress this information into 2 minute means (and standard deviations) of systolic, mean, diastolic pressure and pulse interval. An example of this type of 24 hour record is illustrated in Fig. 4-10. Time, in hours, is displayed along the horizontal axis, and the computed systolic, mean and diastolic pressures, and heart rate along the vertical axis. The percentage of the record edited and marked is also noted. The variation of blood pressure obtained with activity, and the fall in blood pressure with sleep are clearly illustrated by this format.

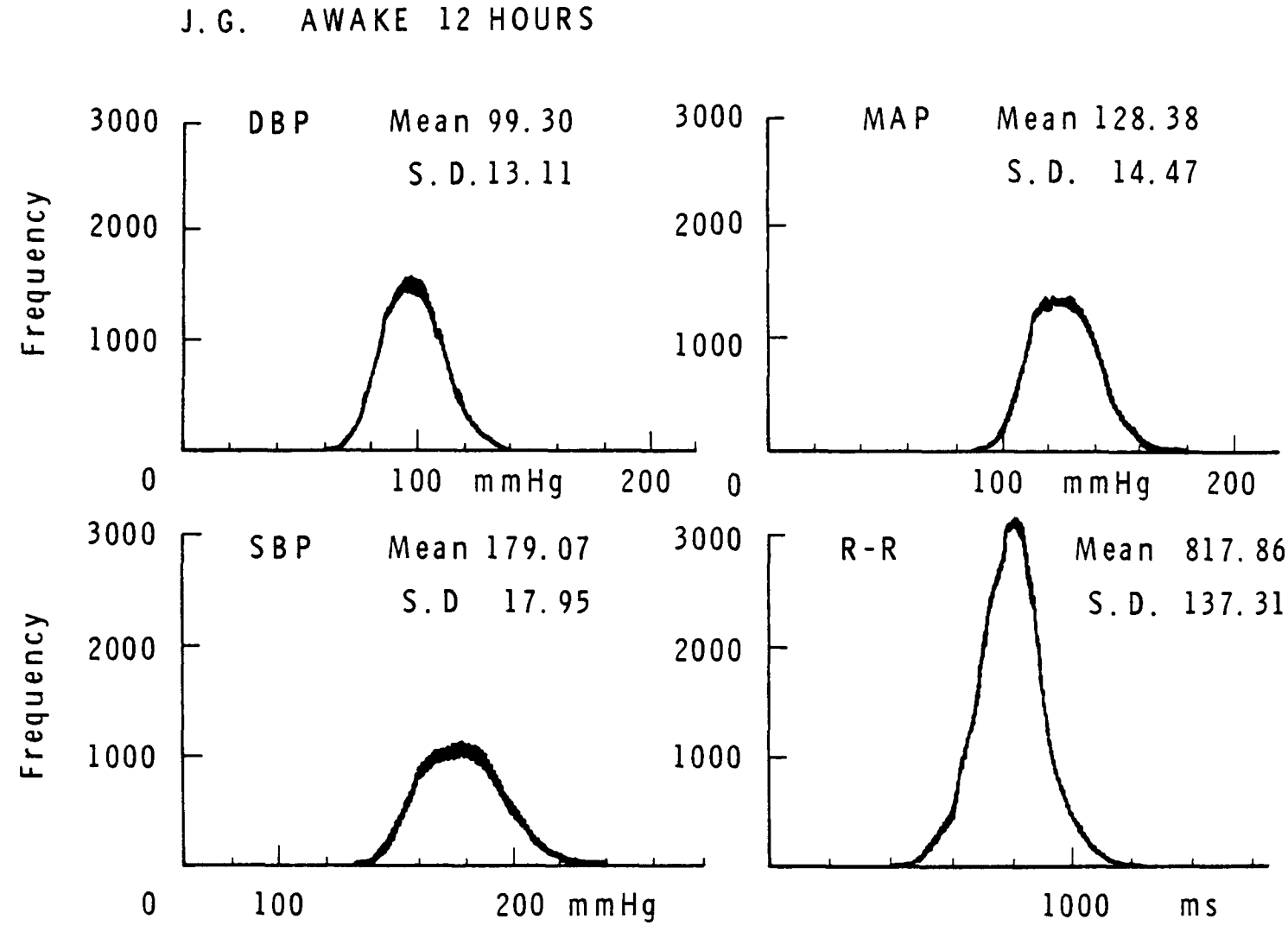

Fig. 4-7 Frequency histograms of diastolic (DBP), mean (MAP) and systolic (SBP) blood pressures and pulse interval (R-R) during 12 waking hours in a patient (J.G.) Means and standard deviations (S.D.) for each waking value are shown.

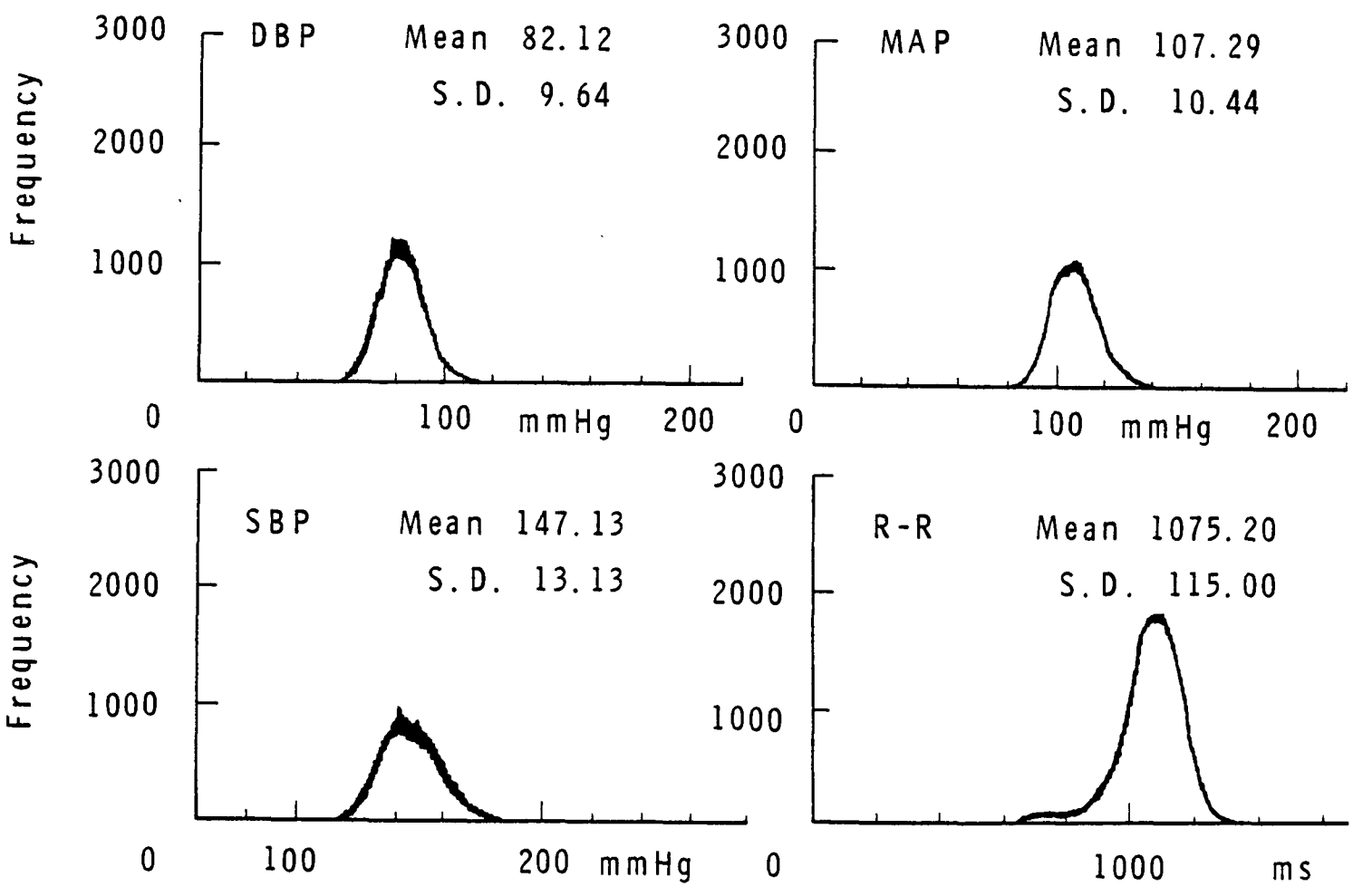

Fig. 4-8 Frequency histogram of diastolic (DBP), mean (MAP) and systolic (SBP) blood pressures and pulse interval (R-R) during 8 sleeping hours in a patient (J.G.). Means and standard deviations for each sleeping value are shown.

J. G. AWAKE, 12 HOURS ⋯⋯, and ASLEEP 8 HOURS ▬▬.

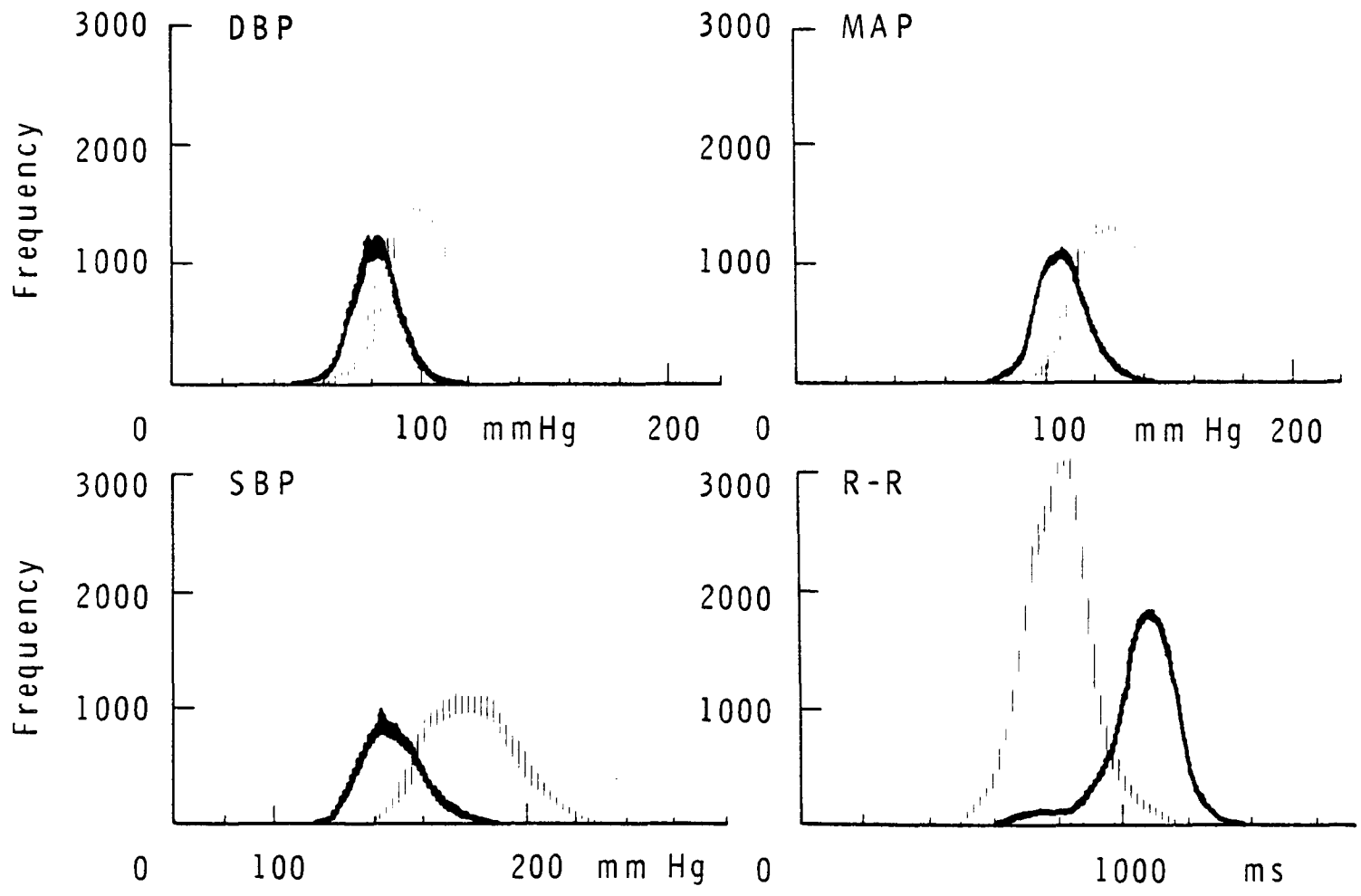

Fig. 4-9 Frequency histogram of diastolic (DBP), mean (MAP) and systolic (SBP) blood pressures and pulse intervals (R-R) from Fig. 4-7 and Fig. 4-8 to show these values in the same subject while awake (hatched line) and asleep (solid line).

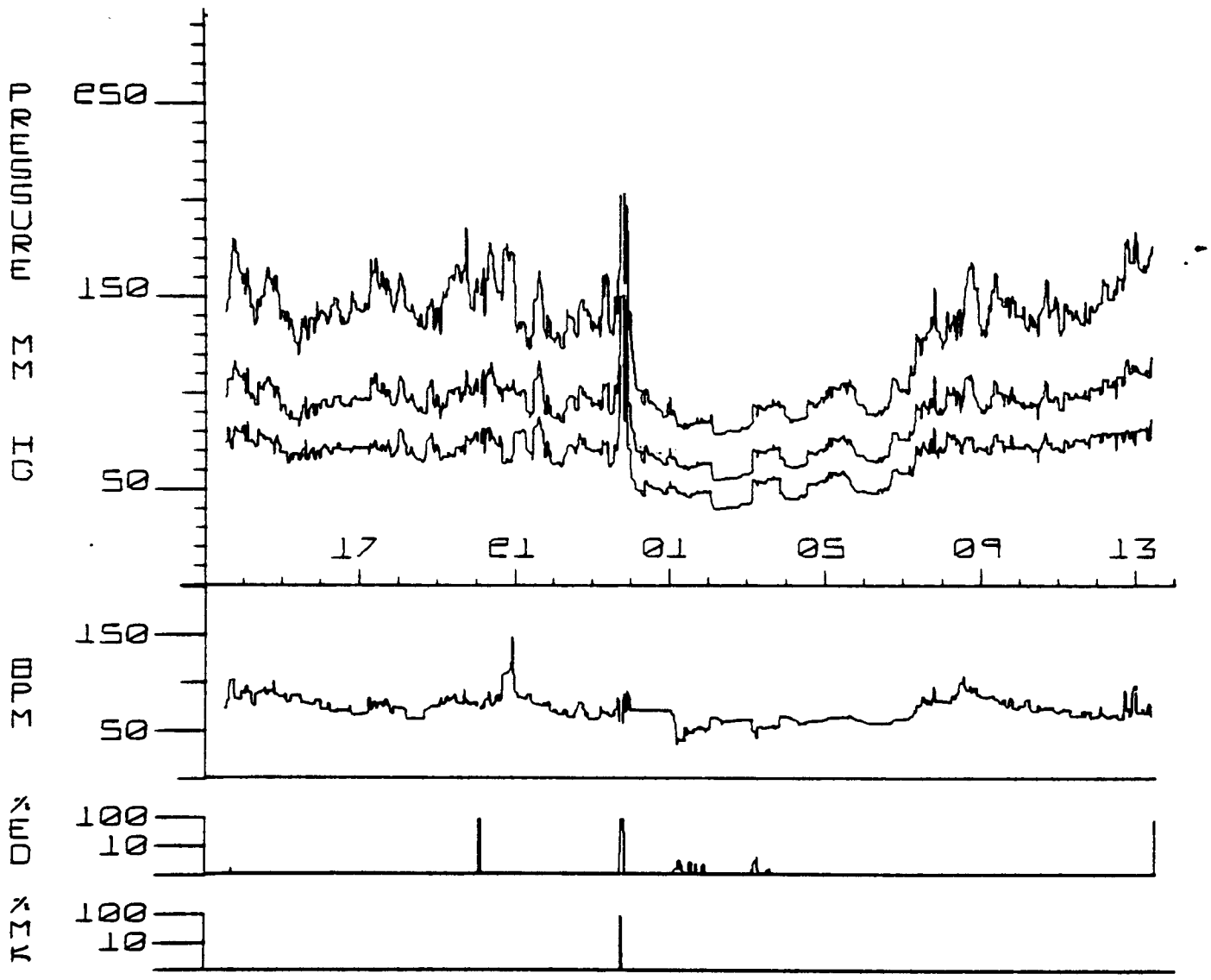

Fig. 4-10 A twenty-four hour blood pressure record from one subject showing systolic, mean, and diastolic blood pressure (upper tracing) and heart rate (lower tracing) during work (1300-1700 hours), driving (1700-1745 hours), return to hospital (2000 hours), home, resting (2200-2400 hours), coitus (2400 hours) and sleep (2400-0700 hours).

Fig. 4-11 Decwriter print-out of blood pressures (mm Hg), pulse intervals (ms) and calculation of Baroreflex sensitivity (slope) and weighting factor (W) for each delay (D). Data are computed over 15 second epochs; the linear regressions are of the points selected by the investigator.

JFAN75 DANIELS R 1 1/5/79
RUN NO-- 14

Baseline

TYPE	DISTOLIC M	DISTOLIC SD	MEAN M	MEAN SD	SYSTOLIC M	SYSTOLIC SD	R---R M	R---R SD	PULSE NO
EPOCH	65.9	2.6	89.8	2.9	128.0	4.6	917.3	38.2	15
EPOCH	69.2	1.8	94.4	2.0	134.8	4.3	972.5	59.9	12
MAX	71.7		96.8		140.9		1060.0		27
MIN	61.3		85.5		118.8		850.0		27
TOTAL	67.3	2.8	91.8	3.3	131.0	5.5	941.9	53.6	27

Phenylephrine Injection

EPOCH	66.8	2.8	91.8	1.5	133.1	4.6	1012.5	53.2	4
EPOCH	65.6	2.5	89.4	1.8	126.5	2.8	968.7	79.7	8
MAX	68.9		92.9		136.0		1090.0		12
MIN	61.3		86.9		122.2		850.0		12
TOTAL	66.0	2.4	90.2	1.9	128.7	4.5	983.3	68.8	12

Response

EPOCH	68.6	2.8	93.0	3.7	130.5	3.8	920.0	59.3	8
EPOCH	72.9	5.1	98.0	6.3	138.2	10.5	1096.2	121.0	13
EPOCH	80.2	2.8	106.8	2.4	152.9	5.3	1275.8	130.1	12
EPOCH	76.1	2.5	103.1	2.2	145.1	4.6	1058.6	53.3	14
EPOCH	76.6	1.7	101.6	2.3	140.0	3.7	938.0	28.6	5
EPOCH	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0
MAX	84.9		111.0		162.8		1600.0		52
MIN	64.0		87.6		121.2		820.0		52
TOTAL	75.1	4.9	101.0	5.9	142.4	9.7	1085.2	151.6	52

Linear Regressions

RUN NO 14
REGRESSION---X,Y=S,R
START TIME= 30.00 PULSES= 19 32

NO	D	CORR	SLOPE	INCPT	XSD	YSD	VAR	T	W
14	0	0.927	13.945	-836.82	11.1	167.0	2.658	8.553	0.376
14	1	0.787	11.853	-507.93	11.1	167.2	7.211	4.414	0.139
14	2	0.714	10.274	-258.66	11.1	159.7	8.473	3.530	0.118
14	3	0.648	8.883	-50.09	11.1	152.0	9.061	2.951	0.110

Calculation of baroreflex sensitivity

Smyth (1967) plotted systolic pressure against the preceding pulse interval by hand. Later, Gribbin (1974) recorded the pressure wave simultaneously onto paper and magnetic tape for subsequent analysis with the aid of a computer. A real-time FORTRAN IV programme was used in the present investigation.

The arterial pressure was recorded onto magnetic tape, ultra-violet light sensitive paper, and on-line to the Data-General Eclipse S-200 computer. A print-out of the values for pressure and pulse interval during each 15 second epoch of the baseline, injection phase, and pressure rise was obtained at the end of each phenylephrine injection (Fig. 4-11). Systolic, mean and diastolic pressure and pulse interval were displayed on the visual display unit, over the entire run, and each cardiac cycle was numbered (Fig. 4-12). In order to select the pressure pulses for inclusion in the regression equation (defined by the solid vertical lines in Fig. 4-13), the programme allowed the operator to view a smaller portion of the run in greater detail and ascertain the point at which arterial pressure began to rise (Fig. 4-13).

With the assistance of the computer, the slope of each regression line and the significance of the regression equation could be calculated within 5 minutes, allowing the number of injections needed to determine an individual's baroreflex sensitivity to be estimated during the experiment.

Effect of respiration on baroreflex sensitivity

Smyth (1967) excluded those beats which fell during inspiration from these calculations, citing the potential influence of sinus

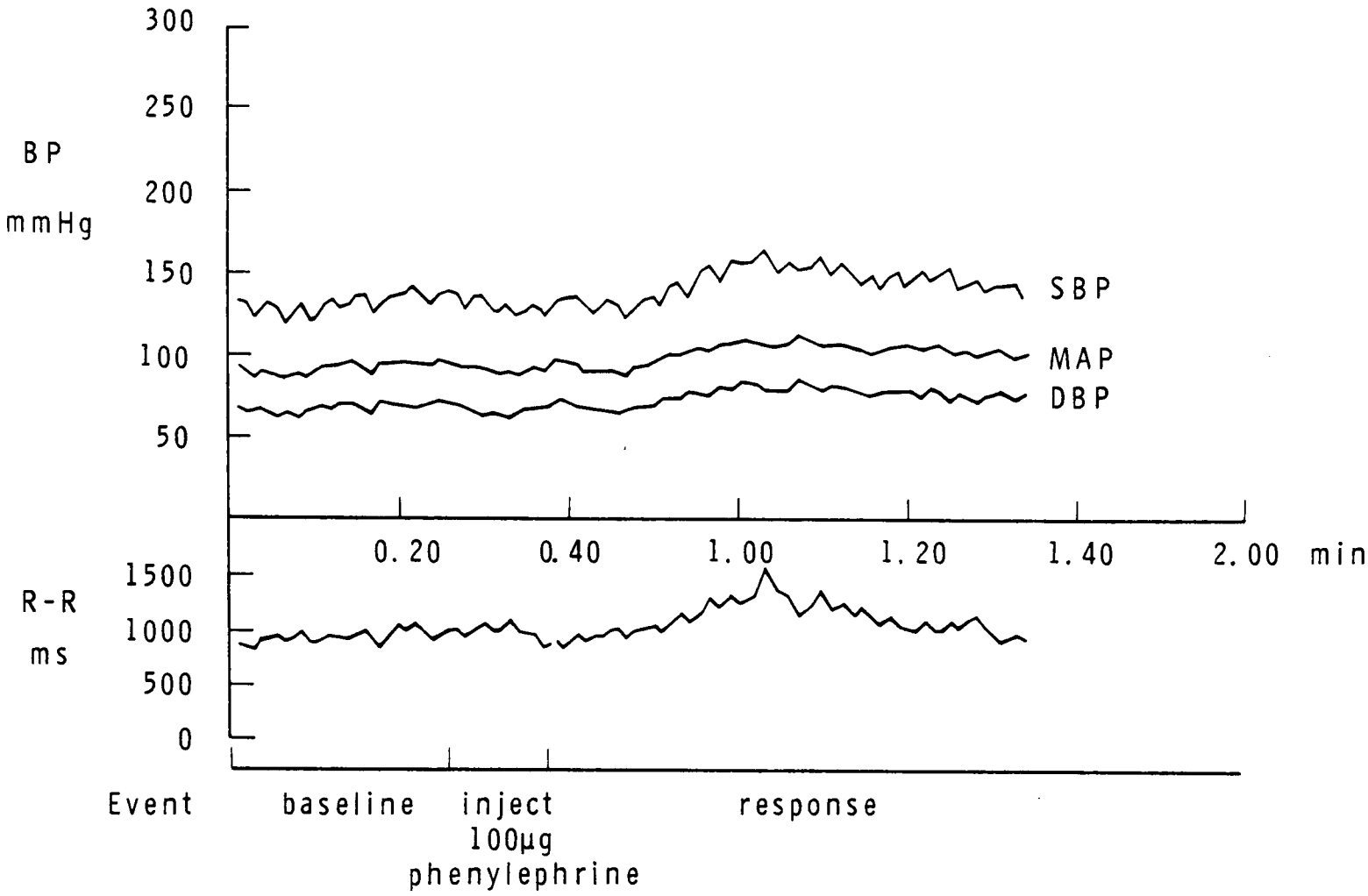

Fig. 4-12 Systolic (SBP), mean (MAP) and diastolic (DBP) blood pressure and pulse interval (R-R) during one phenylephrine injection.

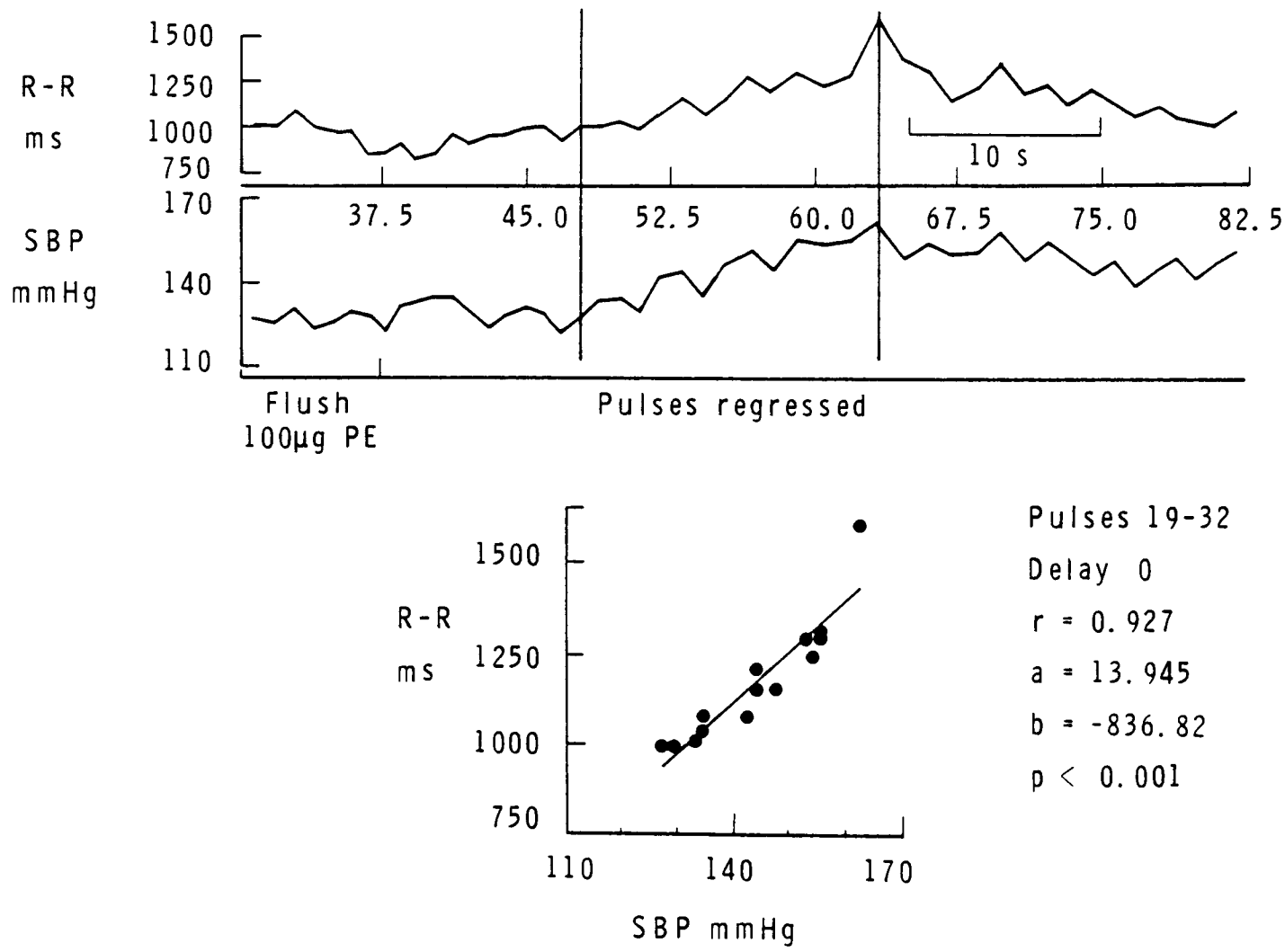

Fig. 4-13 Magnification of Fig. 4-12, examining the pulses about the pressure rise (above). The solid vertical lines denote the pulses which are regressed; linear regression between the pulse interval (R-R) and the preceding systolic pressure (SBP) with a delay of 0 cardiac cycles is graphed (below).

arrhythmia on the linear regression. He noted that the difference in slope when inspiratory beats were excluded was greater in some patients than in others, but did not assess this statistically. Certainly, sinus arrhythmia may have been enhanced by sleep in his study.

Pickering (1970) examined regression equations from 50 injections in 11 consecutive subjects, taken at rest, during sleep, and during light exercise. In 7 of these, sinus arrhythmia was prominent. As the inclusion of respiratory beats made little difference in the slope to the regression line in subjects with poorer slopes, i.e., less than 15 ms/mm Hg, he concluded that there was little benefit in their exclusion. The respiratory cycle was ignored in the calculation of baroreflex sensitivity in this study, as the patients in this study would be predicted to have slopes under 15 ms/mm Hg on the basis of their age and arterial pressures (Gribbin et al., 1971).

Effect of selecting different starting points for the regression equation

Smyth et al. (1969) began the regression equation with the beat where the pressure began to rise. According to Pickering (1970) this was often difficult to define. He therefore started from the end of the phenylephrine injection, i.e. about ten beats before the drug took effect. He compared this with starting from the trough of pressure immediately before the onset of the pressure rise, and from the first beat of the pressure rise which exceeded the highest resting value in fifty consecutive injections in four subjects with good slopes, studied at rest and during exercise. The steepest slopes were obtained with the third method, the best correlations

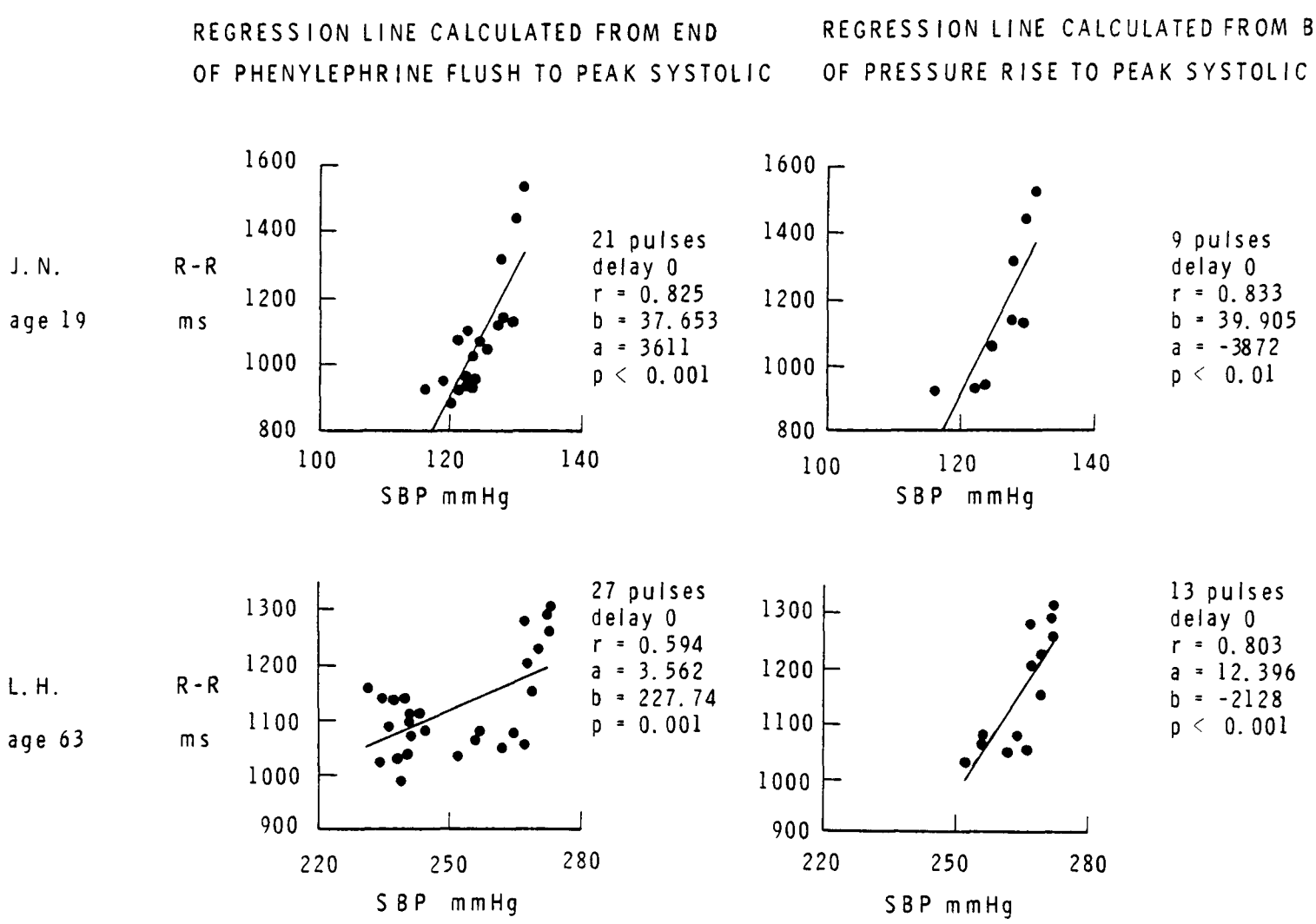

Fig. 4-14 Regression lines calculated from end of phenylephrine injection to peak systolic pressures (left panels) and from beginning of pressure rise to peak systolic blood pressure (right panels) in one young borderline hypertensive (J.N.) and one elderly hypertensive (L.H.) subject.

between systolic pressure and pulse interval with the second, but the more significant probability values with the first (not surprising, as the degrees of freedom would be greater). As the starting point of the pressure rise was not always clear, Pickering (1970) chose the first method, stating furthermore that the regression equations by the third (used by Smyth) did not always include sufficient numbers of points to achieve statistical significance, although the slopes obtained were up to 40% steeper ($P<0.001$).

The selection of four young healthy individuals for this comparison may have contributed to this decision. The relationship between pulse interval and systolic pressure at rest tends to be highly significant on its own in young normal subjects (Fig. 4-14, upper left) but diminishes with increasing age and pressure (Fig. 4-14, lower left). If the regression equation is calculated from the end of the injection, a 'dog leg' in the points tends to occur in older, more hypertensive subjects (Fig. 4-14, lower left). Pickering noted this effect in some subjects, but did not explore its significance, suggesting that it might be diminished by shifting the linear regression so that a delay of one cardiac cycle was interposed between the pressure pulse and the subsequent pulse interval it affected reflexly.

This effect appeared to be most pronounced in the older, hypertensive group, comprising most of the subjects in the study. Moreover, it was felt that the calculation of the regression equation should begin with the onset of the pressure rise if one wished to accurately estimate the baroreflex response to acute changes in pressure. The FORTRAN IV programme and the use of

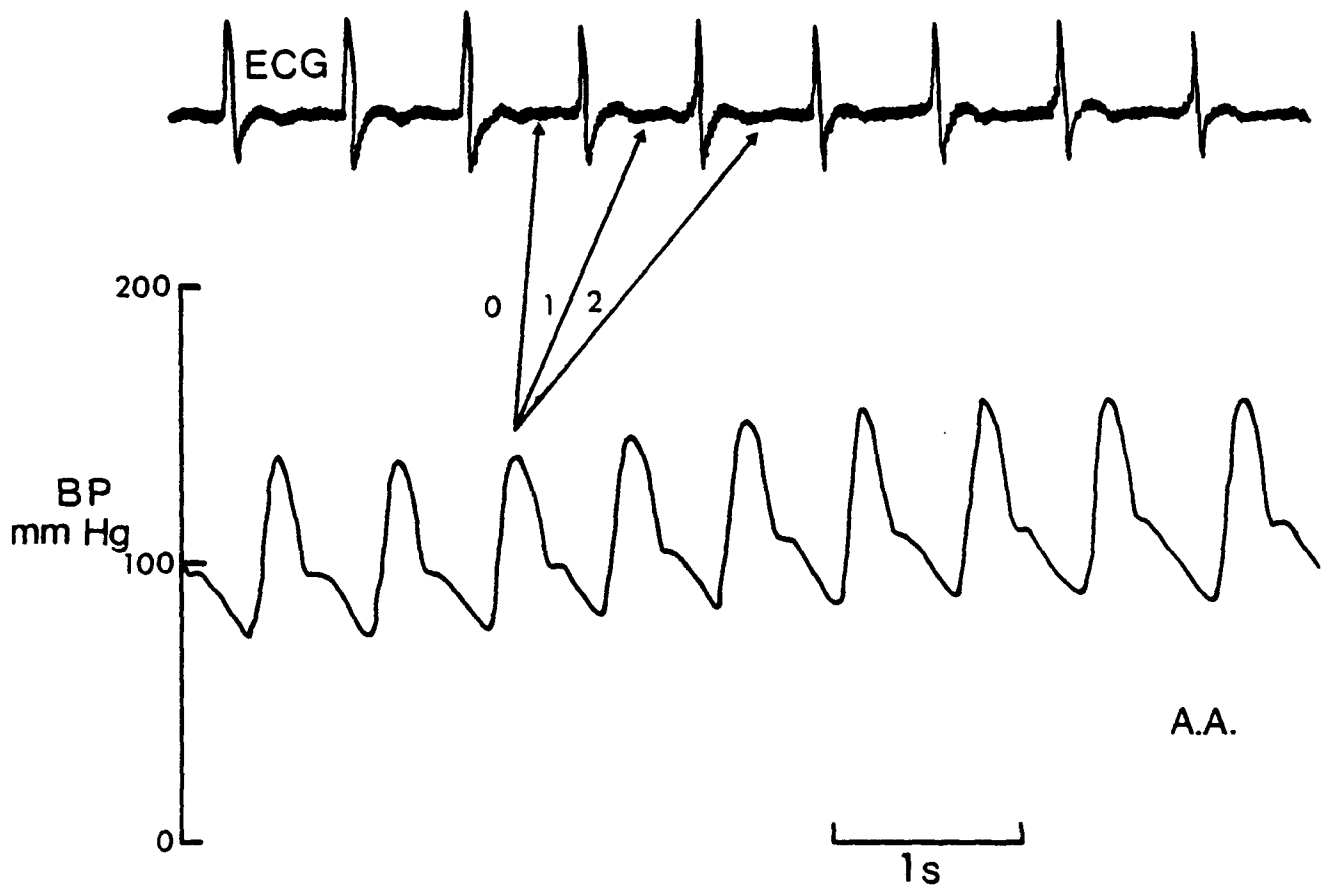

Fig. 4-15 The relationship between pulse interval and the immediately preceding pressure pulse may be strongest (delay 0), or may improve when a shift of one (delay 1) or two (delay 2) cardiac cycles are interposed between them.

weighting in the comparison of slopes were therefore adopted so that this onset could be more accurately determined.

Conduction time of the baroreflex arc

For each of 330 phenylephrine injections, Pickering and Davies (1973) calculated regression equations when shifts, or delays from -2 to +7 cardiac cycles were interposed between the systolic pressure and the pulse interval regressed against it. (See Fig. 4-15, in which shifts of 0, +1 and +2 are displayed.) These injections were performed with the subjects at rest and during bicycle exercise, and while they were breathing high and low concentrations of oxygen and carbon dioxide. This allowed differentiation between the effects of respiration and the effects of heart rate alone on the correlation obtained. The correlation coefficient varied with the shift employed, but was usually best for a shift of 0 or +1, i.e. consistent with the reflex nature of the bradycardia.

Provided that the heart rate was less than 75/min, the best correlation was obtained if each beat was related to the pulse interval immediately following. For faster heart rates, the correlation was better than with a delay of +1. The conduction time of the reflex loop appeared to be about 775 msec. As the time interval between the occurrence of the P wave on the electrocardiogram and the arrival of the pressure wave at the carotid sinus was about 300 msec, the conduction time of the reflex from the baroreceptors to the SA node was about 475 msec. In some instances, possibly due to respiration, the most significant correlation coefficients were obtained with delays of +2, +3, or +4.

Similar findings were noted in this study. The delay which

Table 4-2

The delay giving the best correlation between systolic pressure and subsequent pulse interval.

Delay	No. of Patients	Mean Heart Rate	S.D.	Mean Pulse Interval
0	32	70.3	8.6	854 msec
+1	16	79.1	12.3	758
+2	9	78.1	14.6	768
+3	4	76.0	17.4	789

The difference between mean heart rates in the groups with delay of 0 and 1 is significant ($P<0.02$, unpaired t-test). The difference between mean heart rates in the group with delay 0 and the mean heart rates in the groups with delays of 2 or 3 is not significant.

gave the best correlation between systolic pressure and pulse interval overall was calculated for each patient. The highest correlation coefficients occurred with delays of 0 or +1. Those patients with a delay of +1 had significantly faster heart rates. In a few patients, the best correlations were obtained with delays of 2 or 3 cardiac cycles (Table 4-2). A baroreflex slope could not be calculated using positive delays in one patient (H.D.) with renal artery stenosis. He developed pulsus alternans during the phenylephrine injections, and his systolic pressure was in fact related to his diastolic filling time (delay of -1). He was excluded from the calculations involving BRS in this study.

Effect of regressing pulse interval against systolic rather than mean blood pressure

Discharge from the carotid sinus nerve is pulsatile; its peak frequency coincides with the peak of the pressure wave (Bronk and Stella, 1932; Christensen, Warner and Pryor, 1967). Therefore most authors have related pulse interval to the preceding systolic pressure (Smyth et al., 1969; Bristow, Honour, Pickering, Sleight and Smyth, 1969; Pickering, 1970). Gribbin (1974) compared this with regressing pulse interval against mean arterial pressure, and found that the regression lines thus obtained were virtually identical ($r=0.95$, $P<0.001$). Higher slopes were noted in subjects with poorer baroreflexes when pulse interval was regressed against mean arterial pressure, and in normotensive individuals when regressed against systolic, but in both instances the difference between the two methods was trivial.

Calculation of weighted mean baroreflex sensitivity

Previous authors have discarded those regression lines with a correlation coefficient less than 0.50 (Pickering, 1970) or 0.60 (Watson, Stallard and Littler, 1979b), or which were not statistically significant (Smyth et al., 1969). The arithmetical mean of the remaining slopes was then calculated for each patient.

This calculation presumes that for each injection of phenylephrine a regression line with similar variance is described. As can be seen in Table 4-3, this is not borne out. Here the range of variances obtained from 5 or 6 significant (i.e., $P<0.05$) regressions in 15 consecutive patients is noted. When the F-ratio test for equality of variances (comparing the maximum and minimum variances) was performed (Bailey, 1964), highly significant differences were observed, particularly in borderline hypertensive subjects. The slope of the regression line may differ from one injection to the next, as changes in central input may affect the cardiovagal component of the baroreflex arc acutely. Only an estimate of the 'true' baroreflex sensitivity in a particular individual can be obtained with any one phenylephrine injection. Many 'estimates' may be required to obtain a sample mean slope approaching the 'true' mean. Some of these estimates will be better than others; these will have little variance of their points about the regression line. These may have a greater variance, and yet still be found 'statistically significant'. Inclusion of slopes with greatly differing variances would bias the calculation of an arithmetical mean. Instead, the regression coefficients were weighted, as recommended by Armitage (1971).

The computer program was devised to assist in the calculation

Table 4-3

Comparison of Maximum and Minimum Variance obtained from the calculation of slopes of regression lines in 15 patients.

Patient	No. of Runs[+]	Range of Variances	$F^{\ddagger}_{\ddagger}$	f1	f2	$p^{\ddagger\ddagger}_{\ddagger}$
M.S.	6	0.125 - 0.685	5.48	10	13	<0.02
A.W.	5	0.270 - 1.210	4.48	11	9	0.10>P>0.02
R.D.	6	1.990 - 17.159	8.62	6	12	<0.02
J.B.	6	1.020 - 6.632	6.50	12	17	<0.02
B.P.	6	6.930 - 13.485	2.38	5	6	n.s.
M.T.	6	0.525 - 6.265	11.95	5	11	<0.02
J.S.	5	0.078 - 1.722	22.08	13	6	<0.02
M.H.	6	0.055 - 0.391	7.11	5	8	<0.02
M.M.	5	1.840 - 21.934	11.92	11	18	<0.02
J.D.	6	0.342 - 1.846	5.40	4	10	0.10>P>0.02
B.B.	6	0.201 - 3.830	19.05	5	15	<0.02
J.G.	6	1.419 - 7.475	5.27	9	6	0.10>P>0.02
S.L.	6	0.144 - 0.978	6.79	4	11	<0.02
A.A.	6	1.137 - 3.389	2.98	8	20	0.10>P>0.02
W.J.	5	0.604 - 2.315	3.83	12	19	<0.02

[+] Number of runs which had correlation coefficients with P of <0.05.

$\ddagger$ $F = var(b_1)/var(b_2)$

$\ddagger\ddagger$ P Values are from Documenta Geigy tables (Diem and Lentner, 1970). These give P values for a one-tailed test for 0.05 and 0.01 only.

of weighted mean slopes. The pulse interval was regressed against the systolic pressure for delays of 0, 1, 2 and 3 cardiac cycles. A regression line with its regression coefficient, or slope (b_i), variance ($var(b_i)$),

$$var(b_i) = \frac{\Sigma (y_1 - \bar{y})^2 (1-r^2)}{\Sigma (x_1 - \bar{x})^2 (n-2)} \qquad (1)$$

and its t statistic (t_i)

$$t_i = \frac{b_i}{\sqrt{var(b_i)}} \qquad (2)$$

were calculated for each delay, and the appropriate delay for each patient was calculated from the arithmetical mean of his correlation coeffients. A copy of these calculations appears in Fig. 4-13. A weighting factor, (w_i), inversely proportional to its variance, was given for each slope

$$w_i = \frac{1}{var(b_i)}. \qquad (3)$$

For several slopes, b_1, b_2, b_3, b_4,...b_i, believed to be measuring the same 'true' slope, a better approximation of the 'true' slope (i.e., better than the arithmetical mean) would be the weighted mean slope, $\bar{b}$, where

$$\bar{b} = \frac{\Sigma w_i b_i}{\Sigma w_i} \qquad (4)$$

The weighted mean slope $\bar{b}$ has a standard error,

$$S.E.\ \bar{b} = \sqrt{\frac{1}{\Sigma w_i}} \qquad (5)$$

As can be seen from Fig. 4-13, the weighting factor was calculated for each regression. The weighted mean slope and its standard error were then calculated by hand.

Estimates of baroreflex sensitivity with less variance were thus given a greater weighting, and the need to adopt sometimes arbitrary criteria for the exclusion of certain slopes was removed. Data were excluded from the calculation of weighted means if ectopic beats occurred, the phenylephrine failed to increase blood pressure above the fluctuations of resting sinus arrhythmia, a full bladder or anxiety prevented the patient from relaxing, if coughing, scratching, noise or movement coincided with the injection, or if the patient fell asleep.

The adoption of weighted means reduced the slopes obtained by 7%, but significantly narrowed the confidence limits attached to each estimate of the 'true' slope (Table 4-4), particularly important in the present study in which many patients might be expected to have similar baroreflex sensitivities, on account of their ages and levels of blood pressure.

Table 4-4

Comparison of mean slopes and their standard errors obtained either by weighted means or arithmetical means of those regression lines with a $P<0.05$ in 15 patients.

Name	Weighted mean slope (ms/mm Hg) and standard error expressed as a percent		Arithmetical mean slope (ms/mm Hg) and standard error expressed as a percent	
M.S.	3.281	6.4	3.236	11.8
A.W.	3.652	9.1	3.827	9.6
R.D.	13.302	6.6	13.924	8.0
J.B.	11.099	4.9	12.039	8.2
B.P.	29.388	4.5	31.125	10.0
M.T.	4.279	9.7	6.843	16.1
J.S.	3.218	7.1	3.557	7.3
M.H.	2.030	7.1	2.157	9.1
M.M.	12.746	8.4	14.114	13.2
J.D.	4.354	7.7	5.419	18.3
B.D.	7.736	4.2	7.432	5.4
J.G.	10.246	5.5	9.896	6.2
S.L.	4.524	5.2	4.667	3.8
A.A.	8.614	6.0	8.985	9.8
W.J.	7.364	6.9	7.662	7.9
mean ±S.D.	8.389±6.867	6.6±1.6	8.992±7.206	9.6±3.9
t			2.909	3.777
p v. weighted mean slope			<0.02	<0.005

Estimation of Plasma Noradrenaline

Blood was drawn from the antecubital vein, after 15 minutes' quiet rest, before mental arithmetic (supine: 10 patients), isometric exercise (sitting: 52 patients), and bicycling (sitting: 52 patients). Additional samples were obtained in the last minute of mental arithmetic (10 patients), isometric exercise (52 patients), and bicycling (52 patients), and 3 minutes after the end of mental arithmetic (10 patients), isometric exercise (50 patients), and bicycling (49 patients).

The first millilitre of blood was discarded. A second 10 ml. sample was obtained, and centrifuged for 10 minutes at room temperature (1000G). The plasma was aspirated, frozen for 2 hours in liquid nitrogen, then stored at approximately -40^{o}C for up to three months. Catecholamine concentrations are stable under these conditions (Sever, 1978).

Noradrenaline Assay

Plasma noradrenaline concentration was measured in the Department of Clinical Pharmacology, St. Mary's Hospital, London, with an assay based on the radioenzymatic technique of Henry et al. (1975). A freshly prepared solution of metabisulphate, 50 mg/ml (100 µl) and H_2O (three ml) were added to plasma (one ml). Noradrenaline (1.0 ng and 2.5 ng) was added to duplicate samples as internal standards. The pH was adjusted to 8.6 with 1M-Tris HCl containing 2% EDTA (0.5 ml). Catecholamines were then isolated from plasma by adsorption onto alumina (50 mg) (prepared according to the method of Anton and Sayre, 1962) and rotated for 15 minutes. The samples were then centrifuged for 10 minutes at 5^{o}C (1000G), washed three times with H_2O (three ml) and the catecholamines eluted from the alumina with

0.2M-HCl (250 µl).

To 100 µl of eluate were added H_2O (100 µl) and a freshly prepared reaction mixture containing in 50µl: 2M-Tris HCl containing 5% EDTA and glutathione, 1.55 mg/ml, (pH 9.2) (38 µl), [^{3}H]-S-adenosyl-methionine (SAM) (New England Nuclear) (2 µCi; 2 µl), and purified bovine adrenal phenylethanolamine-N-methyltransferase (PNMT) (protein concentration 5 mg/ml; 10 µl), which was prepared according to the method of Axelrod (1962). The reaction mixture was also added to four blanks containing H_2O (100 µl) and 0.2M-HCl (100 µl).

The preparation was incubated at 37^{o}C for one hour. Noradrenaline was converted to tritiated adrenaline by PNMT, with [^{3}H]-SAM acting as a methyl donor. The reaction was stopped by 2M-Tris HCl containing 5% EDTA and 0.5M-Na_3PO_4 (pH 8.6) (2 ml). The radio-labelled adrenaline was then isolated by adsorption onto alumina (100 mg), by repeating the procedure used in the first stage of the assay. Adrenaline was eluted from the alumina with ice cold 0.1M perchloric acid (one ml). A freshly prepared solution (100 µl) containing adrenaline bititrate (50 µg), and unlabelled SAM (100 µg) in 0.2M-HCl was added to this, followed by tungsto-phosphoric acid, 0.25 g/ml (200 µl) in order to precipitate excess [^{3}H]-SAM.

The tubes were left on ice for 10 to 15 minutes and then centri-fuged (1000G) for 5 minutes. The supernatant was transferred to tubes containing 0.5M-Na_3PO_4 (pH 7.3) (one ml) and diethylhexophosphoric acid - toluene 1% (v/v) (10 ml), shaken for 10 minutes, then centrifuged. The toluene layer (9 ml) was transferred to plastic scintillation vials containing Liquifluor scintillant (400 µl) (New England Nuclear).

The samples were then counted for 10 minutes (6880 Liquid Scintillation Mark III, Searle Analytic).

This radioenzymatic assay is selective for noradrenaline; other naturally occurring amines or their metabolic products are either not adsorbed onto alumina or are not N-methylated under the conditions used. Although the assay is said not to detect the 40% to 60% of noradrenaline that is protein bound (Henry et al., 1975), it has been suggested that some protein bound noradrenaline is adsorbed onto the alumina and subsequently assayed (Sever, 1978).

A standard curve was constructed from the counts per minutes for the blanks and two internal standards (1.0 ng and 2.5 ng). The plasma noradrenaline concentration for each sample was then read from the standard curve. Recovery of noradrenaline with this assay is approximately 30%. Recovery from the adsorption to alumina is about 60-80% on each occasion, and recovery from toluene is about 90%. The assay is sensitive to 25 pg of noradrenaline.

A known concentration of noradrenaline, from a standard plasma pool, was assayed with each batch. Recoveries from this pool were used to calculate between assay (or inter-assay) variation. The internal standards were used to calculate the within assay (intra-assay) variation and the overall efficiency of the reaction.

The mean coefficient of intra-assay variation for the 17 assays performed in 1978-9 was 8.7% (range 3-13%) and the mean coefficient of inter-assay variation was 9.6% (range 4-17%). Repeated assay of a plasma pool that had lower values than usual increased this coefficient of inter-assay variation. The mean coefficient of intra-assay variation for the 3 assays performed in 1980 was 13.6% and the mean coefficient of inter-assay variation for all 20 assays performed in this study was 9.4%.

Studies in rats

Production of renovascular hypertension

A clip was first prepared by clamping a short strip of silver (c. 5 mm) around a metal plate 0.18 mm thick. This was placed around the left renal artery of 180-200 g male Wistar rats which were anaesthetised with ether. Four groups, comprising rats with renovascular hypertension (RHR) of 3, 7, 14 and 25 days' duration were produced. Normotensive rats (NCR) equivalent in age to RHR of 0 and 25 days were included as controls. On the appropriate day the animals were briefly anaesthetised with ether and polythene cannulae (Portex) were inserted into the left femoral artery (0.4 mm i.d., connected to a cannula of 0.76 mm i.d.) and left femoral vein (0.5 mm i.d.). The wound was infiltrated with local anaesthetic (lignocaine hydrochloride 1%) and sutured. The animals were allowed to waken. Pressure was measured with a Statham transducer (P23 Gb) and simultaneously recorded through a pre-amplifier (Model 7PIE) and driver amplifier on a Grass polygraph (Model 7D), and onto magnetic tape (Racal Thermionic Store 4). The frequency response of the entire system was reasonably flat to 10 Hz and varied with the length of the arterial cannulae. In view of the high heart rates (300-500 bpm) and low frequency response, only mean arterial pressures were noted. The arterial pressure trace, mean arterial pressure (obtained by damping the arterial blood pressure signal through a second D.C. driver amplifier), and heart rate (the pressure tracing was amplified by an A.C. Micro-voltmeter (Levell) and input into an ECG Tachograph pre-amplifier,

Grass Model 7P4F and D.C. driver amplifier) were recorded on polygraph paper (Grass C25-16), usually at a paper speed of 5 mm/s.

RHR were considered to be hypertensive if their mean blood pressure was greater than 125 mm Hg three days following clipping of the left renal artery (RHR 3) and greater than 145 mm Hg in the later groups (RHR 7, RHR 14, RHR 25). Approximately 60% of the rats which were clipped in this fashion developed hypertension. The remainder were discarded. Eight animals with high blood pressure were included in each study group.

Reversal of renovascular hypertension

After 25 days of renovascular hypertension the tail artery was cannulated under brief ether anaesthesia and the animals allowed to recover. If a mean arterial pressure greater than 145 mm Hg was observed in these animals, they were considered to be hypertensive and used in the subsequent experiments. The remaining rats were discarded. The experimental animals were re-anaesthetised with ether and an incision made in the left flank to expose the renal artery. The silver clip around the artery was removed and the wound was infiltrated with lignocaine hydrochloride (1%) and sutured.

Groups of 8 rats were then studied 1, 3, 7, 14 and 25 days following declipping (D-RHR). Rats with renovascular hypertension of 25 days' duration (RHR 25) and NCR equivalent in age to these rats (NCR 25) were used as controls. In addition, NCR older by 25 days (NCR 50), and equivalent in age to the D-RHR 25 group, were studied.

Estimation of baroreflex sensitivity (BRS)

One microgram (µg) of phenylephrine (PE) (Boots, Nottingham), injected intravenously along with 0.02 ml of normal saline, produced a pressure rise of 20 to 50 mm Hg, and a reflex bradycardia in normal animals. No change in pressure occurred if 0.02 ml of saline alone was injected. Between 6 and 8 determinations of baroreflex sensitivity, spaced 5 minutes apart, were made. The first four which were used to confirm the patency of the cannulae and to accustom the rats to the presence of the investigators, were not included in the analysis. Animals were fully awake for at least 40 minutes by the time of these last four determinations.

The animals were then sacrificed, weighed and their hearts extirpated. The left and right ventricles were dissected free and weighed.

Analysis of data

The arterial pressure recordings were transferred at 1/2 tape speed from magnetic tape onto the a/d system where they were sampled at a frequency of 100 Hz. This modification to the multitasking FORTRAN IV programme described previously obtained greater resolution of the pressure tracing at the higher cardiac frequency of rats.

As with the other programmes, first derivatives of the series of samples were used to detect troughs and upstrokes. The trough to peak threshold in this instance was the standard deviation of the 250 samples appearing in each 2.5 second time interval.

The linear regression module corrected for the slower tape

BAROREFLEX SENSITIVITY IN THE RAT

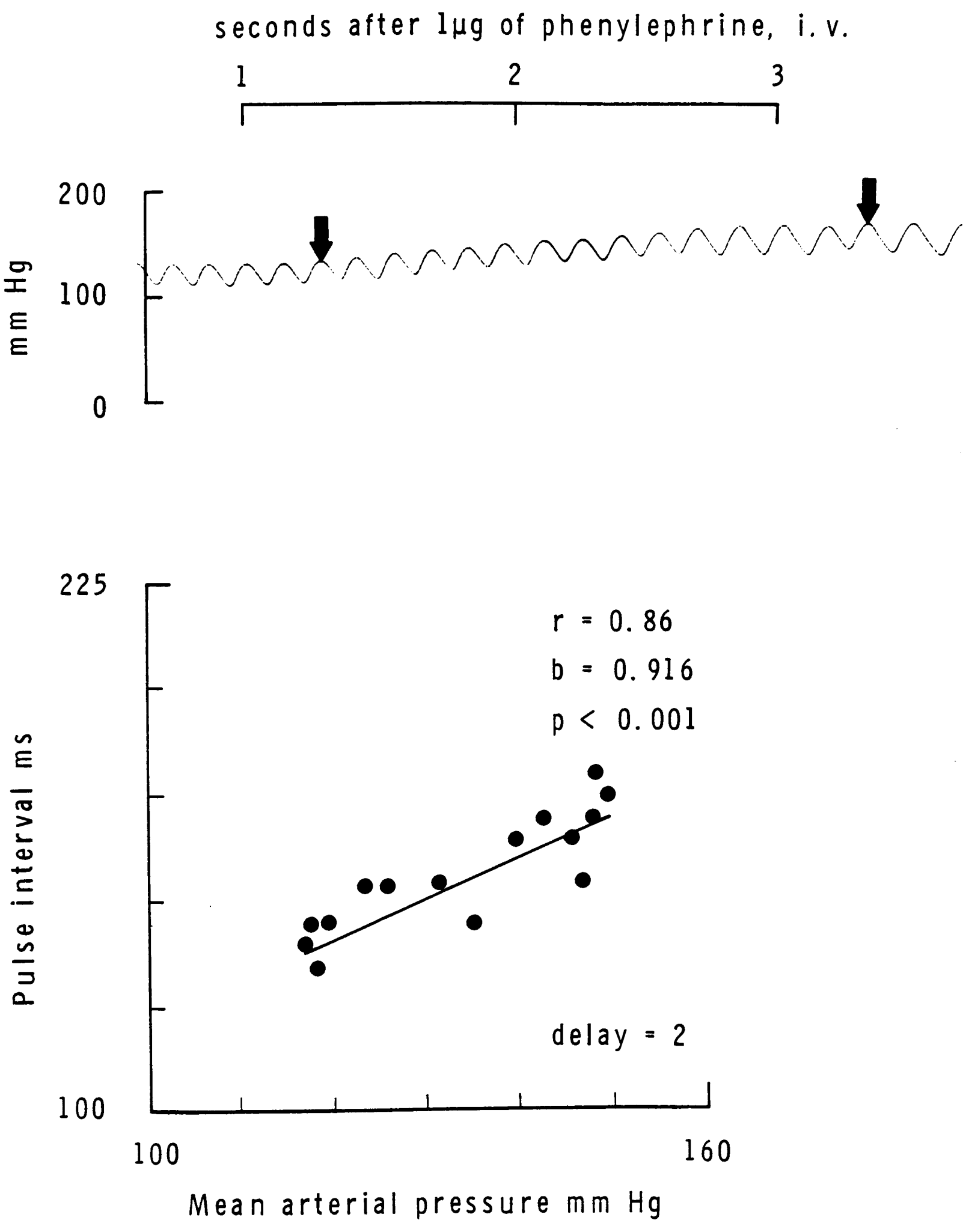

Fig. 4-16 Upper trace. Blood pressure rise induced by phenylephrine injection. Pressure pulses between arrows are used in the calculation of BRS.

Lower trace. Regression of pulse interval against mean arterial pressure over the course of the pressure rise. A delay of 2 cardiac cycles was interposed between the pressure pulse and the pulse interval regressed against it. Slope calculated to be 0.916 ms/mm Hg.

speed by halving the R-R coordinates in the graphic displays and statistical computations. The reflex change in pulse interval was correlated with the mean (rather than the systolic) arterial pressure during each phenylephrine induced pressure rise, and the slope of the linear regression line obtained was taken to be a measure of the sensitivity of the baroreflex arc in the rat (see Fig. 4-16).

In the human, the delay between the pressure rise and the reflex bradycardia may vary from 0 to 2 cardiac cycles, depending on the time delay of the reflex arc (Pickering and Davies, 1973). The time delay between the pressure rise and the reflex bradycardia in these animals was observed to vary from 1 to 15 cardiac cycles. A computing facility to regress pulse intervals with a delay of up to 20 cardiac cycles against preceding mean arterial pressures was incorporated. The longer delays were rarely required. The cardiac cycle which gave the best correlation between the pulse interval and mean arterial pressure was noted for each determination and its slope and variance were calculated. A weighted mean slope and its standard error using these values, rather than the value for the best delay overall in any particular rat, were derived for each animal studied. A comparison of the slopes obtained for the fifth determination in all animals, in turn with those of the sixth, seventh, etc., using the paired t-test, revealed no further improvement in slope. It was concluded that the effect of the recent ether anaesthetic on the baroreflex arc was minimal by this time.

Statistics

Both the unpaired student's t-test and the Wilcoxon rank sum test were used for comparison of means between the groups of

rats, as the number of animals in each group made the frequency distribution of the data difficult to assess. The P-values obtained in each instance were identical, except when noted. The equality of variance was tested, using the variance ratio or F-test before the paired t-test was performed; if the F-distribution was significant, the appropriate correction for degrees of freedom was made (Bailey, 1964), and the probability or P-value, in these instances are marked with asterisks in the tables and text. All data on these animals are expressed as means ± S.E.M.

RESULTS

On dira que l'âge, le sexe, le tempérament, l'idiosyncrasie, l'état de veille, de sommeil, d'exercise, de repose, de santé, de maladies, les passions modifient plus ou moins la force du coeur.

- Poisseuille (1828)

SUMMARY OF RESULTS

Studies in man

1. Baroreflex sensitivity was related inversely to age and systolic blood pressure in a curvilinear fashion. Values for baroreflex sensitivity were therefore log-transformed (LBRS).
2. Significant increases in mean arterial pressure and heart rate were seen in all four exercises, more so in physical than in mental exertion.
3. The maximum mean arterial pressure during each exercise was related inversely to LBRS.
4. The absolute increase in mean arterial pressure was not related to the resting mean arterial pressure in any of the exercises. It was related to the increase in heart rate during mental arithmetic, the reaction time test, and isometric exercise.
5. Only with bicycling was the absolute increase in mean arterial pressure related inversely to LBRS.
6. Older subjects had greater absolute increases in mean arterial pressure during bicycle exercise. Maximum heart rates during isometric and bicycle exercise declined with age.
7. Plasma noradrenaline concentrations (PNA) at rest were normally distributed, and were unrelated to age, blood pressure, or LBRS.
8. PNA increased by 78% during bicycle exercise, but did not change in either mental arithmetic or isometric exercise. The maximum mean arterial pressure during bicycle exercise was directly related to the exercise PNA. There was a tendency ($P<0.06$) for subjects with reduced baroreflex sensitivity to release more noradrenaline into the plasma when bicycling.

9. There was no relationship between the values found for plasma noradrenaline and systolic blood pressure at rest and during exercise.
10. Age affected neither resting nor exercising PNA.
11. Short-term and medium-term variability of mean arterial pressure were found to be independent of the absolute level of mean arterial pressure.
12. The variability of ambulatory mean arterial pressure (VMAP) during the waking day was directly related to mean arterial pressure and age. Subjects with poorer baroreflexes had greater variability of their mean arterial pressure; LBRS was found to be the only independent variable which significantly affected VMAP when multiple regression analysis and partial correlations were performed.
13. VMAP was directly related to other indices of sympathetic nervous activity: e.g. the relative increase in PNA during bicycle exercise, and the absolute increase in blood pressure with all four exercises.

Studies in rats

1. There was a significant decrease in baroreflex sensitivity by the third day of 2-kidney 1-clip Goldblatt hypertension. These changes preceded the development of left ventricular hypertrophy, and, as previously shown in this model, also preceded structural vascular adaptation and resetting of the carotid sinus baroreceptor threshold.
2. Baroreflex sensitivity in the 3-day hypertensive group was independent of the level of arterial pressure achieved in individual animals.
3. A further loss of baroreflex sensitivity, which may have been structurally based, occurred later, and was most pronounced after 2 weeks of renovascular hypertension.
4. One day after short term (25-day) 2-kidney 1-clip Goldblatt hypertension was reversed by removal of the renal artery clip, blood pressure and baroreflex sensitivity were not significantly different from pre-hypertensive levels. These changes preceded the regression of left ventricular hypertrophy, and the regression of structural vascular adaptations (as previously shown in this model).
5. Baroreflex sensitivity in the 1-day declipped group was inversely related to the level of arterial pressure in individual animals.
6. A further improvement in baroreflex sensitivity, which may have paralleled the regression of these vascular changes, was seen over the next six days.

CHAPTER 5

RESULTS OF EXPERIMENTS IN MAN

The effect of arterial pressure and age on baroreflex sensitivity

Mean weighted baroreflex slopes, obtained in 61 of the 62 subjects, ranged from 1.607 ms/mm Hg to 38.130 ms/mm Hg, with a mean of 7.789 ms/mm Hg (S.D. 7.480 ms/mm Hg). Systolic blood pressure in these patients ranged from 105.7 mm Hg to 233.7 mm Hg with a mean of 154.2 mm Hg (S.D. 27.5 mm Hg). Mean heart rate was 74.1 bpm (S.D. 11.7 bpm) with a range from 52 bpm to 104 bpm. The subjects ranged in age from 16 to 69 years, with a mean of 45.8 years (S.D. 11.4 years). These data are presented in Table 5-1.

Baroreflex sensitivity was inversely related to age ($r=-0.60$, $P<0.00001$) and systolic pressure ($r=-0.44$, $P<0.0002$). Subjects with higher BRS tended to have lower heart rates ($r=-0.26$, $P<0.02$). Multiple regression analysis revealed age to be the most significant predictor of the baroreflex slope ($F=38.705$, $P<0.005$) followed by heart rate ($F=8.219$, $P<0.01$). The addition of systolic blood pressure to the regression equation

$$BRS = 39.568 - (0.404)\times(age) - (0.180)\times(HR) \qquad (6)$$

with S.E. $b_1 = 0.065$ and S.E. $b_2 = 0.063$

did not significantly reduce the residual variation in the data ($F=2.707$, $0.20>P>0.10$).

The systolic blood pressure of these 61 subjects rose significantly with advancing age ($r=0.51$, $P<0.0001$). This relationship was not as pronounced if mean arterial pressure ($r=0.41$, $P<0.0004$)

Table 5-1

Age, systolic blood pressure, heart rate, and baroreflex sensitivity (BRS) of 61 supine resting subjects.

	Minimum	Maximum	Mean	S.D.
Age	16	69	45.8	11.4
Systolic Blood Pressure (mm Hg)	105.7	233.7	154.2	27.5
Heart rate (bpm)	52	104	74.1	11.7
BRS (ms/mm Hg)	1.607	38.130	7.789	7.480

or diastolic blood pressure ($r=0.23$, $P<0.04$) were studied. Heart rate was unrelated to age ($r=-0.09$, n.s.).

Gribbin (1974), measuring baroreflex sensitivity in both normotensive (n=50) and hypertensive (n=31) subjects noted a curvilinear, inverse relationship between BRS and both age and mean arterial pressure. A linear relationship could be obtained if the data were transformed logarithmically; then age and mean arterial pressure were shown to reduce the sensitivity of the baroreflex independently according to the regression equation:

$$\text{Log}_{10}\ \text{Slope} = 2.47 - (0.0164)\times(\text{age}) - (0.0086)\times(\text{MAP}) \qquad (7)$$

with S.E. $b_1 = 0.0019$ and S.E. $b_2 = 0.0012$.

The addition of pulse interval to this regression equation did not significantly improve its predictive value. The influence of heart rate, the inverse of pulse interval, was not studied.

The distribution of baroreflex sensitivities in the present study is also skewed, as can be seen from Table 5-1. The mean BRS lies closer to the bottom of the range than to the top; one standard deviation below the mean in fact falls outside the range of the data. A curvilinear relationship between baroreflex slope and age, and baroreflex slope and systolic blood pressure could be established in these 61 patients. Therefore the logarithmic transformation of baroreflex slopes (LBRS) was used to represent this variable in subsequent calculations in this thesis. Log_{10} BRS (LBRS) was inversely correlated with age ($r=-0.62$, $P<0.00001$) (Fig. 5-1), and systolic blood pressure ($r=-0.61$, $P<0.00001$) (Fig. 5-2), but not with heart rate ($r=-0.15$, $P<0.12$).

Multiple regression analysis revealed systolic blood pressure to be the most significant independent predictor of LBRS ($F=15.262$,

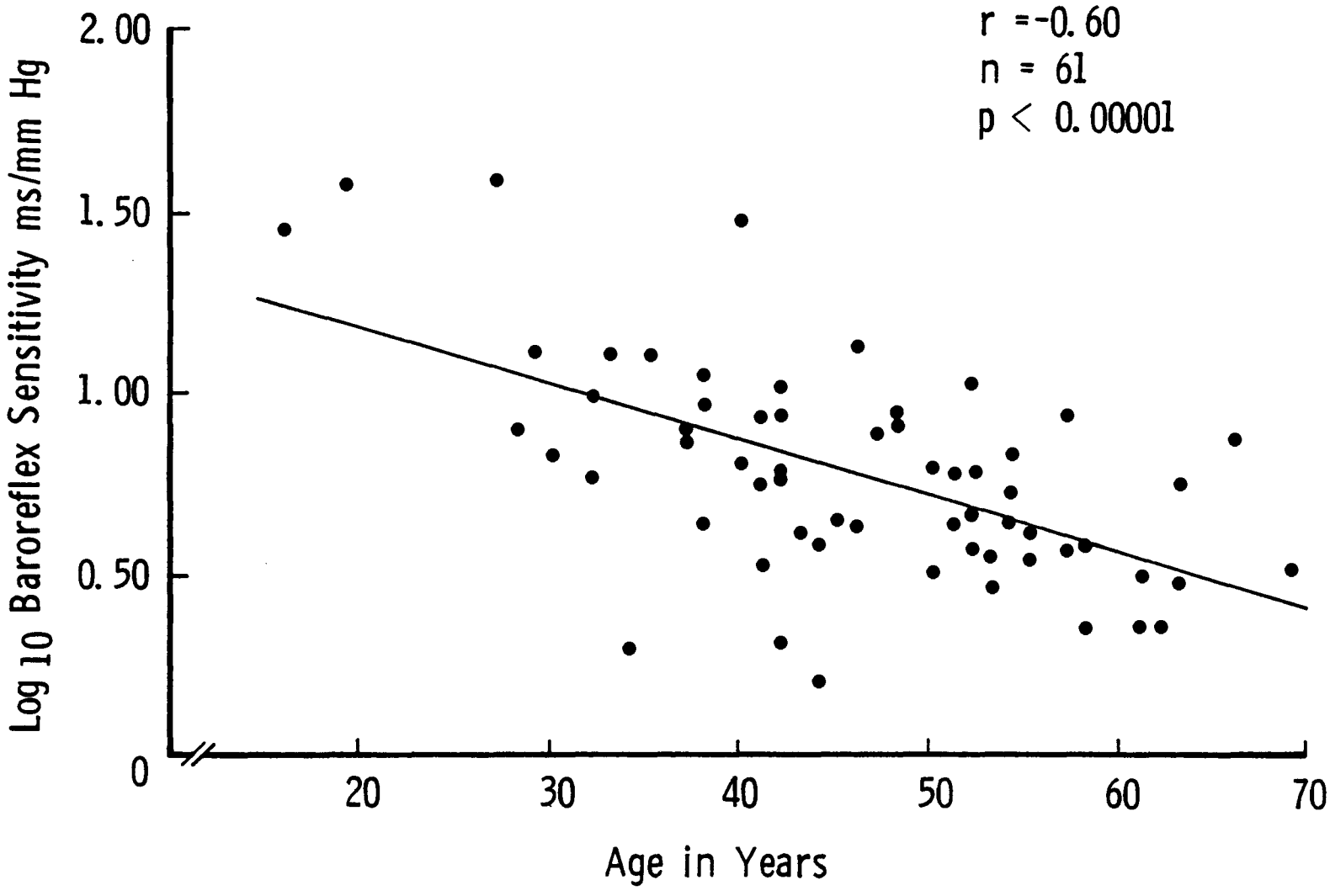

Fig. 5-1 Relationship between baroreflex sensitivity and age.

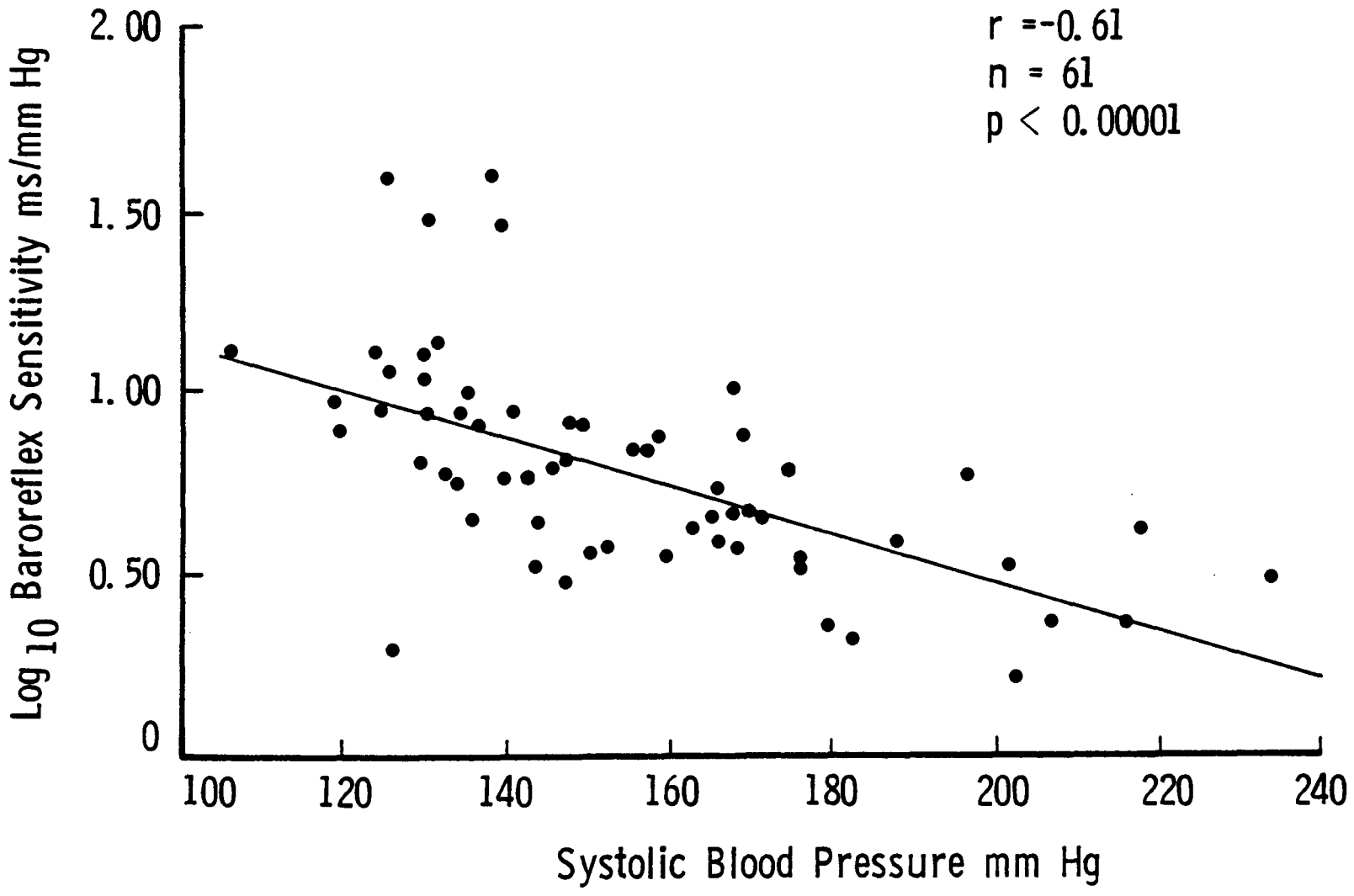

Fig. 5-2 Relationship between baroreflex sensitivity and systolic blood pressure.

P<0.005), followed by age (F=15.277, P<0.005). Their independent effects on the baroreflex slope could be expressed by the regression equation:

$$\text{Log}_{10}\ \text{Slope} = 1.943 - (0.00445)\times(\text{SBP}) - (0.01059)\times(\text{age}) \quad (8)$$

with S.E. b_1 = 0.00116 and S.E. b_2 = 0.00283.

The addition of heart rate to the regression equation did not significantly improve its predictive value (F=3.753, 0.10>P>0.05). Partial correlation coefficients revealed LBRS to be inversely related to SBP (r=-0.43, P<0.001) and age (r=-0.42, P<0.001) but not heart rate (r=0.04, n.s.).

Haemodynamic changes during mental and physical exercise

All 62 patients completed the mental arithmetic and reaction time tests, 61 the isometric exercise, and 59 the bicycle exercise.

The arterial blood pressures and heart rates obtained before, during, and 3 minutes after the end of their exercises are presented in Tables 5-2 to 5-5. Although the exercises were performed in the identical order on every occasion, the subjects appeared to be equally rested before each, and neither increasing familiarity with the laboratory over the course of the 3-hour experiment nor any underlying biological rhythms appeared to influence these results, as baseline mean arterial pressures were similar at rest before mental arithmetic, the first exercise (117.2±18.4 mm Hg; mean ±S.D.) and before bicycling, the last exercise (115.0±19.8 mm Hg, n.s., by Bonferroni method).

Heart rates were higher before bicycling (79.4±11.6 bpm v. 74.9±11.6 bpm, P<0.005, Bonferroni method). The change in posture when the patients were seated on the bicycle may explain the

Table 5-2

Baseline, maximum, and recovery mean arterial blood pressures (mm Hg) and their changes (Δ, %Δ) during mental arithmetic (MA), reaction time testing (RTT), isometric exercise (ISO), and bicycling (BIKE). Means ±S.D. Paired t-test for significance.

Exercise	No.	Baseline	Maximum	Δ	%Δ	P	Recovery	P. v. baseline	P v. maximum
MA	62	117.2±18.4	141.6±22.9	24.4±10.3	20.9	<0.001	118.5±19.3	n.s.	<0.001
RTT	62	123.2±18.8	144.2±21.2	21.0± 9.0	17.1	<0.001	120.0±17.6	<0.001	<0.001
ISO	61	115.8±18.1	149.0±21.8	33.2±10.8	28.0	<0.001	116.9±20.8	n.s.	<0.001
BIKE	59	115.0±19.8	147.9±24.9	32.9±12.7	28.6	<0.001	118.4±20.0	<0.01	<0.001

Table 5-3

Baseline, maximum, and recovery heart rates (bpm) and their changes (Δ, %Δ) during mental arithmetic (MA), reaction time testing (RTT), isometric exercise (ISO) and bicycling (BIKE). Means ±S.D. Paired t-test for significance.

Exercise	No.	Baseline	Maximum	Δ	%Δ	P	Recovery	P v. baseline	P v. maximum
MA	62	74.9±11.6	96.5±14.0	21.6±10.5	28.8	<0.001	75.3±12.3	n.s.	<0.001
RTT	62	74.6±11.2	90.1±13.0	15.5± 6.1	20.8	<0.001	75.2±12.2	n.s.	<0.001
ISO	61	78.0±11.9	96.4±14.6	18.4± 8.2	23.6	<0.001	79.0±12.3	n.s.	<0.001
BIKE	59	79.4±11.6	130.6±20.0	51.2±14.6	65.3	<0.001	96.6±15.3	<0.001	<0.001

Table 5-4

Baseline, maximum, and recovery systolic blood pressures (mm Hg) and their changes (Δ, %Δ) during mental arithmetic (MA), reaction time testing (RTT), isometric exercise (ISO) and bicycling (BIKE). Means ±S.D. Paired t-test for significance.

Exercise	No.	Baseline	Maximum	Δ	%Δ	P	Recovery	P v. baseline	P v. maximum
MA	62	162.7±27.1	193.8±30.8	31.1±12.7	19.2	<0.001	164.1±27.3	n.s.	<0.001
RTT	62	170.2±27.2	195.4±29.3	25.2±11.0	14.8	<0.001	164.3±25.3	<0.001	<0.001
ISO	61	159.2±26.3	202.8±31.1	43.6±14.9	27.3	<0.001	159.6±28.6	n.s.	<0.001
BIKE	59	157.9±30.8	215.4±37.4	57.5±20.3	36.4	<0.001	157.9±28.3	n.s.	<0.001

Table 5-5

Baseline, maximum, and recovery diastolic blood pressures (mm Hg) and their changes (Δ, %Δ) during mental arithmetic (MA), reaction time testing (RTT), isometric exercise (ISO) and bicycling (BIKE). Means ±S.D. Paired t-test for significance.

Exercise	No.	Baseline	Maximum	Δ	%Δ	P	Recovery	P v. baseline	P v. maximum
MA	62	86.0±13.4	104.0±17.8	18.0± 9.2	21.0	<0.001	86.6±14.5	n.s.	<0.001
RTT	62	91.0±14.4	107.4±16.9	16.4± 8.1	18.0	<0.001	89.5±14.0	n.s.	<0.001
ISO	61	87.7±14.1	112.6±17.2	25.0± 8.4	28.5	<0.001	88.6±16.7	n.s.	<0.001
BIKE	59	88.3±15.6	104.0±16.1	15.7±10.1	17.8	<0.001	93.1±15.5	<0.001	<0.001

Table 5-6

Simultaneous multiple comparisons of baseline mean arterial pressure before mental arithmetic (MA), reaction time testing (RTT), isometric exercise (ISO) and bicycling (BIKE). Paired t-statistic.

	RTT	ISO	BIKE
MA	-6.16**	1.07	1.37
RTT	-	4.93**	4.84**
ISO	-	-	0.84

Table 5-7

Simultaneous multiple comparisons of baseline heart rate before mental arithmetic (MA), reaction time testing (RTT), isometric exercise (ISO) and bicycling (BIKE). Paired t-statistic.

	RTT	ISO	BIKE
MA	0.50	-3.72**	-4.51**
RTT	-	-5.76**	-6.65**
ISO	-	-	-2.97*

* P<0.05
** P<0.005
Probability (Bonferroni)

difference between these two sets of figures.

Simultaneous multiple comparisons of resting mean arterial pressure and heart rate, with their respective t- statistics, are shown in Tables 5-6 and 5-7. These probability values also employ the Bonferroni method.

In the mental exercises, the blood pressure tended to rise quickly to its maximum and then be sustained or fall slightly (Figs. 4-2, 4-3). In isometric exercise the mean arterial pressure tended to increase with the duration of the contractions (Fig. 4-4); with bicycling the arterial pressure tended to increase with the intensity of the exercise (Fig. 4-5).

Blood pressure fell immediately after the end of these exercises, sometimes to below the baseline. Heart rates returned to normal within 3 minutes of rest, except after bicycling.

Mental Arithmetic

Mental arithmetic increased mean arterial pressure by 20.9% from 117.2±18.4 mm Hg to 141.6±22.9 mm Hg ($P<0.001$). Similar rises in systolic and diastolic pressure contributed to this increase (Fig. 4-2; Table 5-2).

The maximum mean arterial pressures (MMAP) achieved ranged from 100.3 mm Hg to 196.5 mm Hg. This value was related significantly to the individual's baseline mean arterial pressure (MAP) ($r=0.90$, $P<0.00001$) (Fig. 5-3), and to age ($r=0.42$, $P<0.0004$), and inversely related to LBRS ($r=-0.56$, $P<0.00001$) (Fig. 5-4). The independent effects of these variables on the MMAP were assessed by multiple regression analysis. Baseline MAP was the most significant predictor of MMAP ($F=248.63$, $P<0.001$). The addition

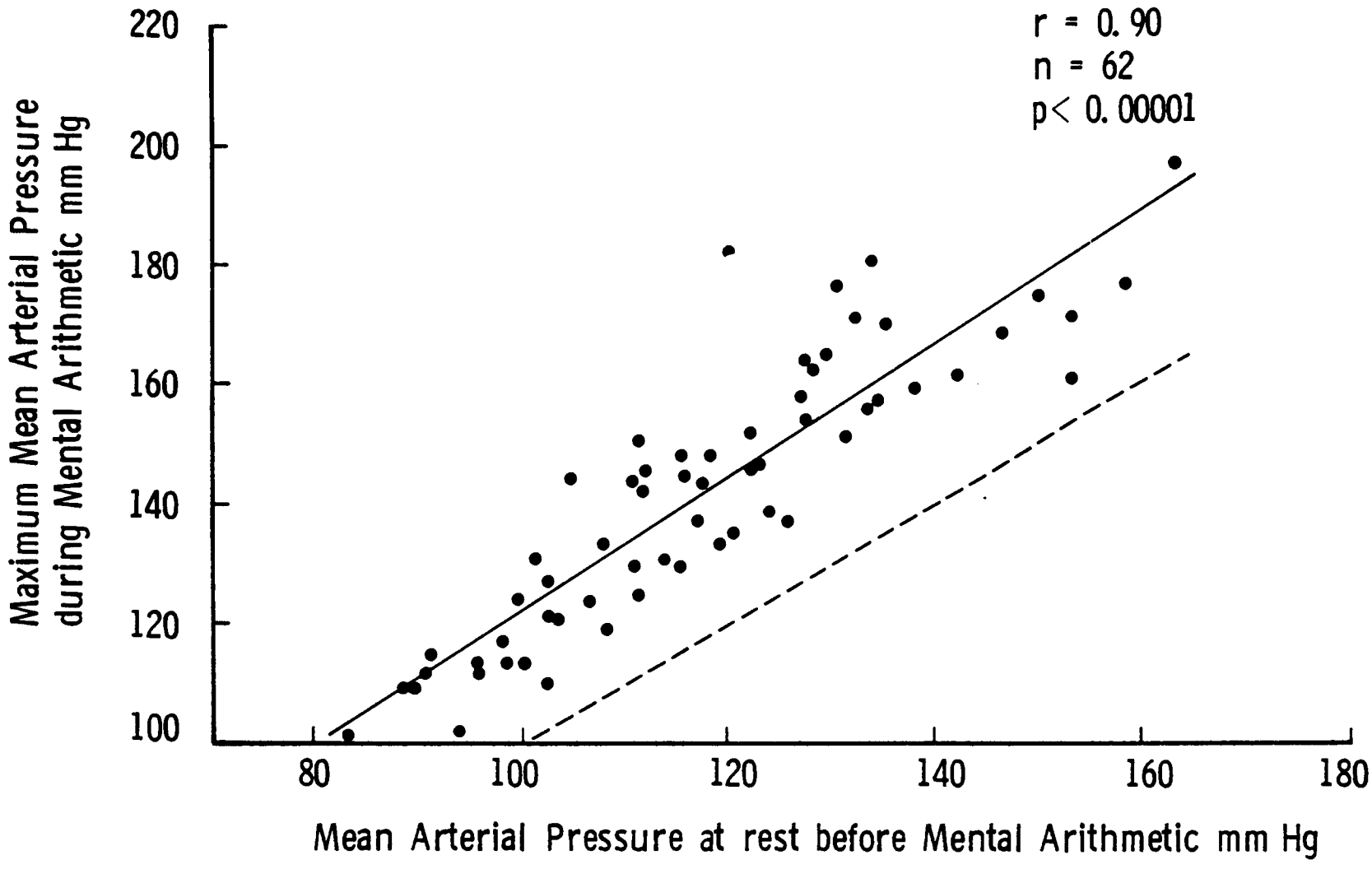

Fig. 5-3 Relationship between maximum and baseline mean arterial pressure during mental arithmetic. Broken line is line of identity.

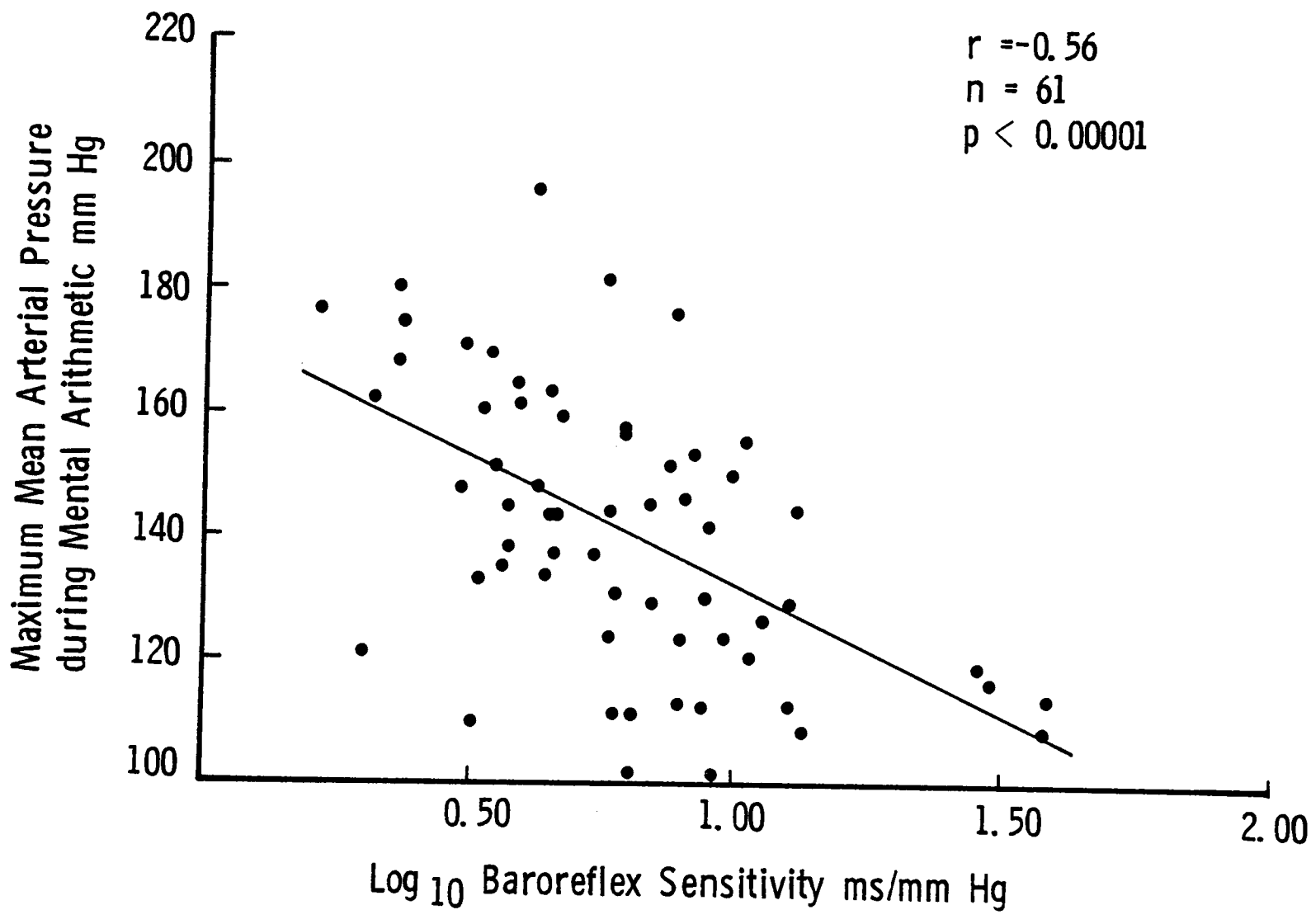

Fig. 5-4 Relationship between maximum mean arterial pressure during mental arithmetic and baroreflex sensitivity.

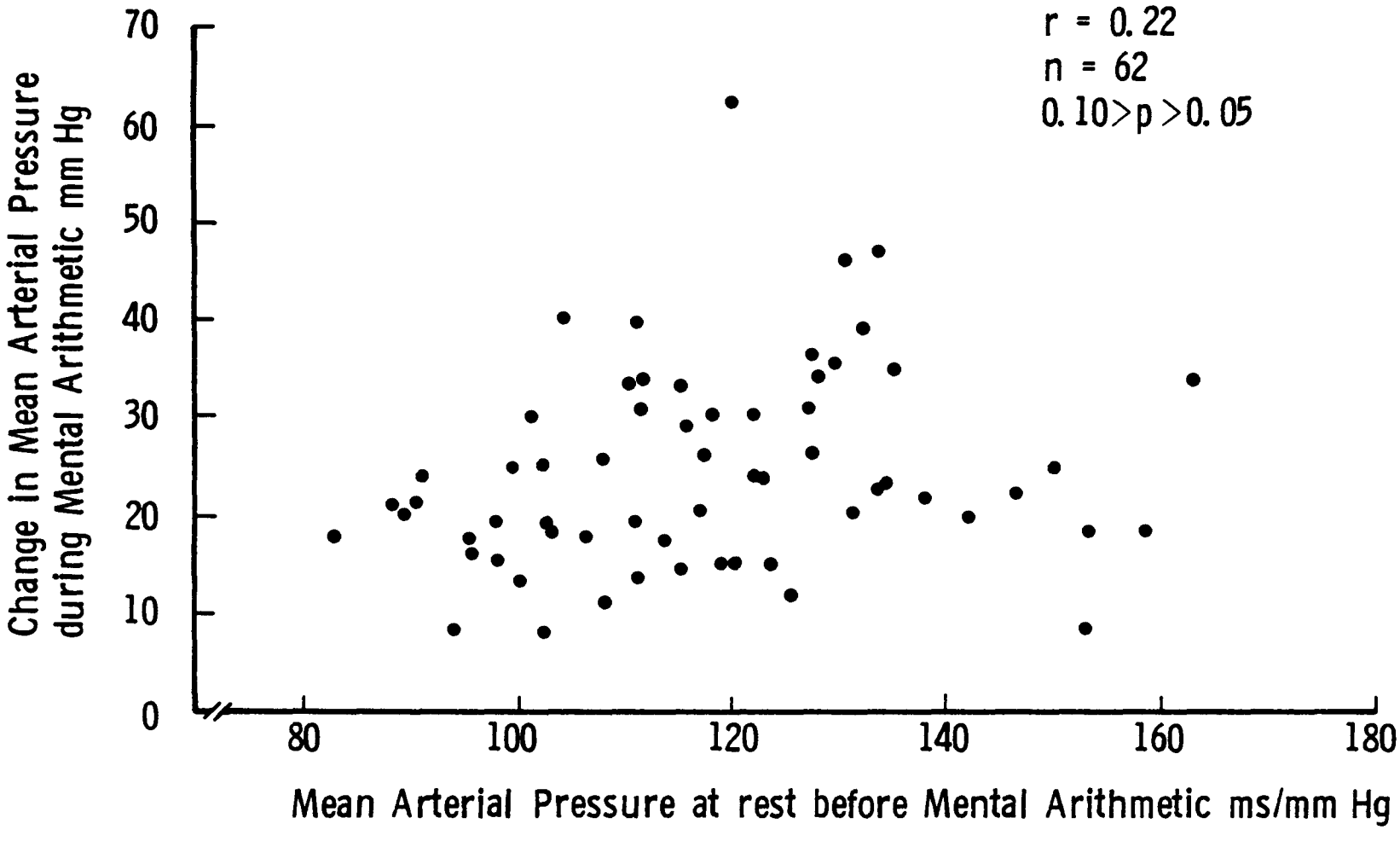

Fig. 5-5 Relationship between the increase in mean arterial pressure and baseline mean arterial pressure during mental arithmetic.

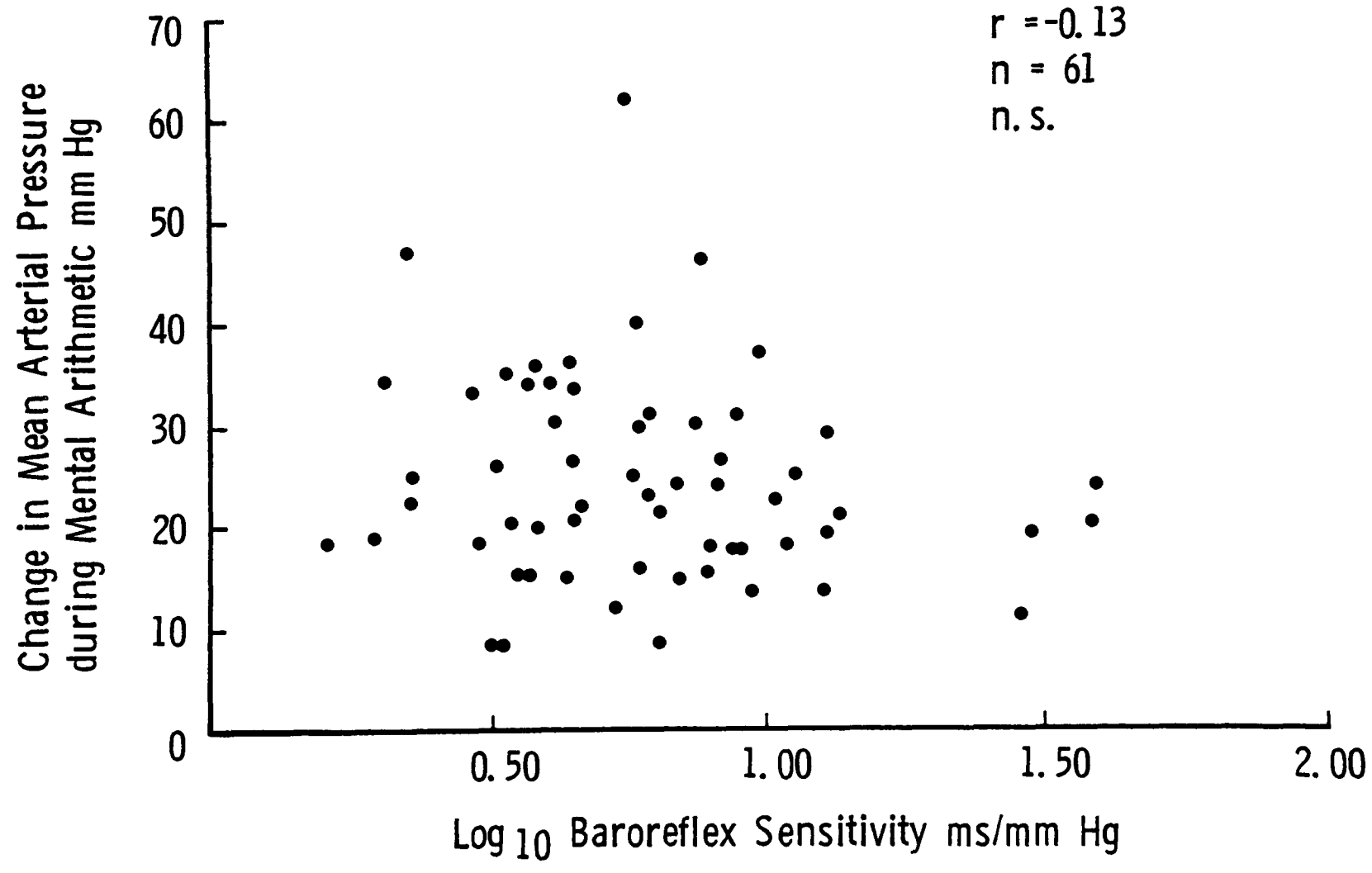

Fig. 5-6 Relationship between the increase in mean arterial pressure during mental arithmetic and baroreflex sensitivity.

of age or LBRS made negligible contributions to the regression equation.

$$MMAP = 10.218 + (1.120) \times (MAP) \quad (9)$$

The standard error of the regression coefficient was 0.071.

The absolute change in mean arterial pressure (ΔMAP) during this exercise (24.4±10.3 mm Hg) was unrelated to the baseline mean arterial pressure ($r=0.22$, $0.10>P>0.05$) (Fig. 5-5), age ($r=0.12$ n.s.), or LBRS ($r=-0.13$, n.s.) (Fig. 5-6), and could not be predicted by multiple regression analysis.

No relationship between the relative (or percentage) increase in mean arterial pressure (%ΔMAP) and baseline MAP ($r=0.06$, n.s.), age ($r=0.02$, n.s.) or LBRS ($r=0.04$, n.s.) could be determined, either by tests of correlation or multiple regression.

Heart rate (HR) rose by 28.8%, from 75.9±11.6 bpm to 96.5±14.0 bpm ($P<0.001$) (Table 5-3). The maximum heart rate (MHR), which ranged from 61.7 to 126.7 bpm, was related significantly to the baseline heart rate (HR) ($r=0.67$, $P<0.001$) but to neither age ($r=-0.21$, n.s.) nor LBRS ($r=0.14$, n.s.) and these latter two variables did not significantly contribute to the regression equation.

$$MHR = 30.191+(0.89) \times (HR) \quad (10)$$

The standard error of the regression coefficient was 0.13.

The increase in MAP was directly related to the increase in HR ($r=0.41$, $P<0.0005$) according to the regression equation.

$$\Delta MAP \doteq 15.82+(0.40) \times (\Delta HR) \quad (11)$$

with a standard error of the regression equation of 0.12. The increase in heart rate was unrelated to the resting MAP ($r=-0.09$, n.s.), the resting heart rate ($r=-0.19$, $0.10>P>0.05$), age ($r=-0.08$, n.s.), or LBRS ($r=0.07$, n.s.).

Table 5-8

Partial correlation coefficients for the independent effect of baseline mean arterial pressure, age, and LBRS, on mean arterial pressure during mental arithmetic (n=62).

	MMAP	ΔMAP	%ΔMAP
MAP	0.850***	0.115	-0.151
Age	0.067	0.067	0.042
LBRS	-0.022	-0.022	-0.029

Table 5-9

Partial correlation coefficients for the independent effect of baseline heart rate, and LBRS on heart rate during mental arithmetic (n=62).

	MHR	ΔHR	%ΔHR
HR	0.666****	-0.204	-0.392***
Age	-0.074	-0.074	-0.077
LBRS	0.026	0.026	0.026

* P<0.05
** P<0.01
*** P<0.005
**** P<0.0001

The relative increase in heart rate (%ΔHR) during mental arithmetic was greater in those with slower resting heart rates ($r=-0.33$, $P<0.02$) but was unrelated to age ($r=-0.03$, n.s.) or LBRS ($r=0.03$). The following equation could be constructed from these data:

$$\%\Delta HR = 64.801-(0.469)\times(HR) \qquad (12)$$

with a standard error of the regression coefficient of 0.18.

The relative, or percentage increase in MAP was directly related to the relative increase in heart rate ($r=0.43$, $P<0.0003$) according to the regression equation

$$\%\Delta MAP = 13.959+(0.238)\times(\%\Delta HR) \qquad (13)$$

with a standard error of the regression coefficient of 0.064.

Partial correlation coefficients for the independent effect of each of these variables in blood pressure and heart rate during mental arithmetic are noted in Tables 5-8 and 5-9.

Reaction Time Test

The reaction time test increased mean arterial pressure by 17.1%, from 123.2±18.8 mm Hg to 144.2±21.11 mm Hg ($P<0.001$). There was a 15% rise in systolic pressure, and an 18% increase in diastolic pressure (Fig. 4-3; Tables 5-2, 5-4, 5-5).

The maximum mean arterial pressure (MMAP), which ranged from 100.8 mm Hg to 184.1 mm Hg, correlated significantly with the baseline MAP ($r=0.90$, $P<0.00001$) (Fig. 5-7), age ($r=0.43$, $P<0.003$), and inversely, to LBRS ($r=-0.62$, $P<0.00001$) (Fig. 5-8). When the independent effects of baseline mean arterial pressure, age, and LBRS on the MMAP were calculated, using multiple regression analysis, the significant predictors of the dependent variable were resting

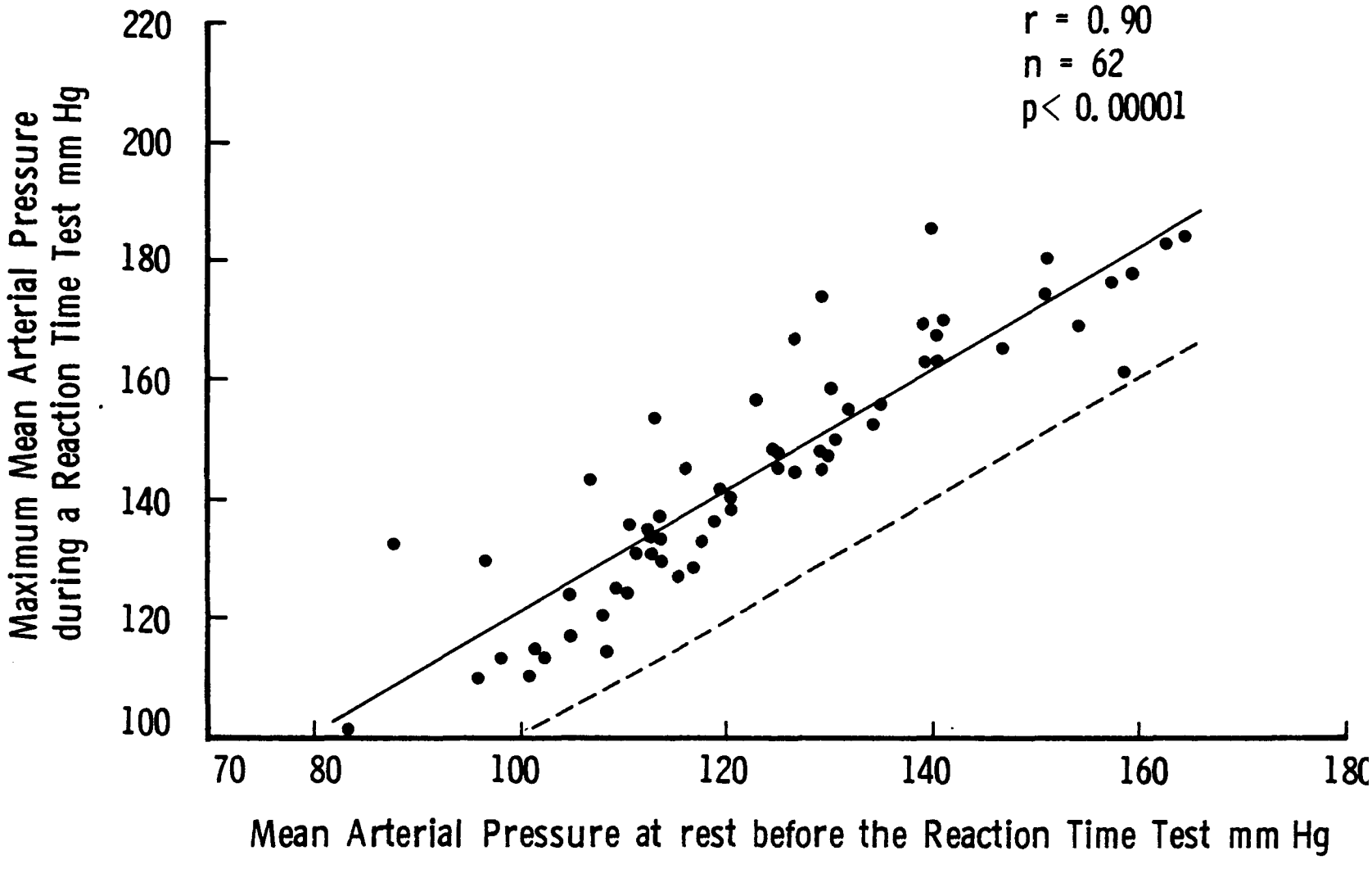

Fig. 5-7 Relationship between maximum and baseline mean arterial pressure during a reaction time test. Broken line is line of identity.

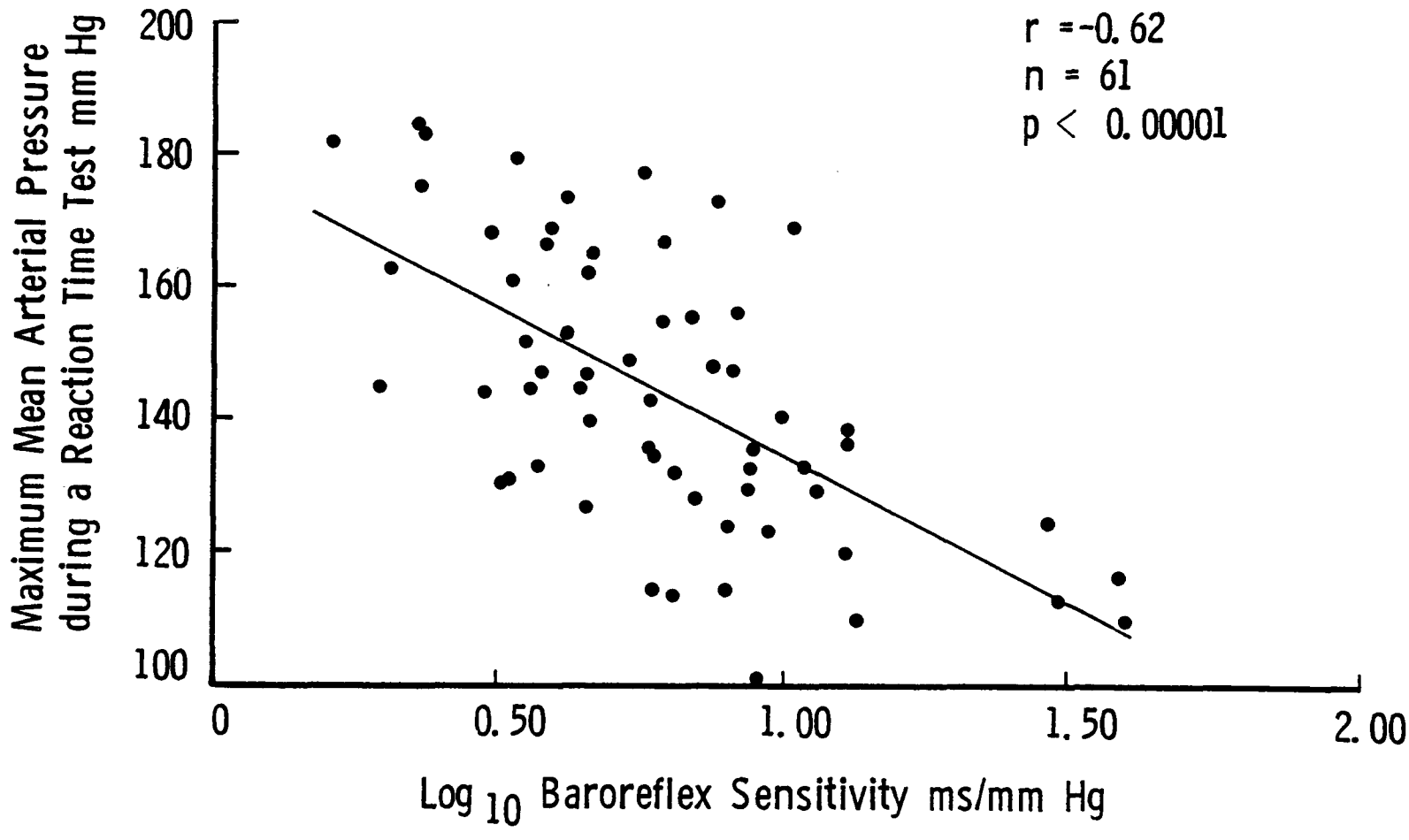

Fig. 5-8 Relationship between maximum mean arterial pressure during a reaction time test and baroreflex sensitivity.

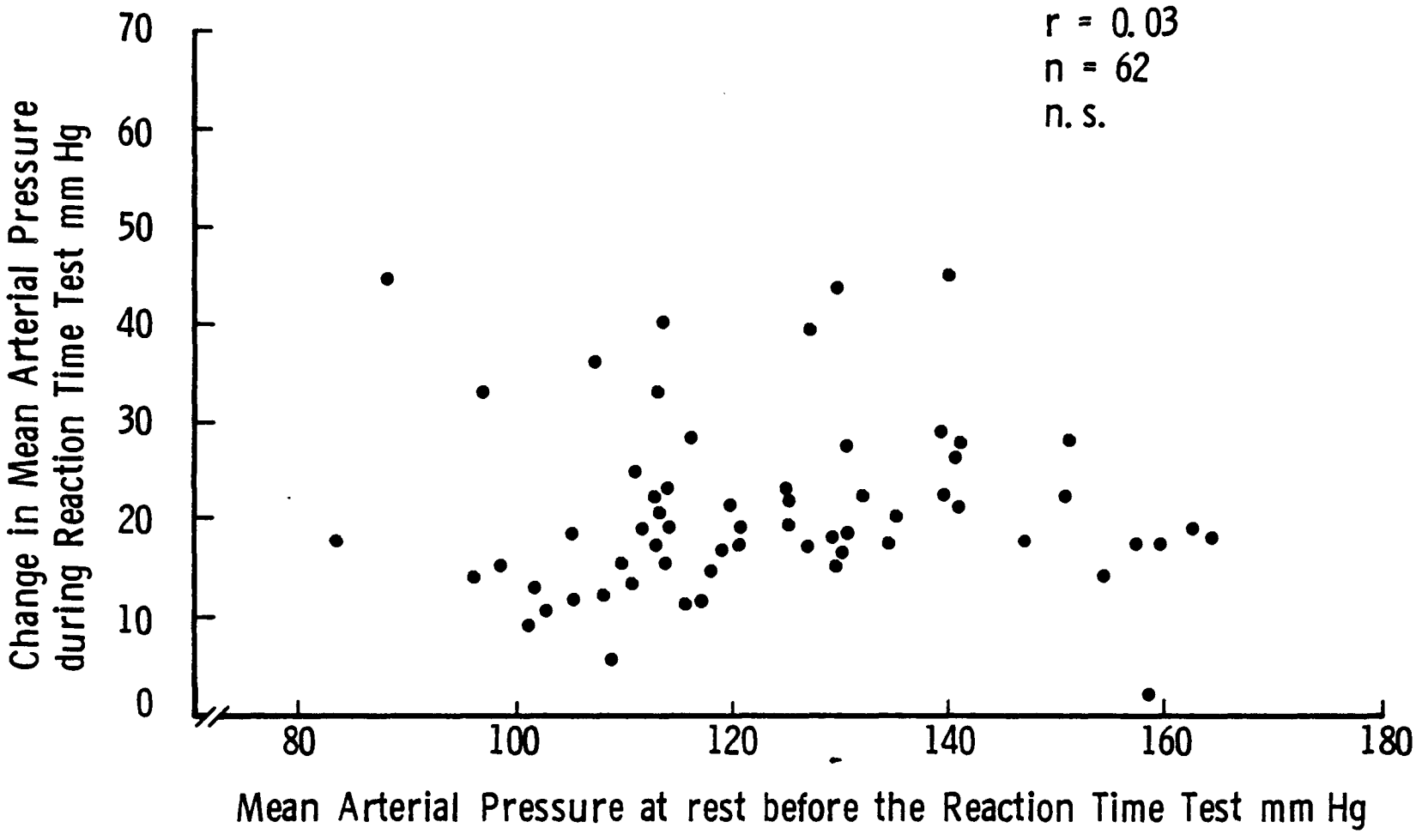

Fig. 5-9 Relationship between the increase in mean arterial pressure and baseline mean arterial pressure during a reaction time test.

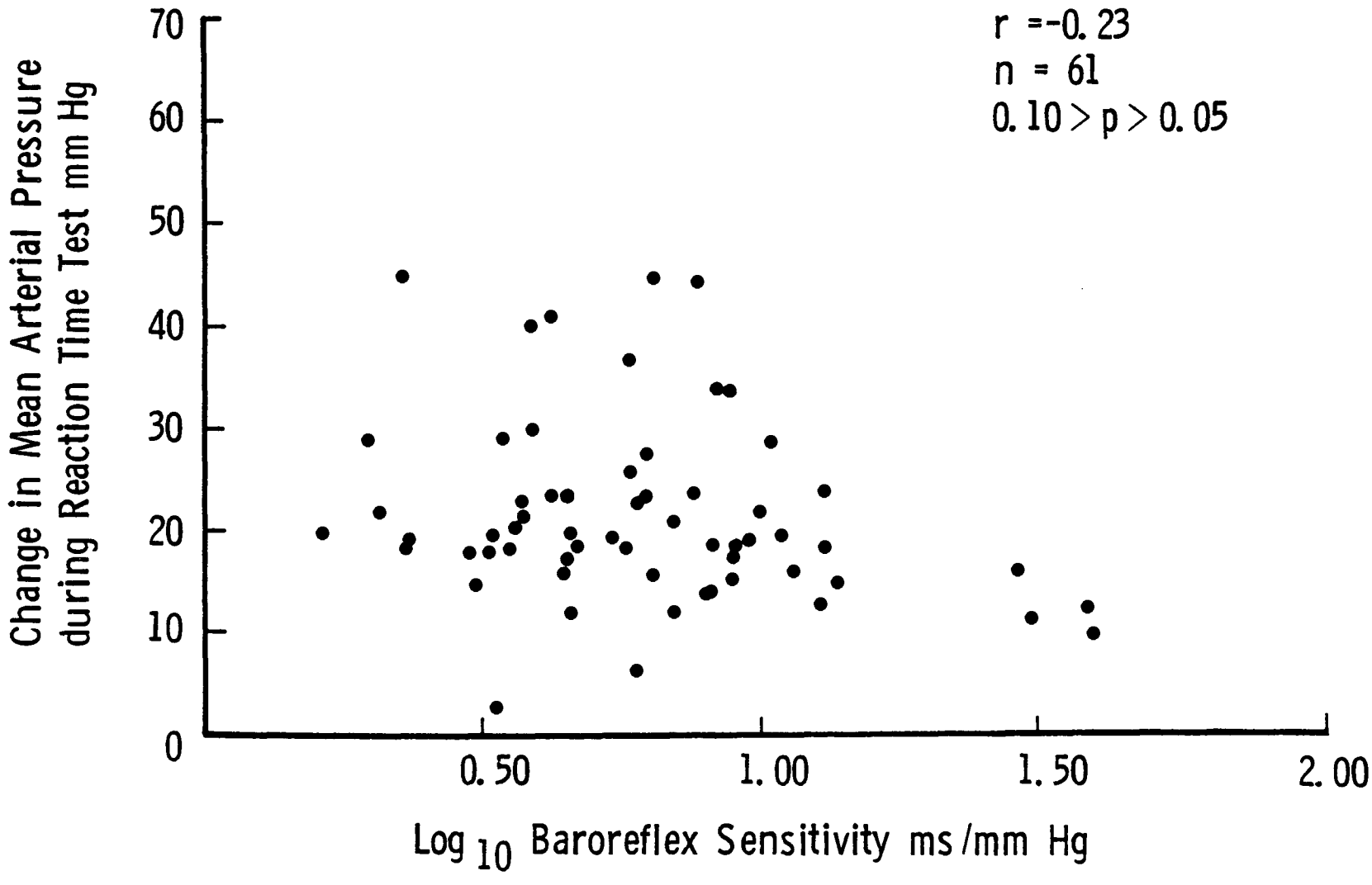

Fig. 5-10 Relationship between the increase in mean arterial pressure during the reaction time test and baroreflex sensitivity.

MAP (F=230.546, P<0.001), followed by age (F=5.151, P<0.05). The independent effect of MAP and age could be expressed by the regression equation

$$MMAP = 13.050 + (0.966)\times(MAP) + (0.253)\times(age) \quad (14)$$

Standard errors of the regression coefficients b_1 and b_2 were 0.064, and 0.112 respectively.

LBRS, which diminished with increasing age and blood pressure, had no additional independent effect on determining the MMAP achieved.

The absolute increase in mean arterial pressure (ΔMAP), which was 21.0±9.0 mm Hg, tended to be higher in the older subjects ($r=0.28$, $P<0.05$), and could be expressed by the regression equation:

$$\Delta MAP = 9.846+(0.233)\times(age) \quad (15)$$

with a standard error of the regression coefficient of 0.104.

Neither LBRS ($r=-0.23$, $0.10>P>0.05$) (Fig. 5-10), nor resting MAP ($r=0.03$, n.s.) (Fig. 5-9), correlated with the absolute increase in pressure, and their stepwise inclusion in the calculations did not improve the regression equation.

Greater relative increases (%ΔMAP) were observed in subjects with lower baseline pressures ($r=-0.29$, $P<0.02$), but these changes were poorly correlated with LBRS ($r=-0.08$, n.s.) or age ($r=0.14$, n.s.). However, the stepwise addition of LBRS to resting MAP significantly reduced the residual variation in the multiple regression equation; both baseline MAP ($F=10.633$, $P<0.005$) and LBRS ($F=5.474$, $P<0.025$) then had independent effects on the pressure rise, with a calculated regression equation of

$$\%\Delta MAP = 50.438-(0.209)\times(MAP)-(9.86)\times(LBRS) \quad (16)$$

with standard errors of the regression coefficients b_1 and b_2 of 0.064, and 4.214, respectively.

The addition of age as a third variable in this equation was not in itself significant, and negated this significant independent contribution of LBRS to the regression equation.

The heart rate increased 15.5%, from 74.6±11.2 bpm to 90.1±13.0 bpm during this exercise ($P<0.001$) (Table 5-3). Maximum heart rate (MHR), which ranged from 64.0 bpm to 133.2 bpm, was significantly related to the resting heart rate ($r=0.78$, $P<0.001$) but not to age ($r=-0.21$, n.s.) or LBRS ($r=0.01$, n.s.). Baseline heart rate was related to MHR by the regression equation

$$MHR = 12.403+(1.041)\times(HR) \qquad (17)$$

The standard error of the regression coefficient, b_1, in this instance, was 0.08.

The increase in MAP was directly related to the increase in heart rate ($r=0.45$, $P<0.0002$), according to the regression equation

$$\Delta MAP = 10.725+(0.665)\times(\Delta HR) \qquad (18)$$

with a standard error of the regression coefficient b_1 of 0.170.

The increase in heart rate was unrelated to the resting MAP ($r=-0.14$, n.s.), the resting heart rate ($r=0.11$, n.s.), or LBRS ($r=0.16$, n.s.). The rise in heart rate declined with age, however ($r=-0.21$, $P<0.05$), and could be predicted by the regression equation

$$\Delta HR = 20.70-(0.11)\times(age) \qquad (19)$$

with a standard error of the regression coefficient of 0.07.

The relative increase (%ΔHR) in heart rate was not related to any of baseline heart rate ($r=-0.10$), age ($r=-0.15$) or LBRS ($r=0.16$). The relative, or percentage, increase in MAP was directly related to the relative increase in heart rate ($r=0.53$, $P<0.00001$) according to the regression equation

$$\%\Delta MAP = (6.68)+(0.51)\times(\%\Delta HR) \qquad (20)$$

with a standard error of the regression coefficient of 0.10.

Table 5-10

Partial correlation coefficients for the independent effects of baseline mean arterial pressure, age, and LBRS on mean arterial pressure during a reaction time test (n=62).

	MMAP	ΔMAP	%ΔMAP
MAP	0.812****	-0.018	-0.260*
Age	0.018	0.156	0.134
LBRS	0.249+	-0.110	-0.123

Table 5-11

Partial correlation coefficients for the independent effects of baseline heart rate, age, and LBRS on heart rate during a reaction time test (n=62).

	MHR	ΔHR	%ΔHR
HR	0.820****	0.076	-0.170
Age	-0.235	-0.123	-0.088
LBRS	-0.254*	0.049	0.089

\+ P<0.10
* P<0.05
** P<0.01
*** P<0.005
**** P<0.0001

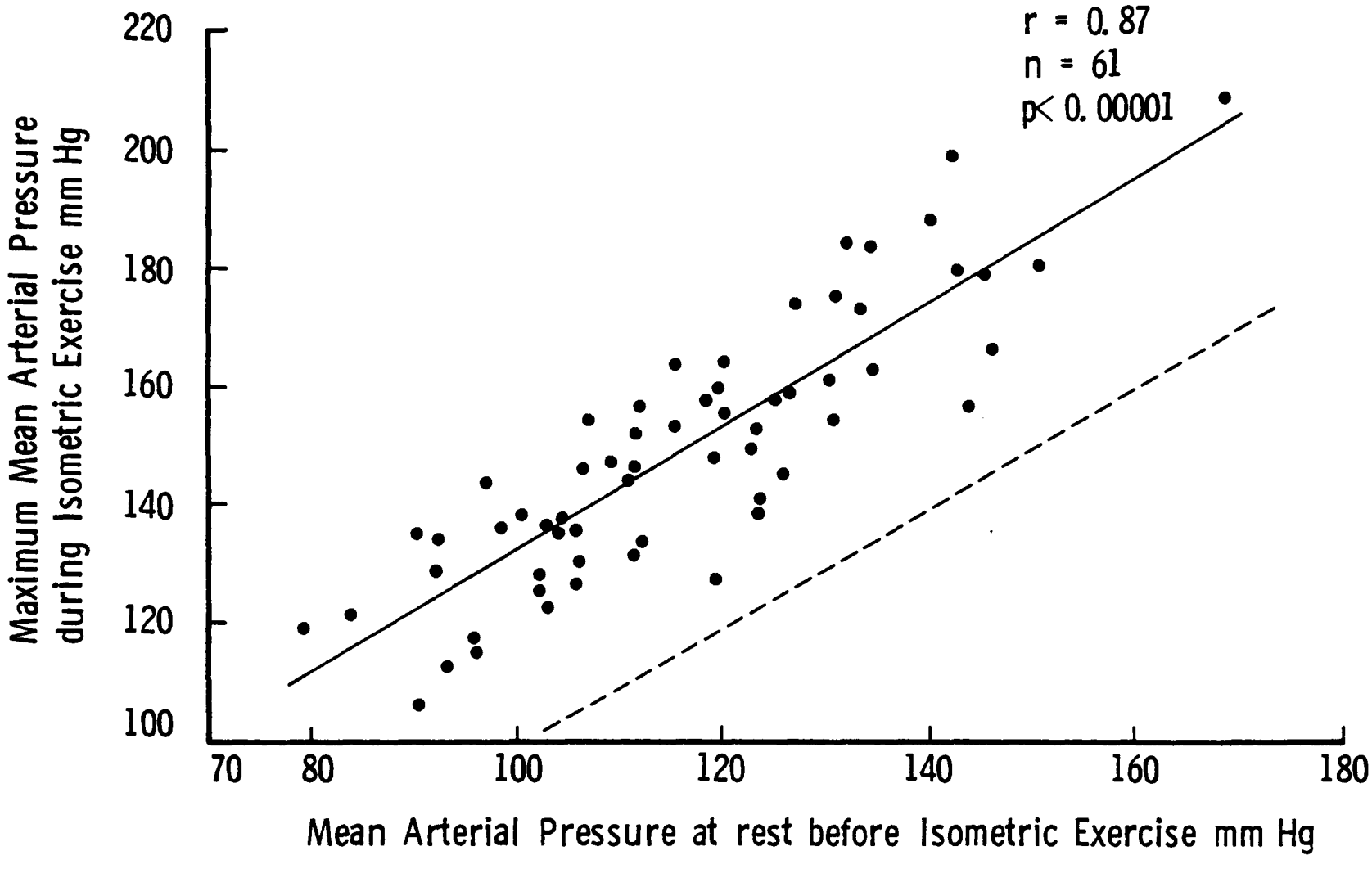

Fig. 5-11 Relationship between maximum and baseline mean arterial pressure during isometric exercise. Broken line is line of identity.

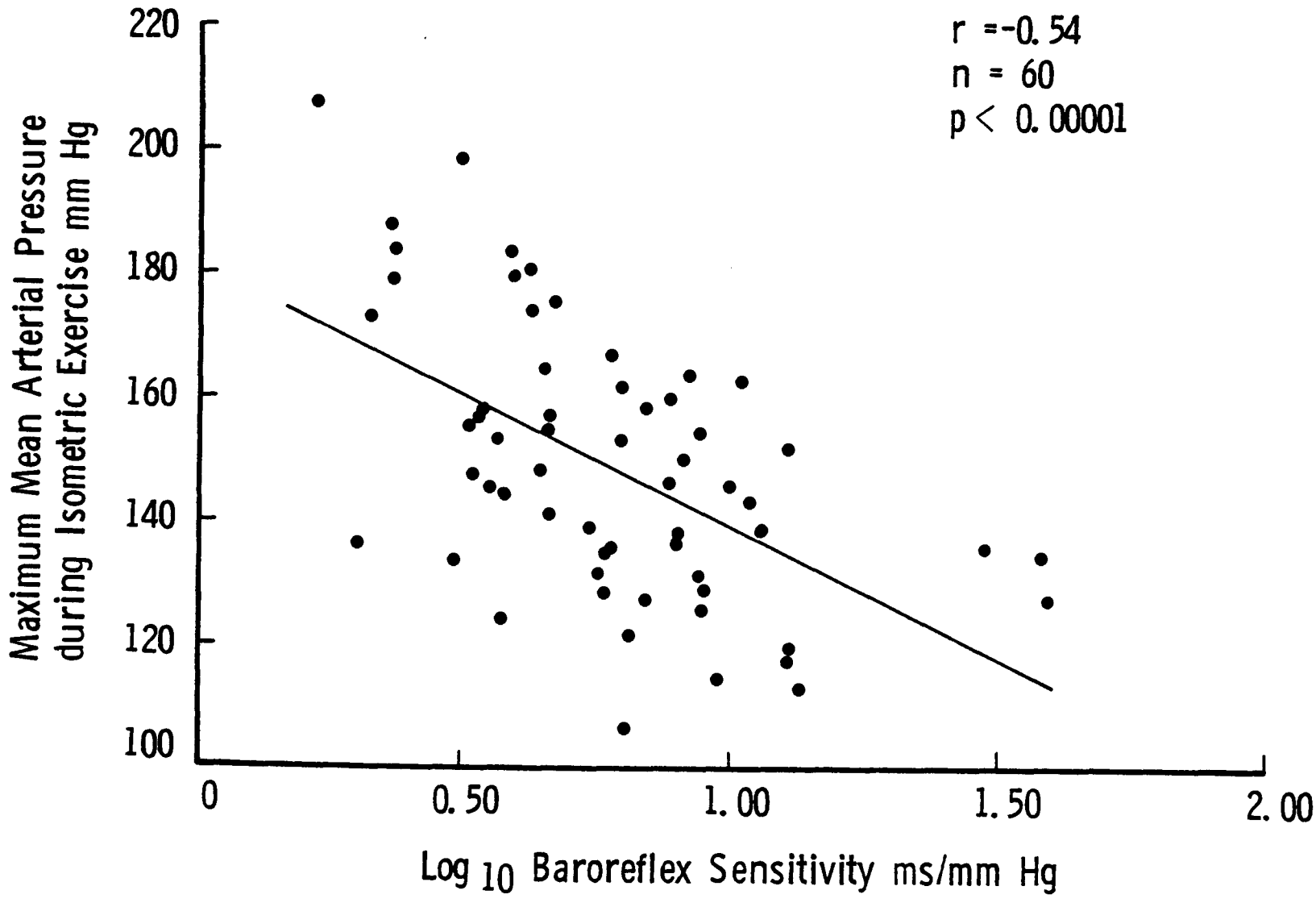

Fig. 5-12 Relationship between maximum mean arterial pressure during isometric exercise and baroreflex sensitivity.

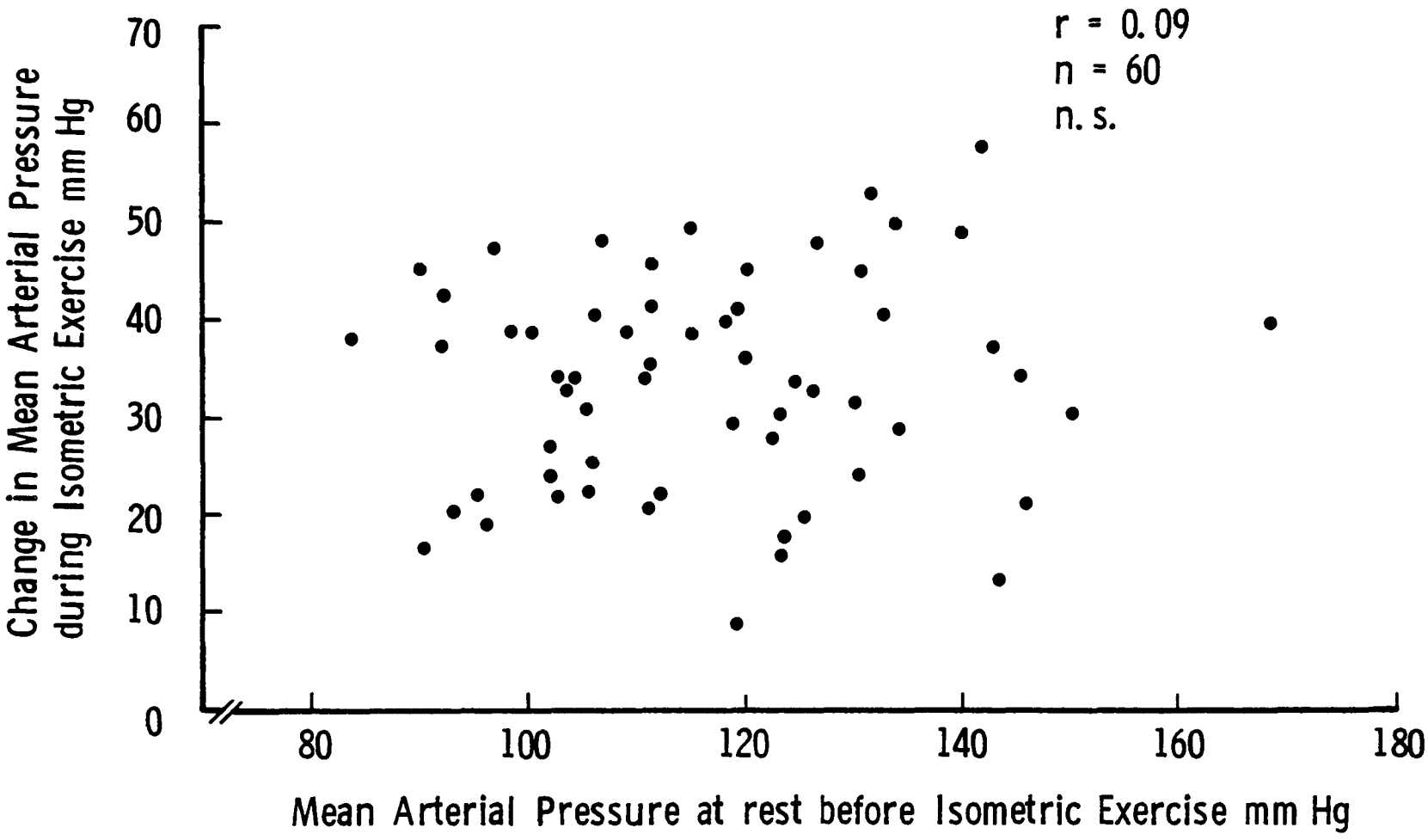

Fig. 5-13 Relationship between the increase in mean arterial pressure and baseline mean arterial pressure during isometric exercise.

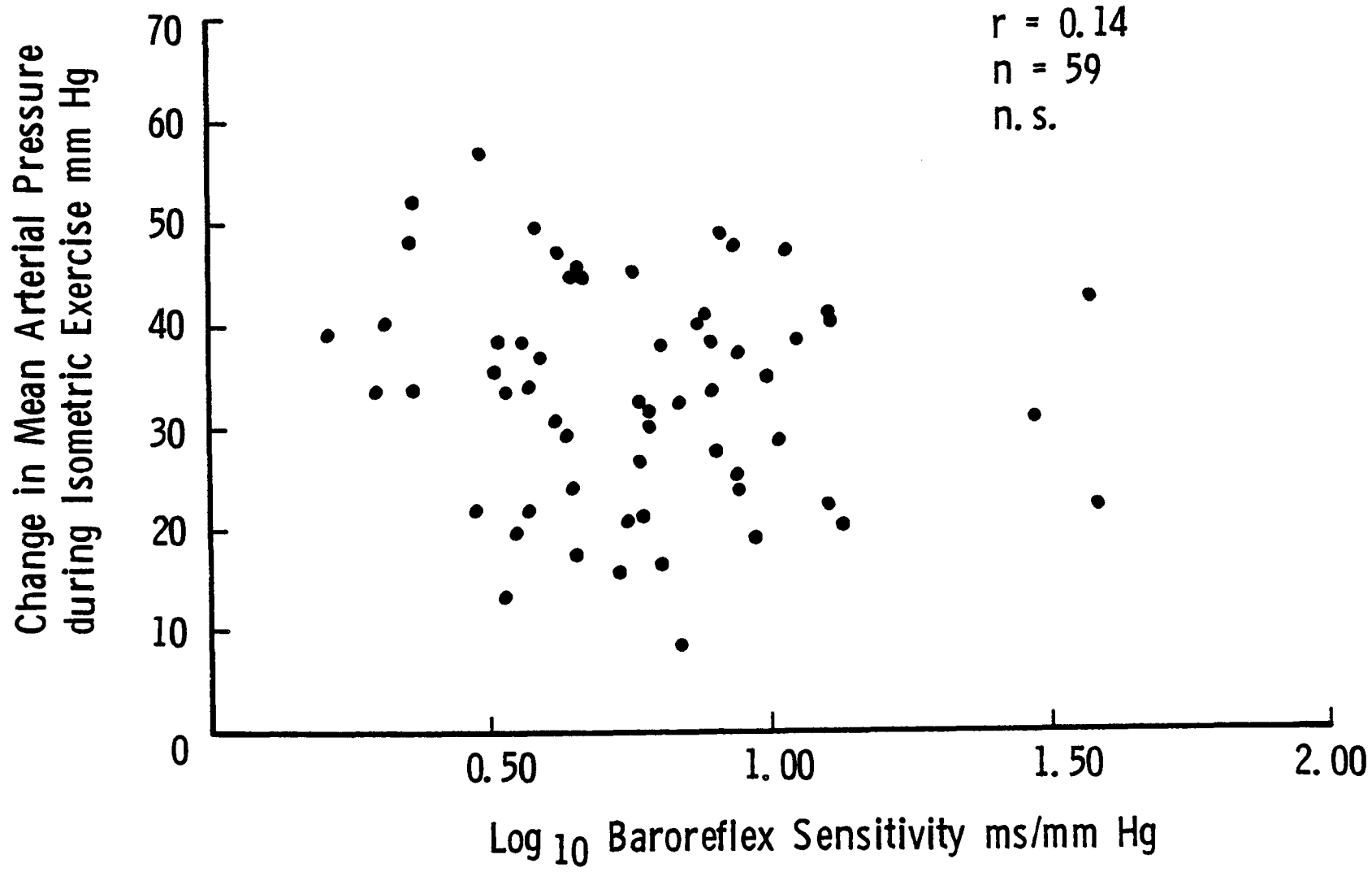

Fig. 5-14 Relationship between the increase in mean arterial pressure during isometric exercise and baroreflex sensitivity.

Partial correlation coefficients for the independent effect of each of these variables on mean arterial pressure and heart rate during the reaction time test are noted in Tables 5-10 and 5-11.

Isometric Exercise

Mean arterial pressure rose from 115.8±18.1 mm Hg at rest to 149.0±21.8 mm Hg during isometric exercise, an increase of 28.0% ($P<0.001$). Similar increases in systolic (27.3%) and diastolic (28.5%) pressures were observed (Fig. 4-4; Tables 5-2, 5-4, 5-5). The maximum mean arterial pressure (MMAP), which ranged from 106.4 mm Hg to 207.4 mm Hg, was significantly related to baseline MAP ($r=0.87$, $P<0.00001$) (Fig. 5-11), the patient's age ($r=0.31$, $P<0.008$), and inversely related to the patient's LBRS ($r=-0.54$, $P<0.00001$) (Fig. 5-12). The colinearity of these three variables became apparent when the independent effect of each on MMAP was calculated by the stepwise multiple regression analysis; MAP was the only independent predictor of MMAP ($F=101.53$, $P<0.001$), according to the equation

$$MMAP = 35.261+(1.011)\times(MAP) \qquad (21)$$

with a standard error of the regression coefficient of 0.100.

The absolute increase in mean arterial pressure (ΔMAP) during isometric contraction (33.2±10.8 mm Hg) was unrelated to baseline MAP ($r=0.09$, n.s.) (Fig. 5-13), age ($r=0.01$, n.s.), or LBRS ($r=0.14$, n.s.) (Fig. 5-14). Therefore, greater relative rises in MAP ($\%\Delta MAP$) were seen at lower pressures ($r=-0.34$, $P<0.002$) and could be predicted by the regression equation

$$\%\Delta MAP = 52.44-(0.203)\times(MAP) \qquad (22)$$

The standard error of the regression coefficient b_1 was 0.071.

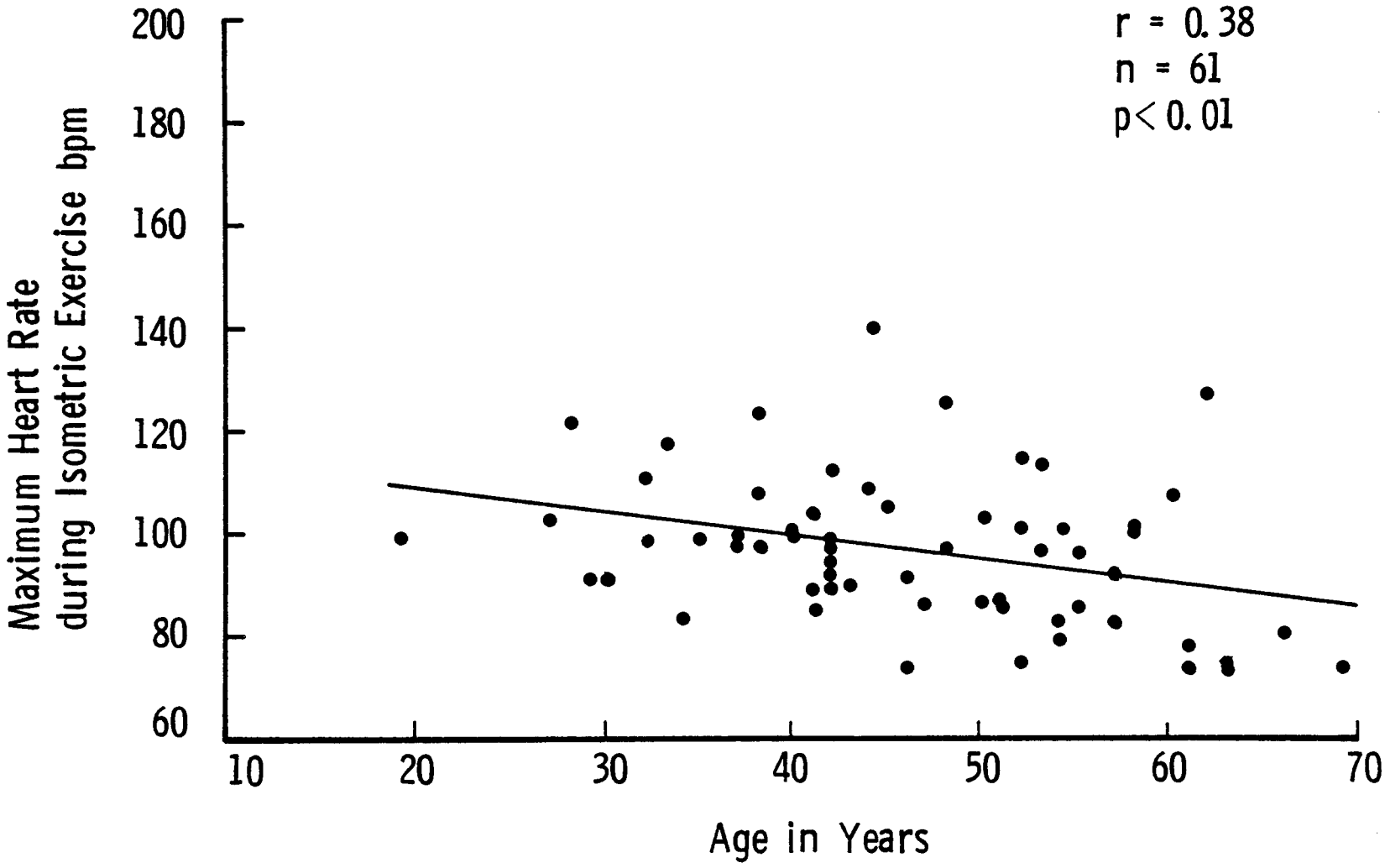

Fig. 5-15 Relationship between maximum heart rate during isometric exercise and age.

Age (r=-0.12, n.s.) and LBRS (r=0.15, n.s.) did not improve the predictive value of this regression equation.

Isometric exercise increased the heart rate by 23.6% (Table 5-3), from 78.0±11.9 bpm to 96.4±14.6 bpm (P<0.001). Maximum heart rate (MHR), which ranged from 73.4 bpm to 139.7 bpm, was related significantly to the baseline heart rate (r=0.62, P<0.001) and tended to decrease with age (r=-0.38, P<0.01) (Fig. 5-15). It was not related to LBRS (r=0.17, n.s.). Only the baseline heart rate appeared to be independently related to the exercise heart rate when multiple regression analysis was performed:

$$MHR = 14.670+(1.042)\times(HR) \qquad (23)$$

S.E. b_1 = 0.10.

The increase in MAP was directly related to the increase in heart rate (r=0.43, P<0.0003), according to the regression equation

$$\Delta MAP = 22.69+(0.57)\times(\Delta HR) \qquad (24)$$

with a standard error of the regression coefficient of 0.15.

The increase in heart rate was unrelated to the resting MAP (r=-0.05, n.s.), the resting heart rate (r=-0.02, n.s.), age (r=-0.24, 0.10>P>0.05), or LBRS (r=0.20, 0.10 P<0.05).

The relative increase in heart rate (%ΔHR) was inversely related to the baseline rate (r=-0.27, P<0.05) but not to age (r=-0.10, n.s.) or LBRS (r=0.15, n.s.). The influence of baseline heart rate on this relative increase could be expressed by the regression equation:

$$\%\Delta HR = 42.57-(0.25)\times(HR) \qquad (25)$$

The standard error of this regression coefficient b_1, 0.12, is relatively large, however.

The relative, or percentage, increase in MAP was directly

Table 5-12

Partial correlation coefficients for the independent effects of baseline mean arterial pressure, age, and LBRS on mean arterial pressure during isometric exercise (n=61).

	MMAP	ΔMAP	%ΔMAP
MAP	0.629****	0.074	-0.183
Age	-0.105	-0.010	-0.030
LBRS	-0.239	-0.070	-0.003

Table 5-13

Partial correlation coefficients for the independent effects of baseline heart rate, age, and LBRS on heart rate during isometric exercise (n=61).

	MHR	ΔHR	%ΔHR
HR	0.668****	-0.068	-0.306*
Age	-0.326*	-0.161	-0.080
LBRS	-0.121	-0.084	0.111

* P<0.05
**** P<0.001

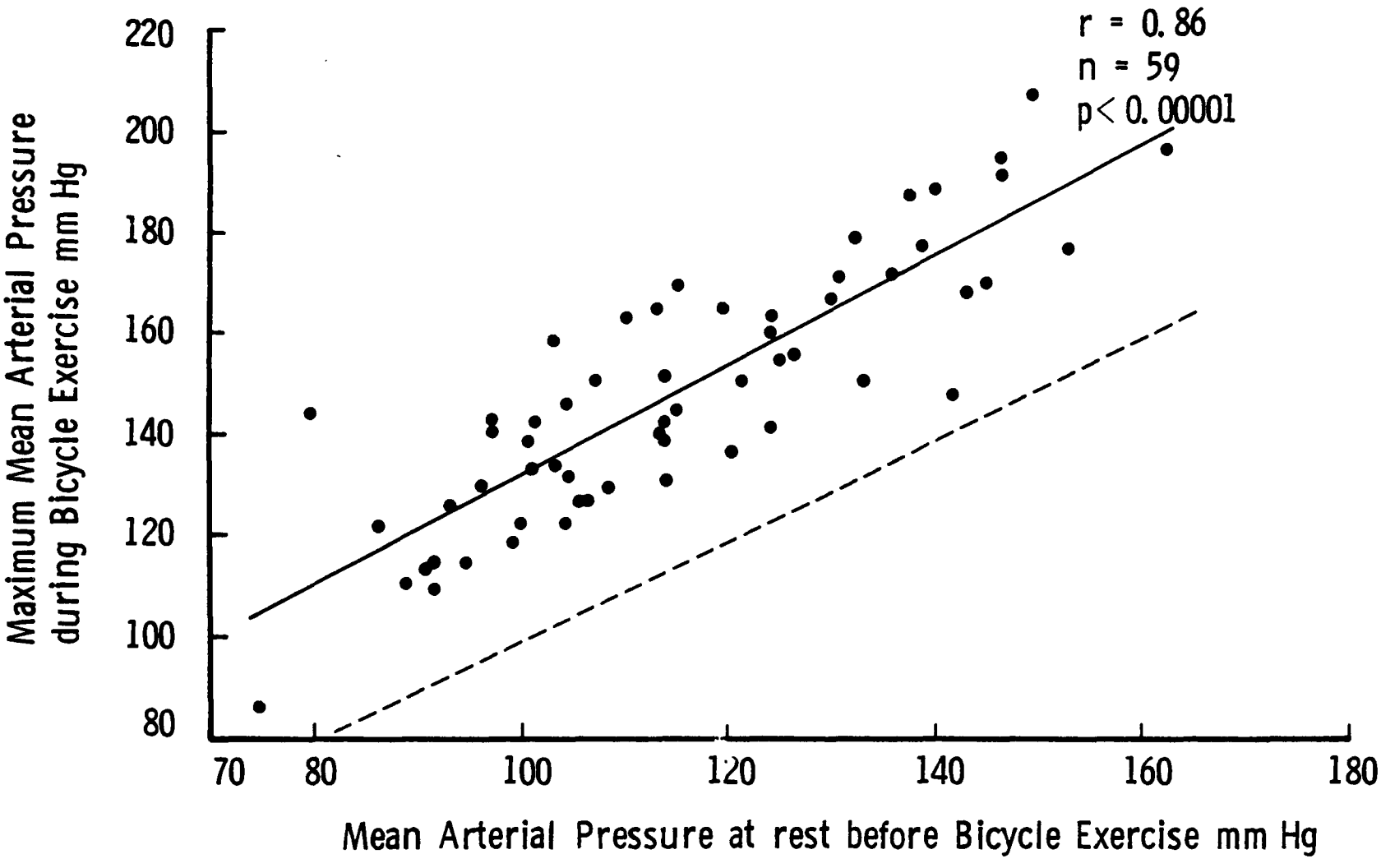

Fig. 5-16 Relationship between maximum and baseline mean arterial pressure during bicycle exercise. Broken line is line of identity.

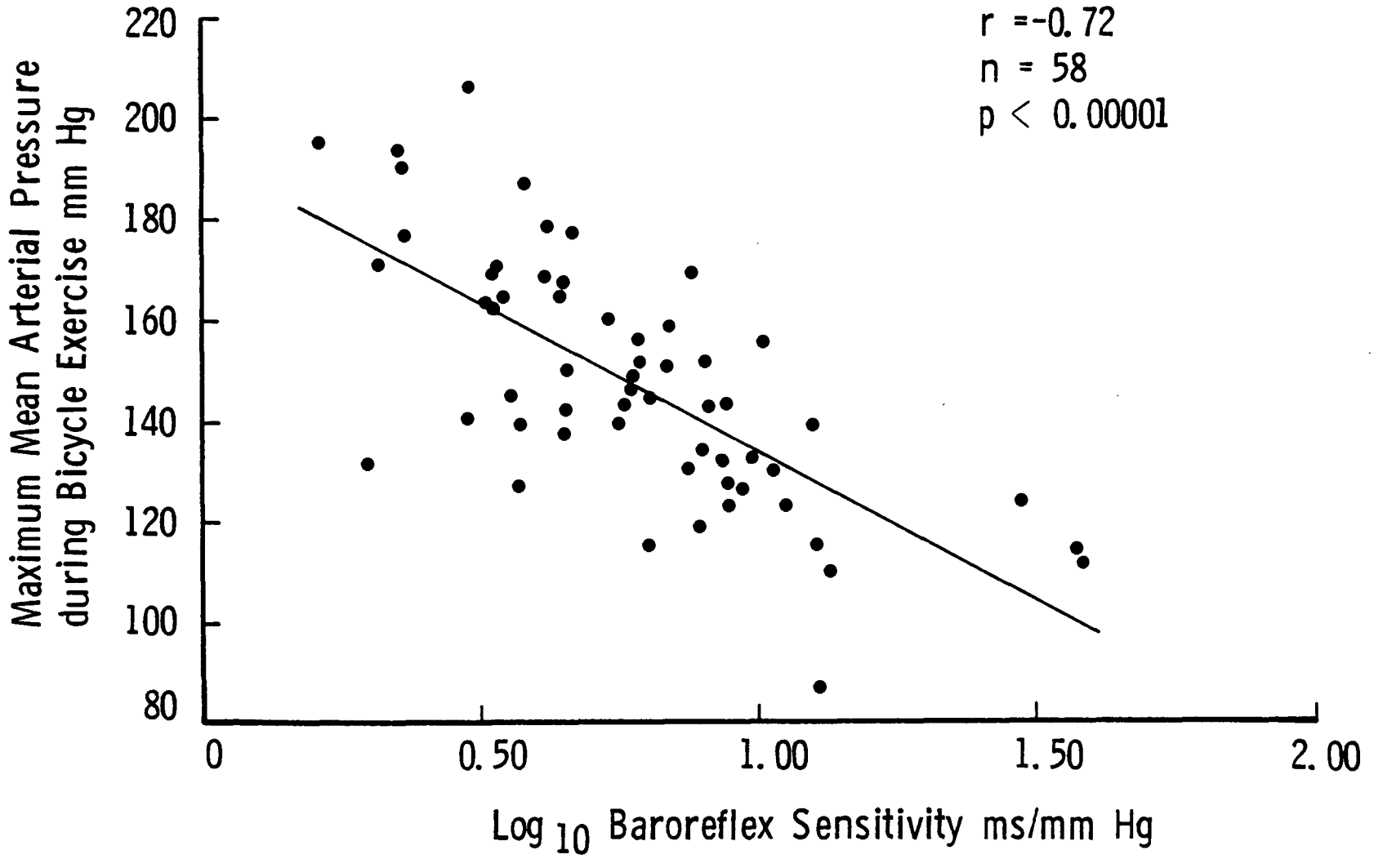

Fig. 5-17 Relationship between maximum mean arterial pressure during bicycle exercise and baroreflex sensitivity.

related to the relative increase in heart rate (0.46, P<0.0002), according to the regression equation

$$\%\Delta MAP = (19.38)+(0.41)\times(\%\Delta HR) \qquad (26)$$

with a standard error of the regression coefficient of 0.10.

Partial correlation coefficients for the independent effect of each of these variables on mean arterial pressure and heart rate during isometric exercise are noted in Tables 5-12 and 5-13.

Bicycle Exercise

Mean arterial pressure rose 28.6%, from 115.0±19.8 mm Hg to 147.9±24.9 mm Hg during bicycle exercise (P<0.001). This increase was achieved through a 36.4% increase in systolic pressure, and a 17.8% increase in diastolic blood pressure (Fig. 4-5; Tables 5-2, 5-4, 5-5). During bicycling, the maximum mean arterial pressures, which ranged from 86.1 mm Hg to 206.3 mm Hg, were related significantly to the baseline or resting MAP (r=0.86, P<0.00001) (Fig. 5-16), and age (r=0.58, P<0.00001), and inversely related to the LBRS (r=-0.72, P<0.00001) (Fig. 5-17).

The most important predictors of MMAP on multiple regression analysis were MAP (F=126.72, P<0.001), and age (F=15.418, P<0.005); together these accounted for 79% of the variance in MMAP. Their independent effects on MMAP could be expressed by the equation:

$$MMAP = 12.842+(0.935)\times(MAP)+(0.590)\times(age) \qquad (27)$$

with standard errors of b_1 and b_2 of 0.083, and 0.150, respectively. The addition of LBRS to this equation did not reduce the residual variance significantly (0.10>P>0.05).

The absolute rise in mean arterial pressure (ΔMAP) during bicycle exercise (32.9±12.7 mm Hg) was correlated significantly

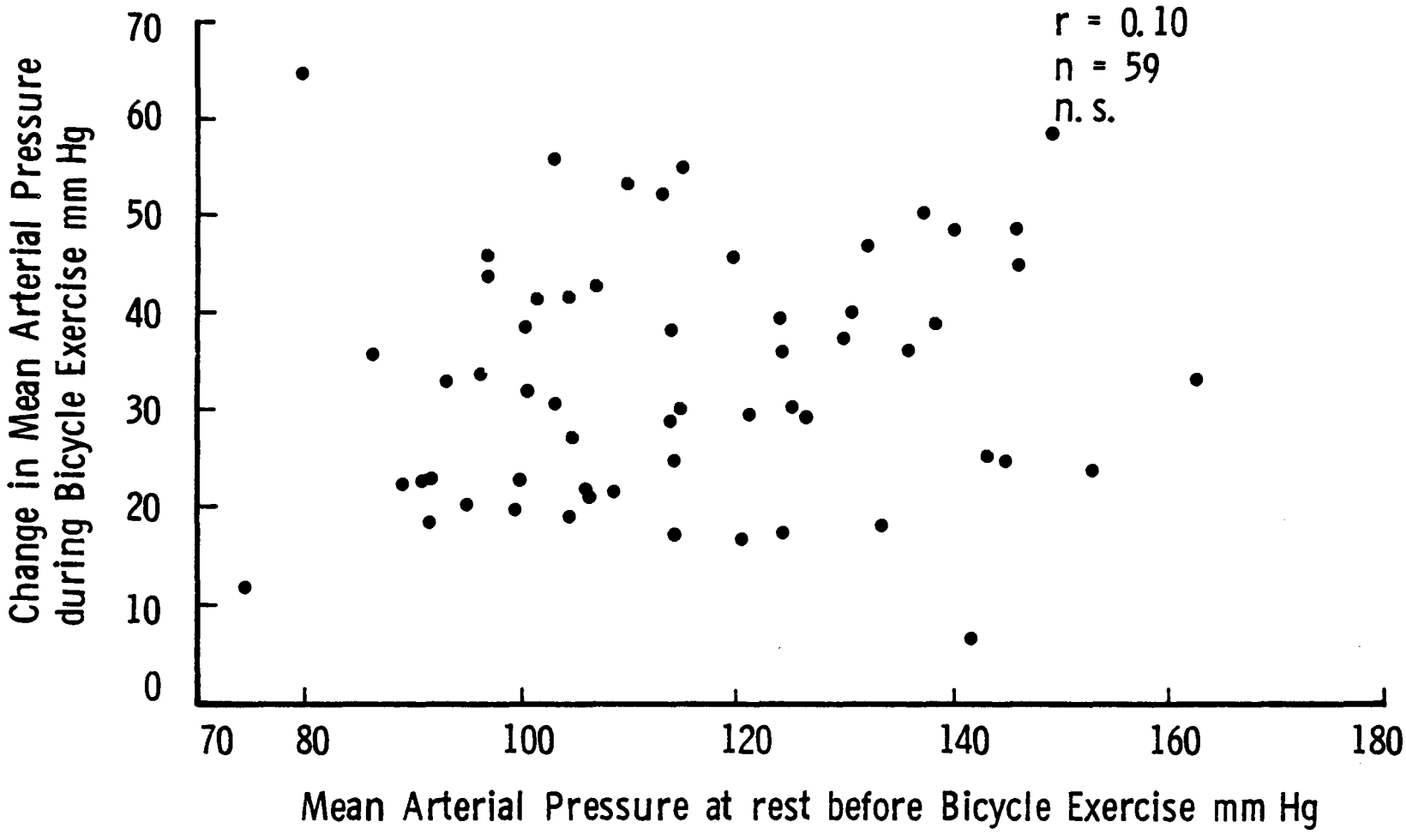

Fig. 5-18 Relationship between the increase in mean arterial pressure and baseline mean arterial pressure during bicycle exercise.

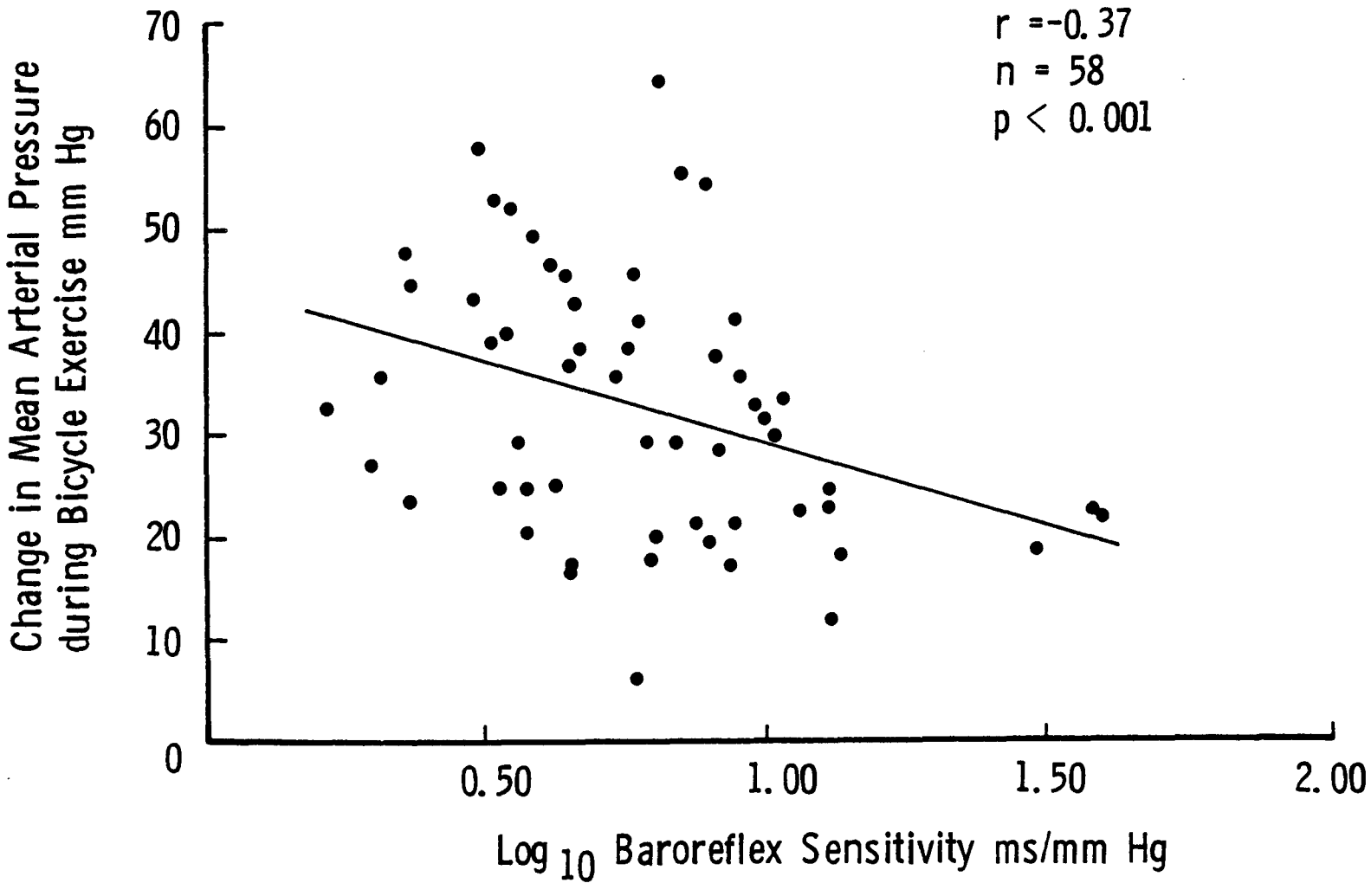

Fig. 5-19 Relationship between change in mean arterial pressure during bicycle exercise and baroreflex sensitivity.

with increasing age ($r=0.47$, $P<0.001$), and diminishing baroreflex sensitivity ($r=-0.37$, $P<0.001$) (Fig. 5-19). There was minimal correlation between the pressure rise and the baseline mean arterial pressure ($r=0.10$, n.s.) (Fig. 5-18). However, the stepwise inclusion of LBRS ($F=3.279$, n.s.) or resting mean arterial pressure ($F=2.795$, n.s.) did not improve the following regression equation significantly:

$$\Delta MAP = 7.560 + (0.542) \times (age) \qquad (28)$$

with a standard error of the regression coefficient of 0.137. The inverse colinearity of LBRS and age may have contributed to this.

Subjects with lower baseline pressures tended to show higher relative increases in MAP (%ΔMAP) during this exercise ($r=-0.29$, $P<0.02$), as did older subjects ($r=0.26$, $P<0.03$). This value was unrelated to LBRS ($r=-0.10$, n.s.) on simple correlation. However, when multiple regression analysis was performed, baseline mean arterial pressure ($F=19.621$, $P<0.005$), age ($F=5.660$, $P<0.025$), and LBRS ($F=4.279$, $P<0.05$), in that order, were found to be significant independent predictors of the pressure change. The total variance in %ΔMAP accounted for by these three variables is only about 32%, however. This multiple regression equation can be expressed as

$$\%\Delta MAP = 70.579 - (0.415) \times (MAP) + (0.374) \times (age) - (14.635) \times (LBRS) \qquad (29)$$

The standard errors of the regression coefficients b_1, b_2, b_3, are 0.094, 0.157, and 7.076 respectively.

Bicycling had the greatest effect on heart rate; an increase of 65.3%, from 79.4±11.6 bpm to 130.6±20.0 bpm was observed ($P<0.001$) (Table 5-3). The maximum heart rate (MHR), which ranged from 87.3 bpm to 184.1 bpm, was related, again, to baseline heart rate ($r=0.47$, $P<0.001$). Older subjects tended to have slower heart rates on exercise ($r=-0.35$, $P<0.01$) (Fig. 5-20); MHR was unrelated to LBRS ($r=0.01$). On

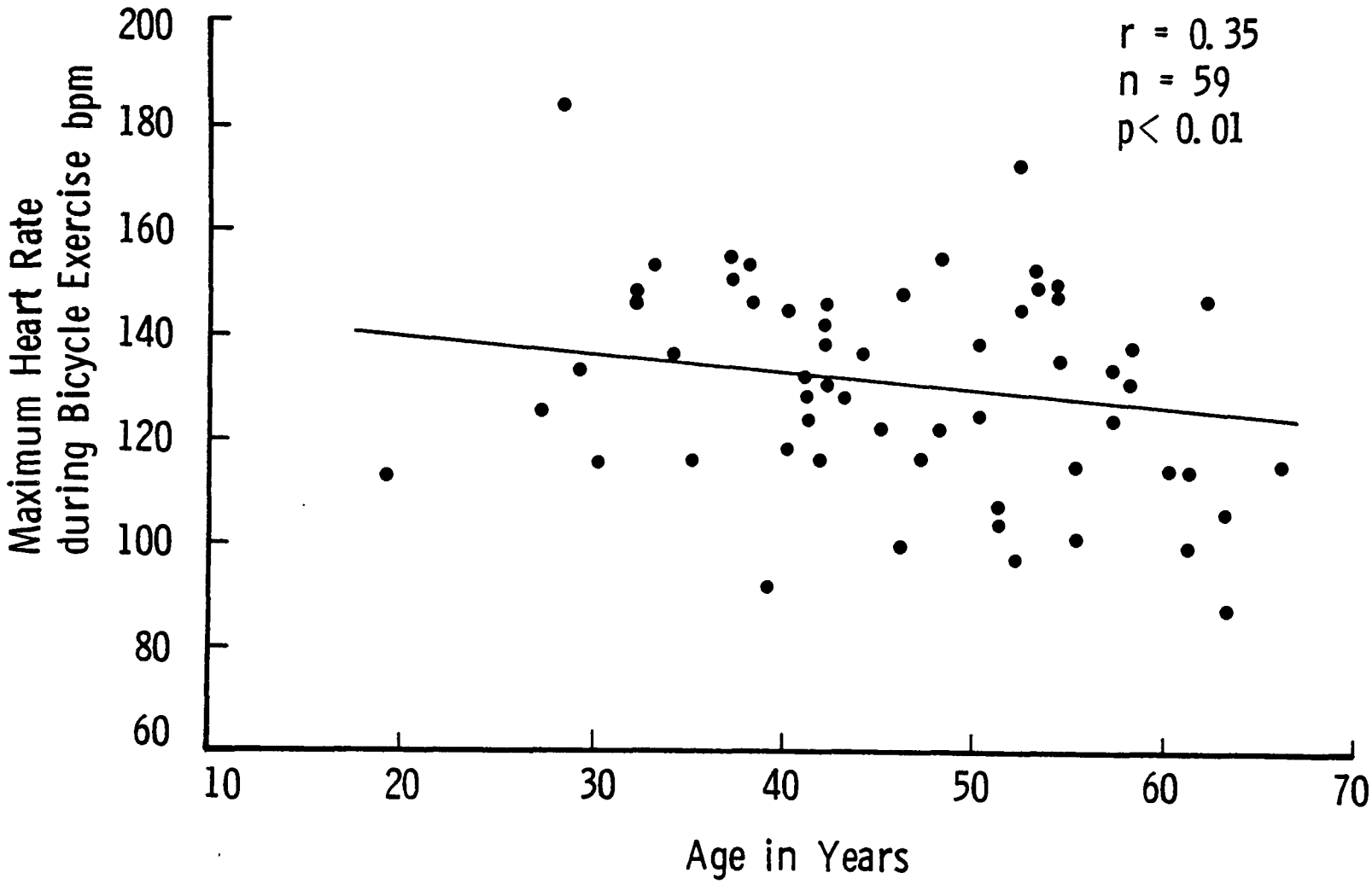

Fig. 5-20 Relationship between maximum heart rate during bicycle exercise and age.

Table 5-14

Partial correlation coefficients for the independent effects of baseline mean arterial pressure, age, and LBRS on mean arterial pressure during bicycle exercise (n=59).

	MMAP	ΔMAP	%ΔMAP
MAP	0.578****	-0.059	-0.297*
Age	0.253^{+}	0.342**	0.286*
LBRS	-0.391***	-0.151	-0.094

Table 5-15

Partial correlation coefficients for the independent effects of baseline heart rate, age, and LBRS on heart rate during bicycle exercise (n=59).

	MHR	ΔHR	%ΔHR
HR	0.461****	0.036	-0.224^{+}
Age	-0.410***	-0.339*	-0.188
LBRS	-0.304*	-0.155	-0.008

\+ P<0.10
* P<0.05
** P<0.01
*** P<0.005
**** P<0.001

multiple regression analysis, both resting heart rate (F=46.000, P<0.005), and age (F=5.417, P<0.025) were significant independent variables in the regression equation

$$MHR = 60.957+(1.115)\times(HR)-(0.407)\times(age) \quad (30)$$

with standard errors of the regression coefficients b_1 and b_2 of 0.16 and 0.17 respectively.

In contrast to the previous exercises, the increase in mean arterial pressure during bicycling was not related to the change in heart rate (r=0.05, n.s.). The increase in heart rate was also unrelated to the resting MAP (r=-0.15, n.s.), resting heart rate (r=0.10, n.s.), or LBRS (r=0.06, n.s.). Older subjects had significantly smaller changes in heart rate with age (r=-0.32, P<0.02) which could be predicted by the regression equation

$$(\Delta HR) = 71.30-(0.43)\times(age) \quad (31)$$

with a standard error of the regression equation of 0.17.

The relative increase in heart rate during bicycling, however, was unrelated to the baseline heart rate (r=-0.18, n.s.), age (r=-0.17, n.s.), or LBRS (r=0.09, n.s.).

The relative, or percentage, increase in MAP was again unrelated to the relative increase in heart rate (r=0.17, n.s.).

Partial correlation coefficients for the independent effect of each of these variables on mean arterial pressure and heart rate during bicycle exercise are noted in Tables 5-14 and 5-15.

Comparison of the four exercises

Significant increases in blood pressure and heart rate were attained with all four exercises (P<0.001) (Tables 5-2 to 5-5; Fig. 5-21). The increase in mean arterial pressure was about 20%

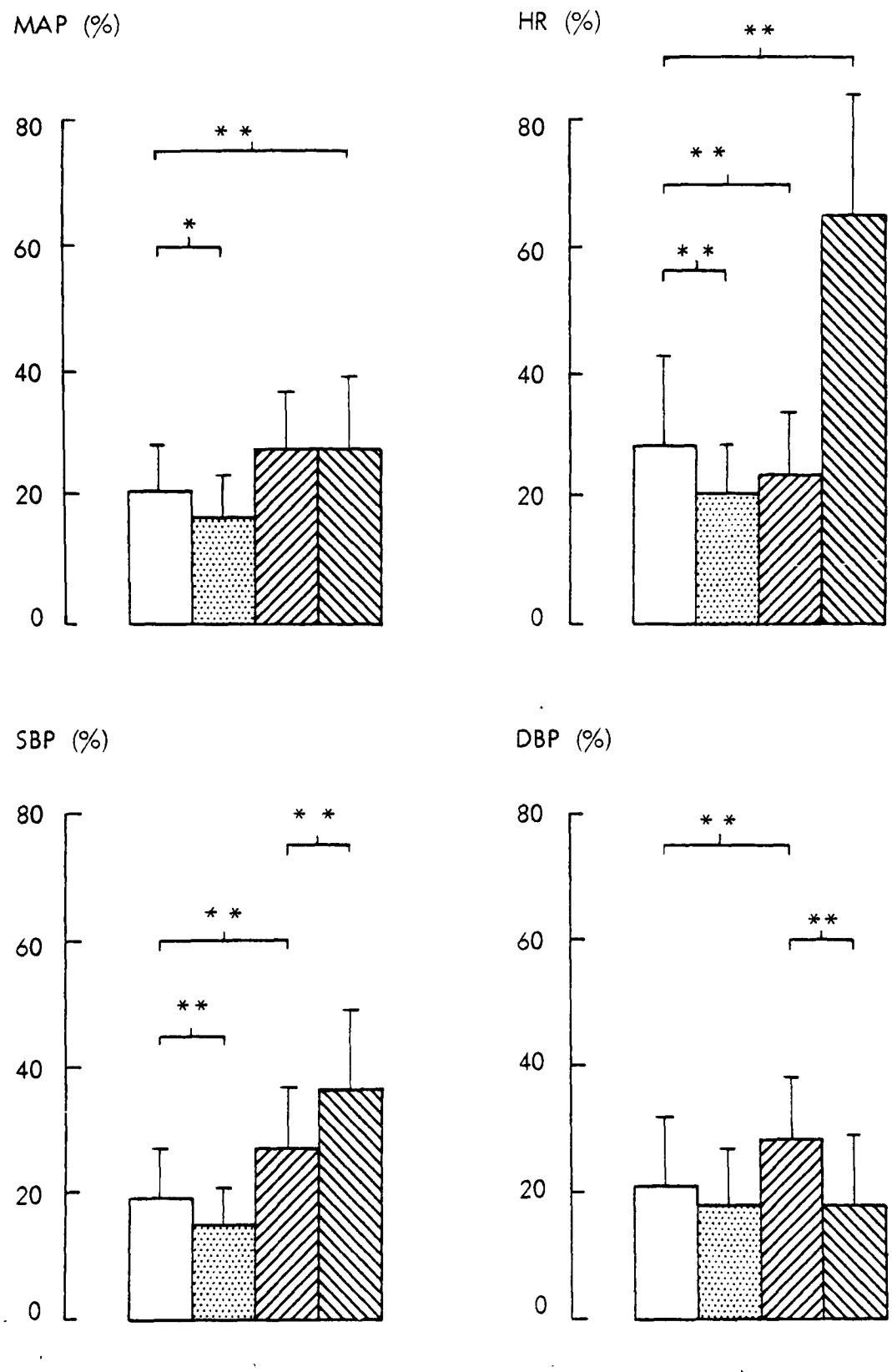

Fig. 5-21 Relative increases in mean arterial pressure (MAP), heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) during mental arithmetic □ , a reaction time test ▒ , isometric ▨ , and bicycling ▨ exercise.

*P<0.05 **P<0.001

Table 5-16

t-statistics from simultaneous multiple comparisons of the relative (or percentage) increases in mean arterial pressure (MAP), heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) during mental arithmetic (MA), reaction time testing (RTT), isometric exercise (ISO), and bicycle exercise (BIKE). Probability value according to the Bonferroni method.

	RTT	ISO	BIKE
MAP			
MA	2.88*	5.23****	4.45****
RTT	-	9.54****	7.80****
ISO	-	-	0.05
HR			
MA	4.84****	3.00*	11.94****
RTT	-	1.50	16.25****
ISO	-	-	16.55****
SBP			
MA	4.04****	5.30****	7.10***
RTT	-	10.56****	9.77****
ISO	-	-	4.27****
DBP			
MA	1.68	-4.70****	0.41
RTT	-	-7.32****	1.07
ISO	-	-	4.02****

* P<0.05
** P<0.01
*** P<0.005
**** P<0.001

with the mental exercises and about 30% with the physical exercises (difference $P<0.001$). During mental arithmetic, the reaction time test, and isometric exercise, the increase in mean arterial pressure was reflected in similar changes in systolic and diastolic pressure.

Simultaneous multiple paired comparisons of the relative changes in blood pressure and heart rate during each exercise were performed. These data appear in Table 5-16. Isometric and bicycle exercise increased mean arterial pressure to the same extent (28%) but in different ways. During bicycle exercise systolic blood pressure increased by 36%, diastolic by 18%, and heart rate by 65%; during isometric exercise systolic blood pressure increased by 27%, diastolic by 28%, and heart rate by 24% ($P<0.001$ v. bicycle exercise for all values, using the Bonferroni method). Mental arithmetic did not increase blood pressure to the same extent as isometric exercise (21% v. 28%, $P<0.001$, using the Bonferroni method), but increased heart rate more (29% v. 24%, $P<0.05$, using the Bonferroni method). The reaction time test had the least effect on blood pressure and heart rate.

Plasma noradrenaline concentrations

Three hundred and thirty samples of venous blood were obtained. Ten were improperly stored, and had to be discarded. Mean plasma noradrenaline concentrations in the remainder, along with their standard deviations, are presented in Tables 5-17 to 5-19.

Plasma noradrenaline concentrations at rest

Three resting blood samples were withdrawn: one before mental arithmetic (547.3±297.3 pg/ml; n=10), when the patients were supine,

Table 5-17

Plasma noradrenaline concentrations (PNA), mean arterial pressure (MAP), and heart rate (HR) before, during, and three minutes after the end of mental arithmetic (mean ±S.D.).

	Rest	Exercise	Recovery
n=	10	10	10
PNA (pg/ml)	547.3±297.3	517.5±250.5	480.8±204.7
Δ from rest	-	-29.8±210.7	-66.5±125.7
%Δ from rest	-	-5.4	-12.2
Δ from exercise	-	-	-36.7±155.9
%Δ from exercise	-	-	-7.1
MAP (mm Hg)	107.9±18.1	127.4±18.4	108.7±17.5
Δ from rest	-	19.5± 9.1*	0.8± 3.8
%Δ from rest	-	18.1 *	0.7
Δ from exercise	-	-	-18.7± 6.9*
%Δ from exercise	-	-	-14.7 *
HR (bpm)	68.9±6.7	93.2±13.2	70.6± 8.1
Δ from rest	-	24.4±11.5*	1.7± 3.9
%Δ from rest	-	35.0 *	2.5
Δ from exercise	-	-	-22.6±10.4*
%Δ from exercise	-	-	-24.2 *

* P<0.001

Table 5-18

Plasma noradrenaline concentrations (PNA), mean arterial pressure (MAP), and heart rate (HR) before, during, and three minutes after the end of isometric exercise (mean ±S.D.).

	Rest	Exercise	Recovery
n=	50	50	48
PNA (pg/ml)	683.9±253.2	741.3±252.8	780.3±352.5
Δ from rest	-	57.4±226.5	88.3±389.8
%Δ from rest	-	8.4	12.9
Δ from exercise	-	-	-31.0±283.4
%Δ from exercise	-	-	-4.2
MAP (mm Hg)	115.2±18.4	148.2±21.1	116.3±21.4
Δ from rest	-	33.0±10.4*	1.0± 8.0
%Δ from rest	-	28.6 *	0.9
Δ from exercise	-	-	-31.9±11.5*
%Δ from exercise	-	-	-21.5 *
HR (bpm)	76.1±9.2	94.9±12.9	77.3±10.1
Δ from rest	-	18.8± 8.8*	1.2± 4.8
%Δ from rest	-	24.7 *	1.6
Δ from exercise	-	-	-17.6± 9.7*
%Δ from exercise	-	-	-18.5 *

* P<0.001

Table 5-19

Plasma noradrenaline concentrations (PNA), mean arterial pressure (MAP), and heart rate (HR) before, during, and three minutes after the end of bicycle exercise (mean ±S.D.).

	Rest	Exercise	Recovery
n=	49	48	45
PNA (pg/ml)	644.7±228.1	1150.6±461.6	939.6±265.6
Δ from rest	-	506.0±438.4*	289.7±196.4*
%Δ from rest	-	78.5 *	44.9 *
Δ from exercise	-	-	-222.6±364.4*
%Δ from exercise	-	-	-45.0 *
MAP (mm Hg)	114.2±20.2	146.5±25.6	118.8±19.0
Δ from rest	-	32.4±13.2*	4.7± 7.4*
%Δ from rest	-	28.4 *	4.1 *
Δ from exercise	-	-	-27.7±12.9*
%Δ from exercise	-	-	-18.9 *
HR (bpm)	77.3±9.1	127.5±18.6	94.8±15.0
Δ from rest	-	50.1±14.2*	17.4± 9.6*
%Δ from rest	-	64.8 *	22.5 *
Δ from exercise	-	-	-32.7± 9.6*
%Δ from exercise	-	-	-25.6 *

* P<0.001

Table 5-20

Simultaneous multiple comparisons of baseline plasma noradrenaline concentrations before mental arithmetic (MA), isometric exercise (ISO), and bicycle exercise (BIKE). Paired t-statistic (n=10 in all groups). No significant differences when probability calculated by Bonferroni method.

	MA	ISO
ISO	-1.83	-
BIKE	2.33	-2.43

Table 5-21

Partial correlation coefficients for the independent effects of age, mean arterial pressure, heart rate, rate-pressure product, and LBRS on plasma noradrenaline concentrations (PNA) at rest (n=49). None of these correlation coefficients achieve statistical significance.

	PNA
Age	-0.10
MAP	0.122
HR	-0.06
(MAP)×(HR)	-0.09
LBRS	-0.03

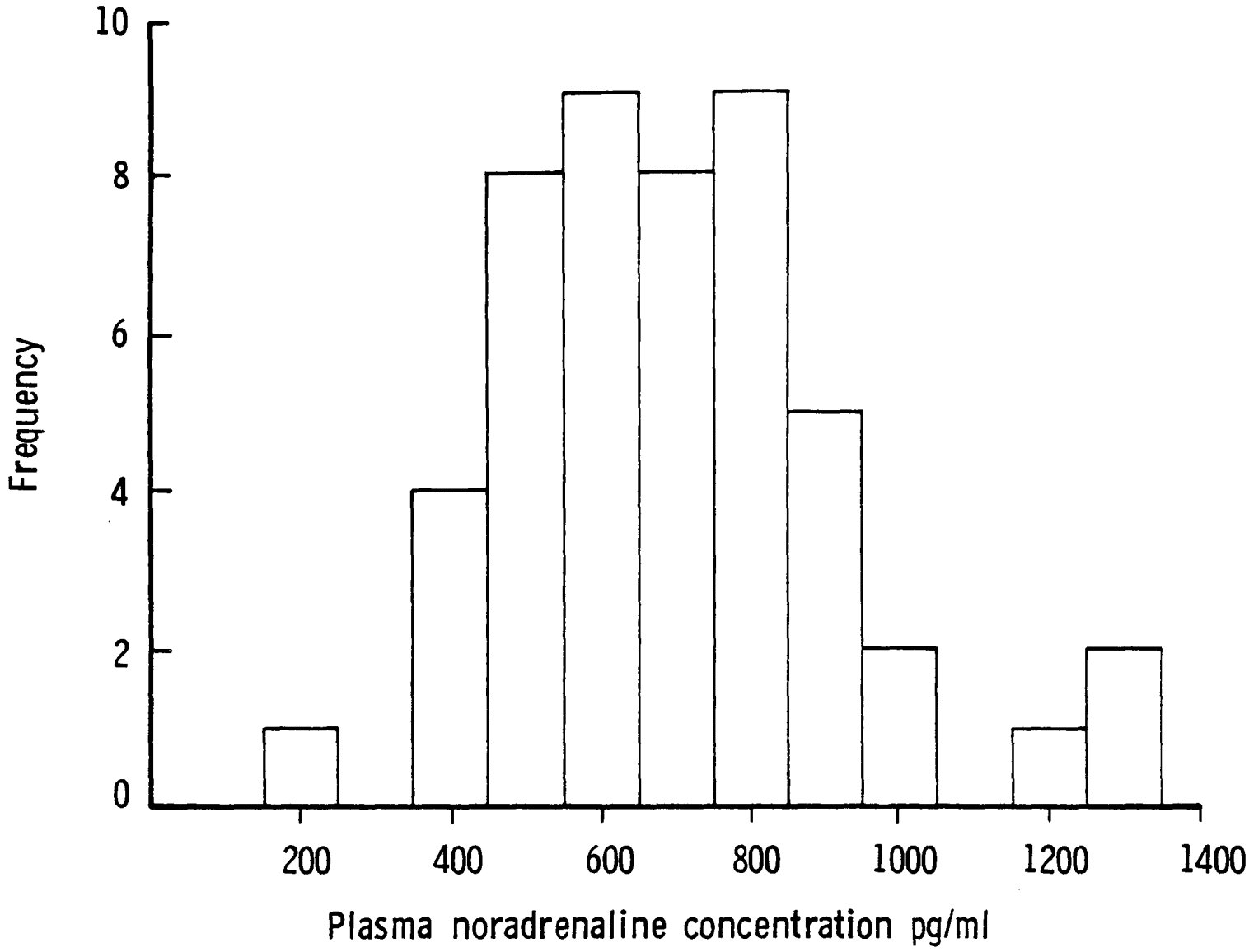

Fig. 5-22 The frequency distribution of plasma noradrenaline concentration in resting subjects (n=49).

Fig. 5-23 Relationship between resting plasma noradrenaline concentration and age (n=49).

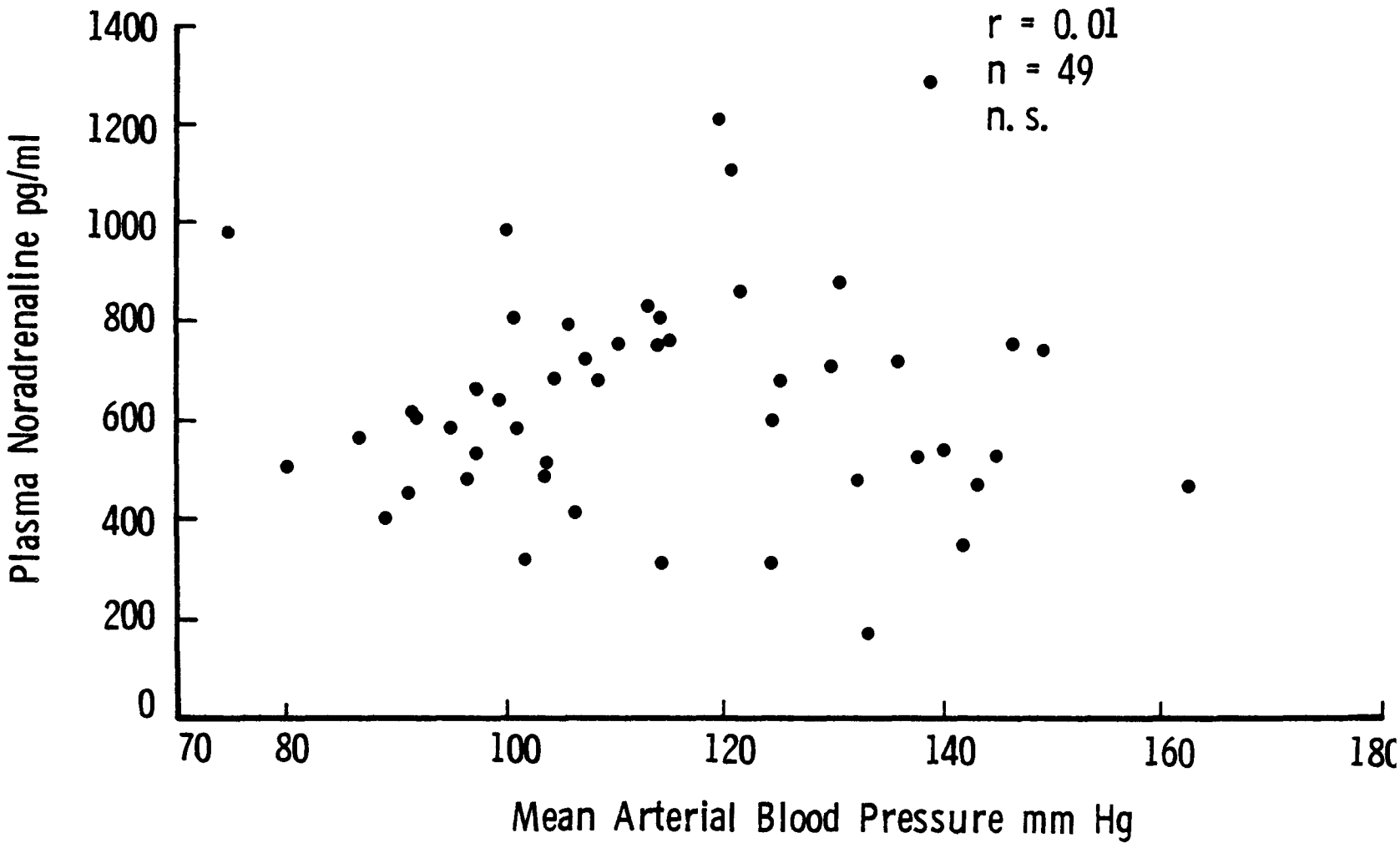

Fig. 5-24 Relationship between resting plasma noradrenaline concentration and mean arterial pressure (n=49).

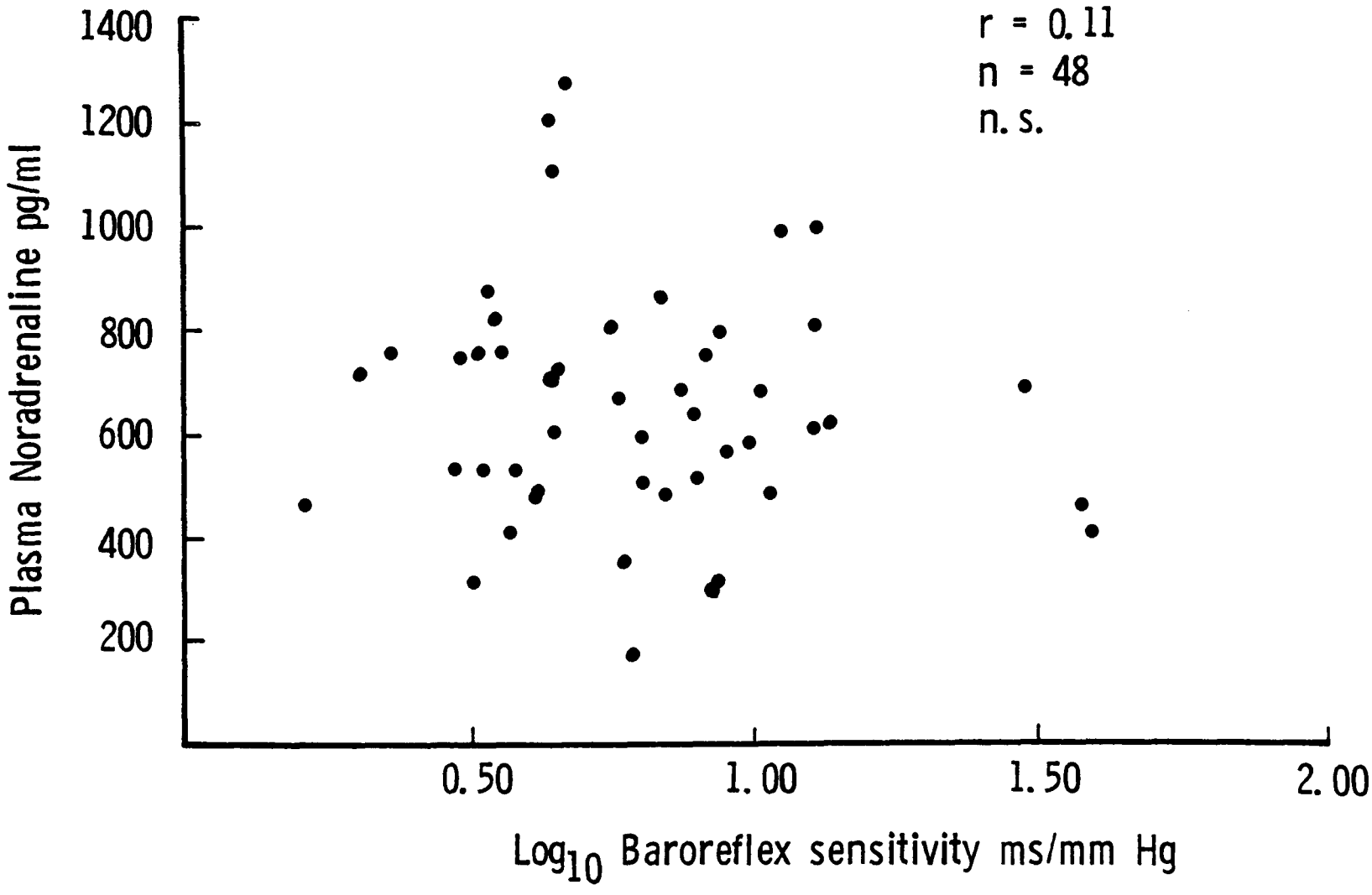

Fig. 5-25 Relationship between resting plasma noradrenaline concentration and baroreflex sensitivity (n=48).

and the other two with the subjects seated, awaiting the isometric (683.9±253.2 pg/ml; n=50), and the bicycling (641.7±226.7 pg/ml; n=49) exercises.

Resting plasma noradrenaline concentrations before mental arithmetic, isometric and bicycle exercise in the 10 subjects studied during all three exercises did not differ significantly from each other (547.3±297.3 pg/ml, 686.2±243.2 pg/ml, and 683.0±238.7 pg/ml respectively), owing to the large variance in these measurements (Table 5-20). The values obtained in the 49 patients sitting awaiting bicycle exercise were therefore used to represent baseline plasma noradrenaline concentrations (PNA) in these calculations.

Resting plasma noradrenaline concentrations were normally distributed (Fig. 5-22), and did not correlate with age (r=0.03, n.s., Fig. 5-23), systolic (r=0.09, n.s.), mean (r=0.01, n.s., Fig. 5-24), or diastolic (r=0.08, n.s.) blood pressure, resting heart rate (r=0.15, n.s.), pulse interval (r=0.12, n.s.), the product of mean arterial pressure and heart rate (r=0.08, n.s.), or LBRS (r=-0.11, n.s., Fig. 5-25). Neither multiple regression analysis nor partial correlation coefficients detected a relationship between any of these variables and PNA. The partial correlation coefficients for the independent effects of each of these variables on resting plasma noradrenaline concentrations are noted in Table 5-21.

Logarithmic transformation of PNA did not improve the correlation between this variable and age (r=0.03, n.s.), systolic (r=-0.12, n.s.), mean (r=0.05, n.s.), and diastolic (r=0.02, n.s.) pressures, heart rate (r=0.14, n.s.), pulse interval (r=-0.11, n.s.), the product of MAP and HR (r=0.04, n.s.) or LBRS (r=-0.09, n.s.). Therefore, the original values for noradrenaline were retained in subsequent calculations.

Plasma noradrenaline concentrations during mental arithmetic

Mental arithmetic increased mean arterial pressure 18%, from 107.9±18.1 mm Hg to 127.4±18.4 mm Hg ($P<0.001$), and increased heart rate 35% from 68.9±6.7 bpm to 93.2±13.2 bpm ($P<0.001$) in these 10 patients. Plasma noradrenaline concentration, which rose in 3 subjects and fell in 7, fell overall from 547.3±297.3 pg/ml to 517.5±250.5 pg/ml (n.s.) (Table 5-17). Exercise plasma noradrenaline concentrations (EPNA) were correlated with resting concentrations ($r=0.72$, $P<0.01$) but bore no relation to either resting ($r=-0.03$, n.s.) or exercising mean arterial pressures ($r=0.20$, n.s.), exercise heart rates ($r=0.35$, n.s.), age ($r=0.10$, n.s.) or LBRS ($r=0.08$, n.s.). EPNA were related to resting PNA by the equation

$$EPNA = 187.1+(0.72)\times(PNA) \qquad (32)$$

with 0.21 as standard error of the regression coefficient.

The relative change in plasma noradrenaline (%ΔPNA) during mental arithmetic was not related to the relative increase in mean arterial pressure ($r=0.49$, $P<0.08$), the change in heart rate ($r=0.10$, n.s.), age ($r=0.40$, n.s.) or LBRS ($r=-0.06$, n.s.). Multiple regression analysis did not assist in the interpretation of these data.

Mean arterial pressure and heart rate returned to baseline values three minutes after the end of mental arithmetic, while PNA continued to fall by 36.7 pg/ml, to 480.8±204.7 (n.s.) (Table 5-17).

Plasma noradrenaline concentrations during isometric exercise

Mean arterial pressure rose 29% during handgrip, from 115.2±18.4 mm Hg, to 148.2±21.1 mm Hg ($n=50$; $P<0.001$). Heart rate increased by 25%, from 76.1±9.2 bpm to 94.9±12.9 bpm ($P<0.001$), and plasma

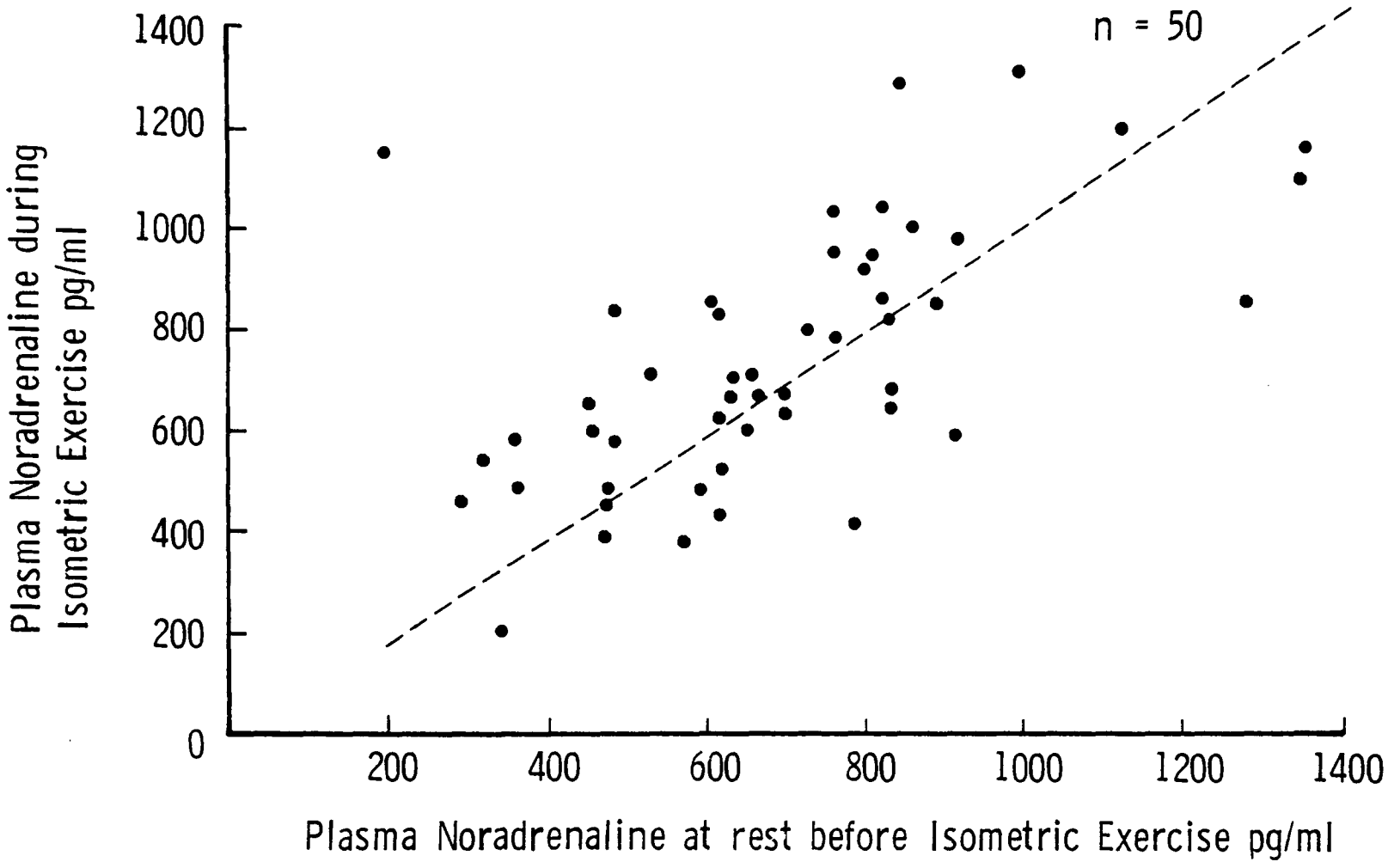

Fig. 5-26 Relationship between plasma noradrenaline concentration during, and at rest before isometric exercise (n=50). Line of identity displayed.

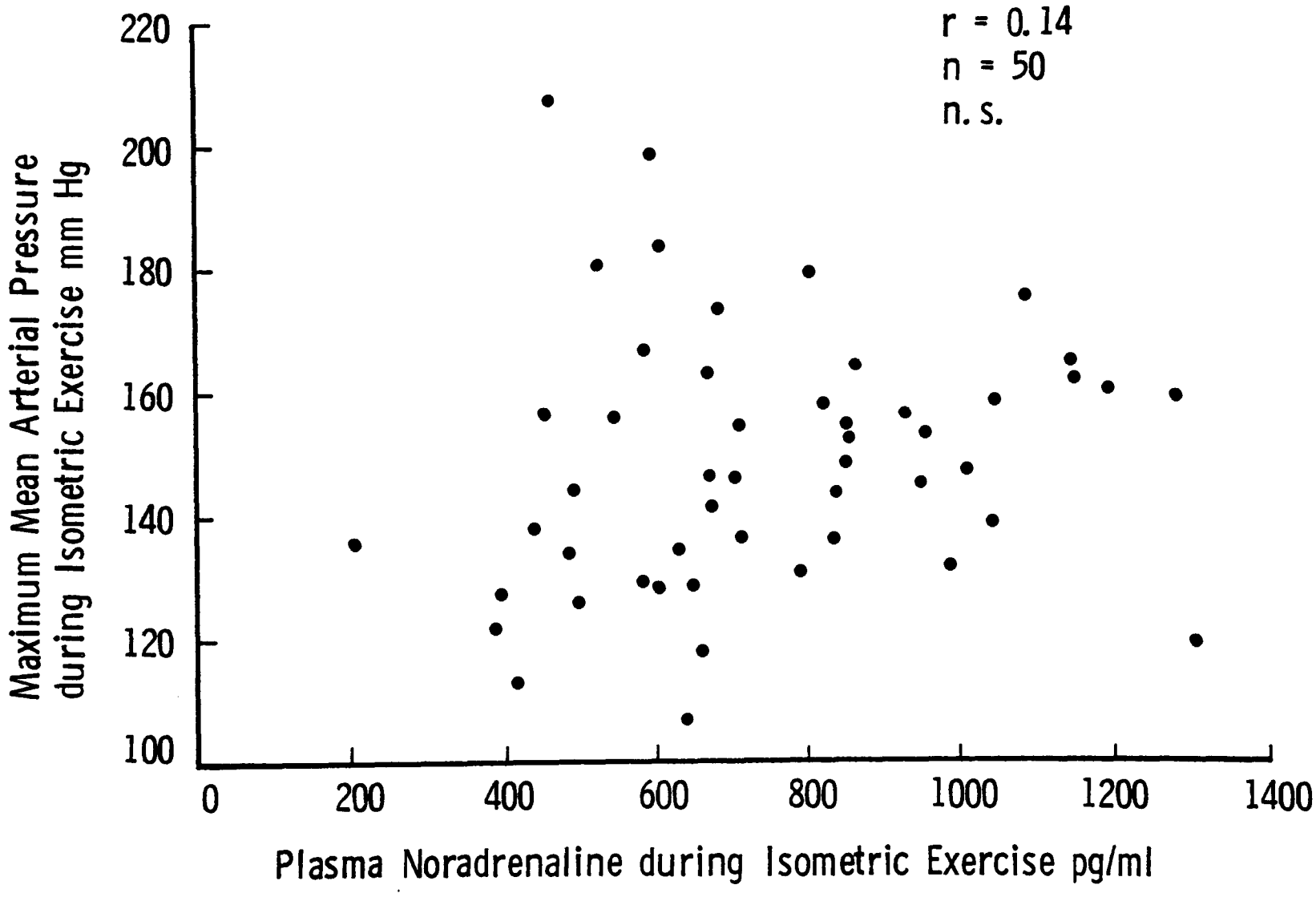

Fig. 5-27 Relationship between the maximum mean arterial pressure and plasma noradrenaline concentration during isometric exercise (n=50).

Table 5-22

Partial correlation coefficients for the independent effects of resting plasma noradrenaline concentration (PNA), age, resting and maximum mean arterial pressure (MAP, MMAP), resting and maximum heart rate (HR, MHR), and baroreflex sensitivity (LBRS) on plasma noradrenaline during isometric exercise (EPNA) and the absolute (ΔPNA) and relative (%ΔPNA) increases in PNA during isometric exercise (n=50).

	EPNA (pg/ml)	ΔPNA (pg/ml)	%ΔPNA
PNA (pg/ml)	0.60***	-0.35*	-0.38**
Age	0.01	0.07	0.09
MAP (mm Hg)	-0.14	-0.12	-0.04
MMAP (mm Hg)	0.18	0.18	0.15
HR (bpm)	0.05	0.14	0.08
MHR (bpm)	-0.01	0.01	-0.02
LBRS	0.05	0.11	0.11

* P<0.05
** P<0.01
*** P<0.001

noradrenaline concentrations by 8.4%, from 683.9±253.2 pg/ml to 741.3±252.8 pg/ml (0.10>P>0.08) (Table 5-18; Fig. 5-26). An increase was observed in 23 patients, no change in 9, and a decrease in 18. Due to this similarity in resting and exercising PNA, there was again a positive correlation between these two variables (r=0.60, P<0.00001) (Fig. 5-26). Mean arterial pressure, whether baseline (r=0.01, n.s.), or exercise (r=0.14, n.s.) (Fig. 5-27), exercise heart rate (r=0.14, n.s.), age (r=0.07, n.s.), and LBRS (r=-0.01, n.s.) were not related to exercise plasma noradrenaline concentrations, either during simple correlations, partial correlations, or multiple regression analysis (Table 5-22). EPNA was related to resting PNA by the equation:

$$EPNA = 331.9+(0.60)\times(PNA) \qquad (33)$$

EPNA was poorly correlated with the systolic (r=0.10, n.s.) or diastolic (r=0.15, n.s.) pressures achieved during isometric contraction.

The relative increase in plasma noradrenaline (%ΔPNA) during isometric exercise was independent of either age (r=0.01) or LBRS (r=0.01, n.s.), and unrelated to the relative increase in mean (r=-0.02, n.s.), systolic (r=0.02, n.s.) or diastolic (r=-0.02, n.s.) pressures, the absolute increase in mean arterial pressure (r=0.04, n.s.) or the change in heart rate (r=-0.05, n.s.). None of these variables achieved a statistically significant relationship with %ΔPNA or ΔPNA with partial correlations or multiple regression analysis (Table 5-22).

Three minutes after the sphygmomanometer bulb was released, blood pressure and heart rate returned to baseline levels. Plasma noradrenaline, on the other hand, was 13% higher than the basal

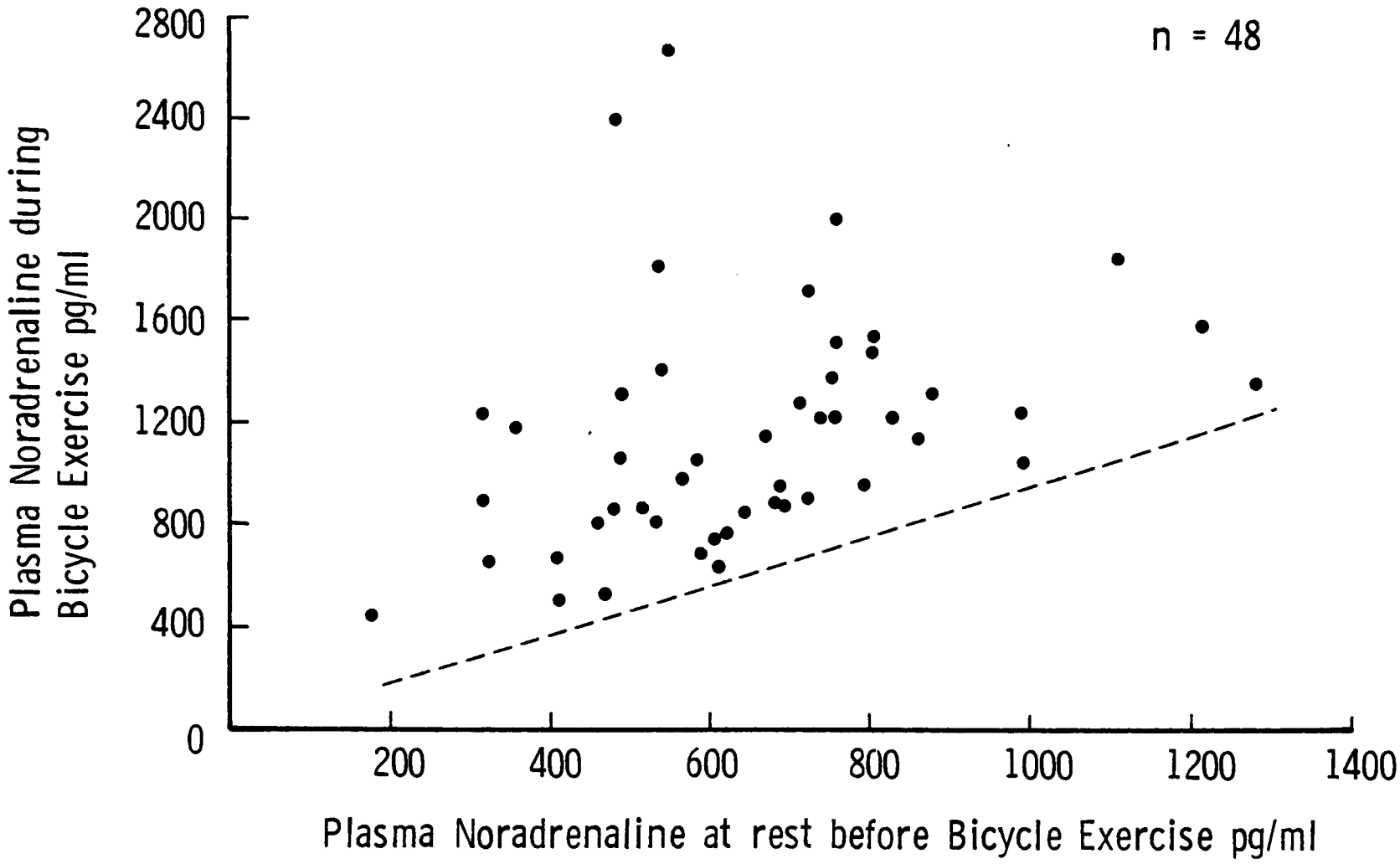

Fig. 5-28 Relationship between plasma noradrenaline concentrations during, and at rest before bicycle exercise (n=48). Line of identity displayed.

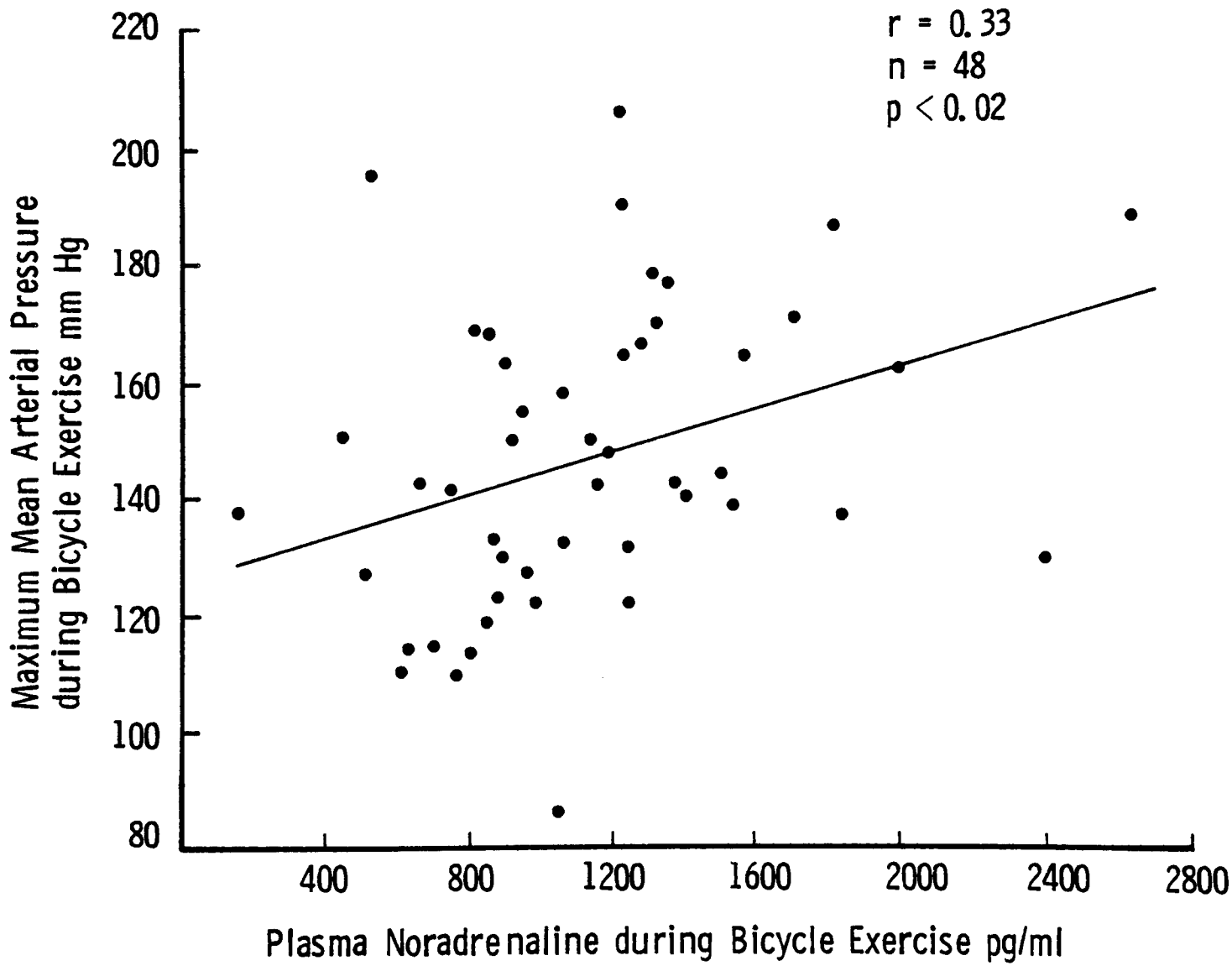

Fig. 5-29 Relationship between maximum mean arterial pressure and plasma noradrenaline concentrations during bicycle exercise (n=48).

levels, 780.3±352.5 pg/ml (Table 5-18), but this increase was only significant at the 12% level.

Plasma noradrenaline concentrations during bicycle exercise

The 48 patients studied during bicycle exercise had similar changes in mean arterial pressure (28%, from 114.2±20 mm Hg to 146.5±25.6 mm Hg, P<0.001), but greater increases in heart rate (65%, from 77.3±9.1 bpm to 127.5±18.6 bpm, P<0.001) when compared with isometric exercise. In contrast, plasma noradrenaline concentrations rose 78% from 644.7±228.1 pg/ml at rest to 1150.6±461.6 pg/ml while bicycling (P<0.001) (Table 5-19). Plasma noradrenaline concentrations rose in all subjects (Fig. 5-28). EPNA was related to resting PNA (r=0.35, P<0.01) (Fig. 5-28), maximum MAP (r=0.33, P<0.02) (Fig. 5-29), and exercise heart rate (r=0.28, P<0.03), but not to resting mean arterial pressure (r=0.17, n.s.) nor age (r=0.20, n.s.). Subjects with better baroreflexes tended to have lower EPNA (r=0.24, P<0.06) (Fig. 5-30). When multiple regression analysis was performed on these data, resting PNA (F=6.901, P<0.02), maximum MAP (F=6.260, P<0.02), and maximum heart rate (F=4.567, P<0.05) had significant independent effects on EPNA, according to the regression equation:

$$EPNA = (0.60)\times(PNA)+(7.06)\times(MHR)+(4.34)\times(MMAP)-803.1 \qquad (34)$$

with 0.23, 2.82, and 2.03 as standard errors of the regression coefficients b_1, b_2, and b_3.

EPNA was also correlated with the maximum systolic (r=0.27, P<0.04), and maximum diastolic (r=0.28, P<0.03) blood pressures during bicycling.

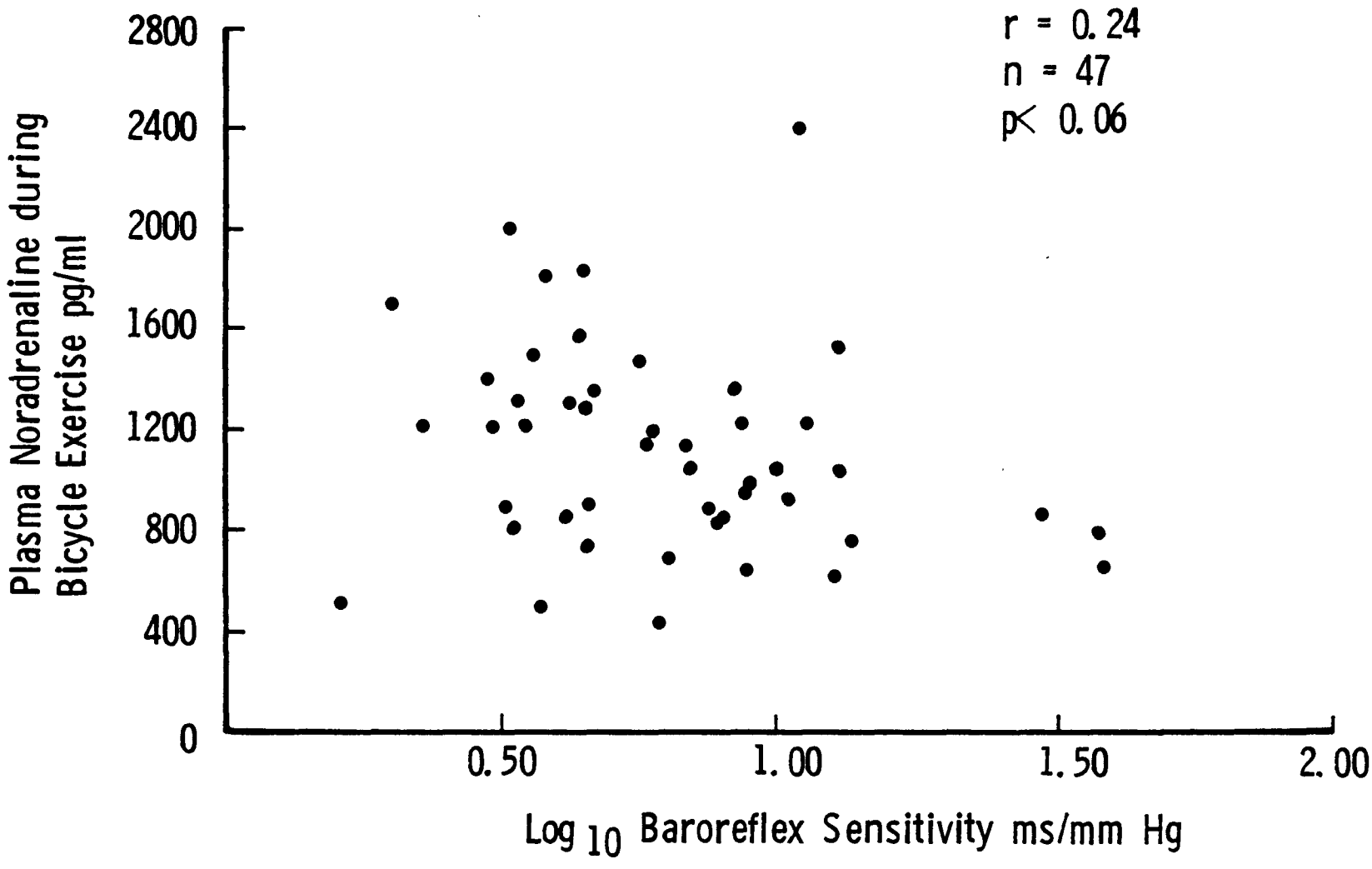

Fig. 5-30 Relationship between plasma noradrenaline concentration during bicycle exercise and baroreflex sensitivity (n=47).

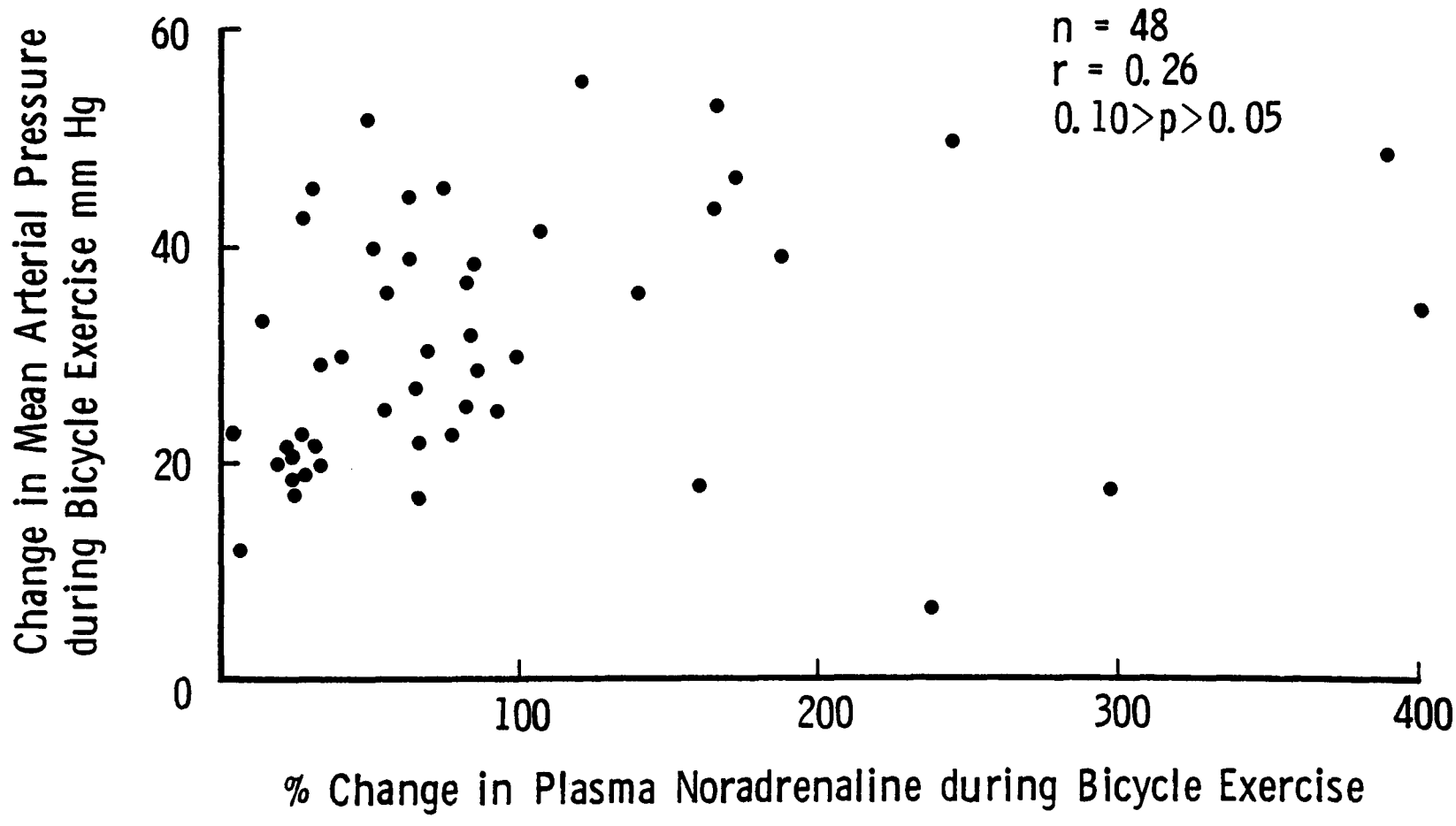

Fig. 5-31 Relationship between change in mean arterial pressure and the relative increase in plasma noradrenaline during bicycle exercise (n=48)。

Table 5-23

Partial correlation coefficients for the independent effects of resting plasma noradrenaline (PNA), age, resting and maximum mean arterial pressure (MAP, MMAP), resting and maximum heart rate (HR, MHR), and baroreflex sensitivity (LBRS) on plasma noradrenaline during bicycle exercise (EPNA) and the absolute (ΔPNA) and relative (%ΔPNA) increases in PNA during bicycle exercise (n=48).

	EPNA (pg/ml)	ΔPNA (pg/ml)	%ΔPNA
PNA (pg/ml)	0.35*	-0.31*	-0.57***
Age	0.03	0.03	0.08
MAP (mm Hg)	-0.27*	-0.27*	-0.13
MMAP (mm Hg)	0.33*	0.33*	0.21
HR (bpm)	0.03	0.03	0.03
MHR (bpm)	0.28*	0.28*	0.28*
LBRS	0.00	0.00	0.08

* P<0.05
** P<0.01
*** P<0.001

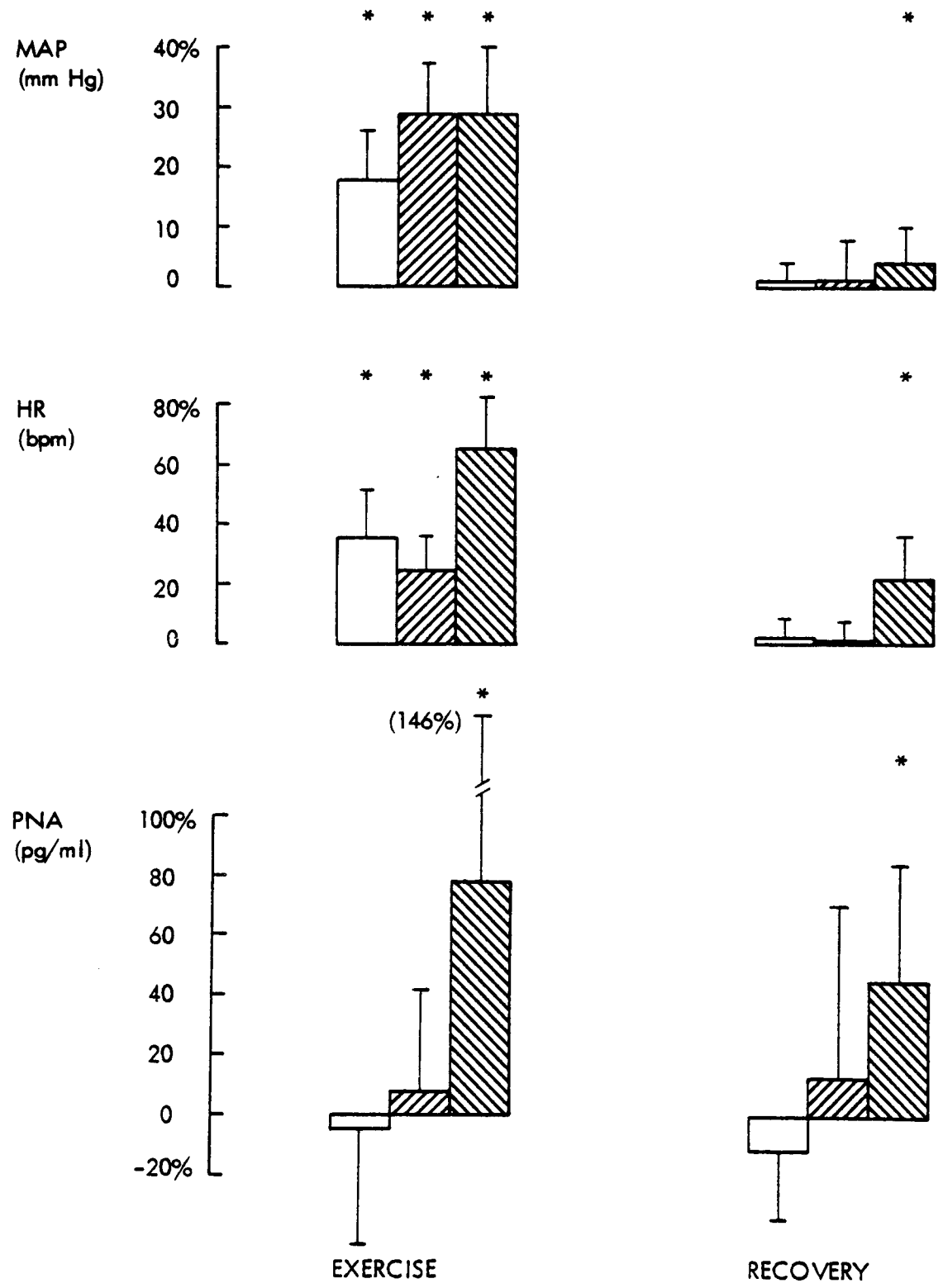

Fig. 5-32 Relative increases in mean arterial pressure (MAP), heart rate (HR), and plasma noradrenaline concentrations (PNA), during and three minutes following mental arithmetic ☐ (n=10; 10), isometric ▨ (n=50; 48), and bicycling ▧ (n=48; 45) exercise (X±S.D.) (*P<0.001).

The relative increase in plasma noradrenaline during bicycle exercise (%ΔPNA) was unrelated to the absolute change in mean arterial pressure (r=0.26, 0.10>P>0.05) (Fig. 5-31) and appeared to be independent of the relative increase in mean arterial (r=0.17, n.s.), systolic (r=0.02, n.s.), or diastolic (r=0.09, n.s.) pressures, the relative increase in heart rate (r=0.10, n.s.), age (r=0.14, n.s.), or LBRS (r=-0.08) and could not be predicted by stepwise multiple regression analysis incorporating all of these variables. Partial correlation coefficients for the independent effect of each of these variables on plasma noradrenaline concentrations during bicycle exercise are noted in Table 5-23. The relative increase in PNA was significantly related to the maximum heart rate achieved during bicycle exercise (r=0.28, P<0.05).

Three minutes after bicycling ended, mean arterial pressure (118.8±19.0 mm Hg), and heart rate (94.8±15.0 bpm) remained significantly elevated from the baseline (<P.001), although they were lower than they had been during exercise (P<0.001). PNA were also elevated (939.6±265.6 pg/ml, P<0.001 v. resting and exercise PNA) (Table 5-19).

Plasma noradrenaline concentrations, heart rate, and arterial pressure during manoeuvres which increase sympathetic nervous activity

The relative increase in mean arterial pressure, heart rate, and plasma noradrenaline concentrations during each of these three exercises appear in Fig. 5-32. Significant haemodynamic changes occurred in two of these manoeuvres without increasing plasma noradrenaline concentrations. It would therefore appear that the log-linear relationship between PNA and systolic blood pressure,

Table 5-24

Plasma noradrenaline concentrations and systolic blood pressure during physical and mental activities (n=10).

	SBP (mm Hg)	PNA (pg/ml)	Log_{10}PNA
Lying	149.8±25.2	547.3±297.3	2.691±0.204
Sitting (before bike)	144.6±21.3	683.0±238.7	2.814±0.138
Mental arithmetic	175.6±26.0	517.5±250.5	2.668±0.208
Isometric exercise	183.0±22.0	670.5±226.9	2.803±0.149
Bicycling	193.2±28.9	880.4±310.4	2.923±0.142

PNA correlated with SBP, r=0.51, n.s., b=0.07, a=119.9

Log_{10}PNA correlated with SBP, r=0.45, n.s., b=92.1, a=-86.7

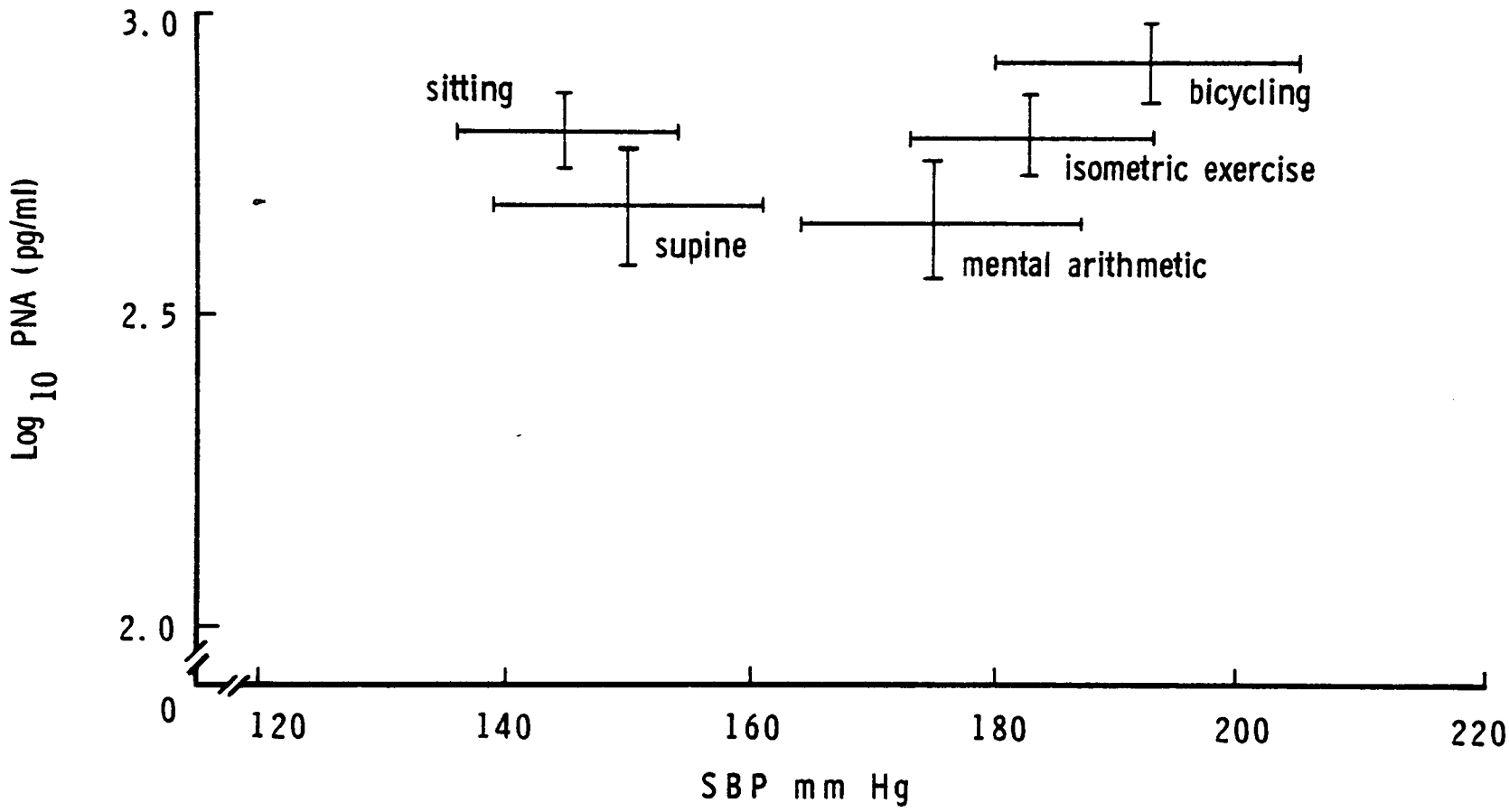

Fig. 5-33 Relationship between log plasma noradrenaline and systolic blood pressure in 10 subjects with essential hypertension at different levels of physical activity.

described by Watson, Hamilton, Reid and Littler (1979) does not apply to all situations in which activation of the sympathetic nervous system occurs. A similar analysis was performed in the 10 subjects in whom PNA was obtained in all three exercises. These data are tabulated in Table 5-24, and appear in Fig. 5-33 as means and their standard errors. Inasmuch as PNA was not altered by two of these exercises, a similar relationship was not observed.

The variability of mean arterial pressure

Short and medium term variability of arterial pressure

Ten two-minute intervals from a twenty-minute segment of the intra-arterial record at about the time of waking were selected in eight subjects in order to study short-term variability of blood pressure. This interval was chosen as blood pressure and heart rate increase significantly at this time of day in all subjects (Floras, Jones, Johnston, Brooks, Hassan and Sleight, 1978). Blood pressure and pulse interval were correlated with their respective standard deviations about each 2-minute interval (VMAP, VSBP, VRR). As can be seen from Table 5-25 and Fig. 5-34, in no instance was the relationship between arterial pressure and its variability significant. In three subjects a positive correlation between pulse interval and its variability was demonstrated (J.H., B.D., G.P.).

All of the waking hours were used to examine medium-term variability in eight subjects. Between 14 and 17 hours were obtained from each record. The mean arterial, or systolic blood pressure for each hour were correlated with its standard deviation for that interval. The variability of mean arterial pressure was unrelated to the level of blood pressure in these patients. In fact,

Table 5-25

The short-term variability (V) of mean arterial and systolic blood pressure (MAP, SBP) and pulse interval (RR): 10 values taken from 2-minute means over a 20-minute period in eight patients.

	VMAP v. MAP	VSBP v. SBP	VRR v. RR
J.H.	0.10	0.22	0.65**
B.D.	0.07	0.21	0.76***
J.W.	0.50	0.25	0.36
S.L.	-0.02	-0.08	-0.30
J.C.	0.24	0.39	0.01
E.D.	-0.31	-0.42	0.54
G.P.	-0.27	-0.06	0.95****
J.G.	0.21	0.37	0.13

Table 5-26

The medium-term variability (V) of mean arterial and systolic blood pressure (MAP, SBP) and pulse interval (RR): taken from hourly means and standard deviations over the waking hours (14-17 hours) of eight patients.

	VMAP v. MAP	VSBP v. SBP	VRR v. RR
J.H.	-0.14	0.20	-0.29
N.H.	0.22	-0.12	-0.15
B.D.	0.28	0.21	0.23
M.S.	-0.26	-0.06	0.23
T.W.	-0.38	-0.47*	0.11
R.T.	0.36	0.52**	-0.07
N.L.	0.46*	0.26	-0.34
J.W.	0.28	0.70***	0.05

* P<0.10
** P<0.05
*** P<0.01
****P<0.001

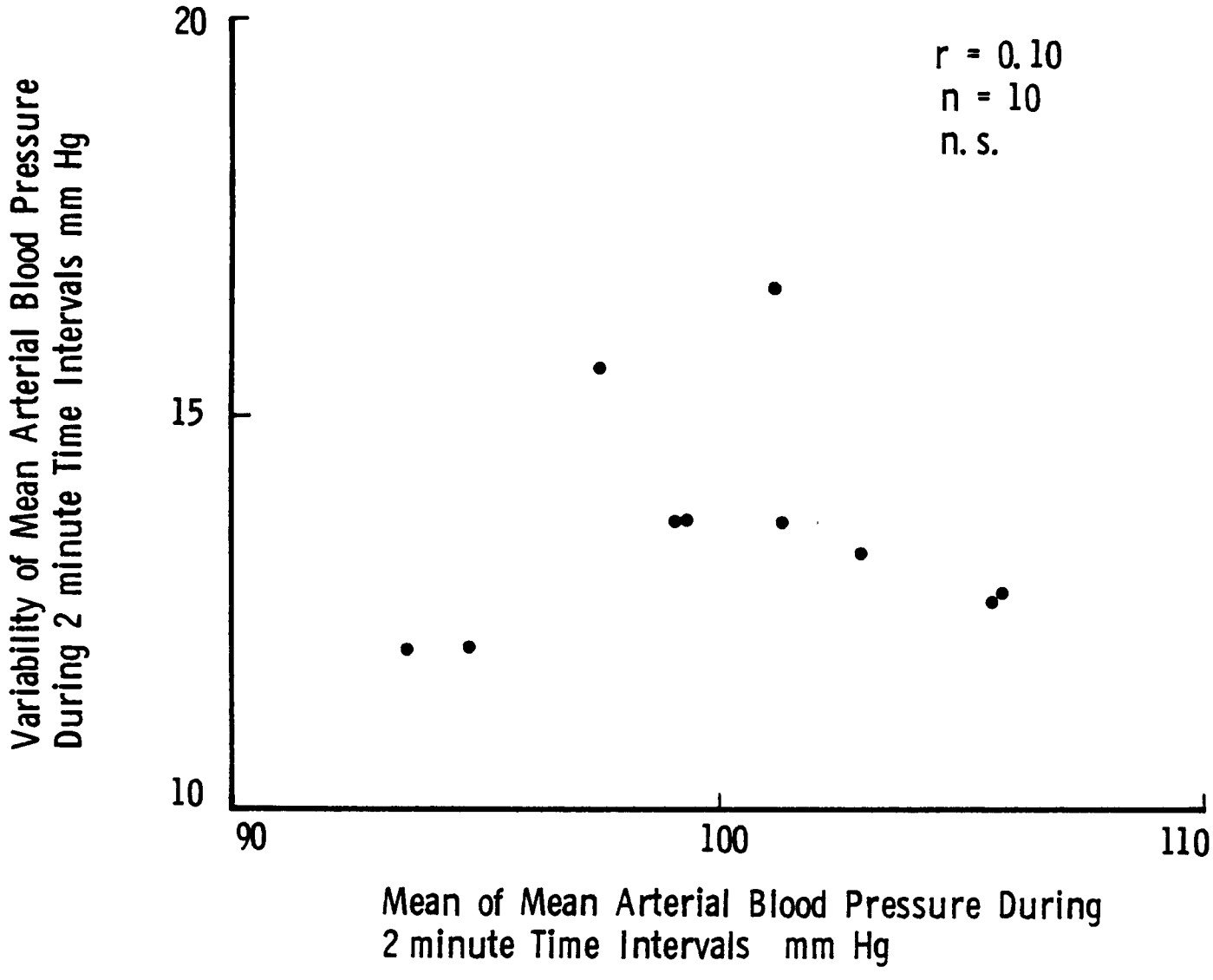

Fig. 5-34 Short term variability of mean arterial pressure (one subject).

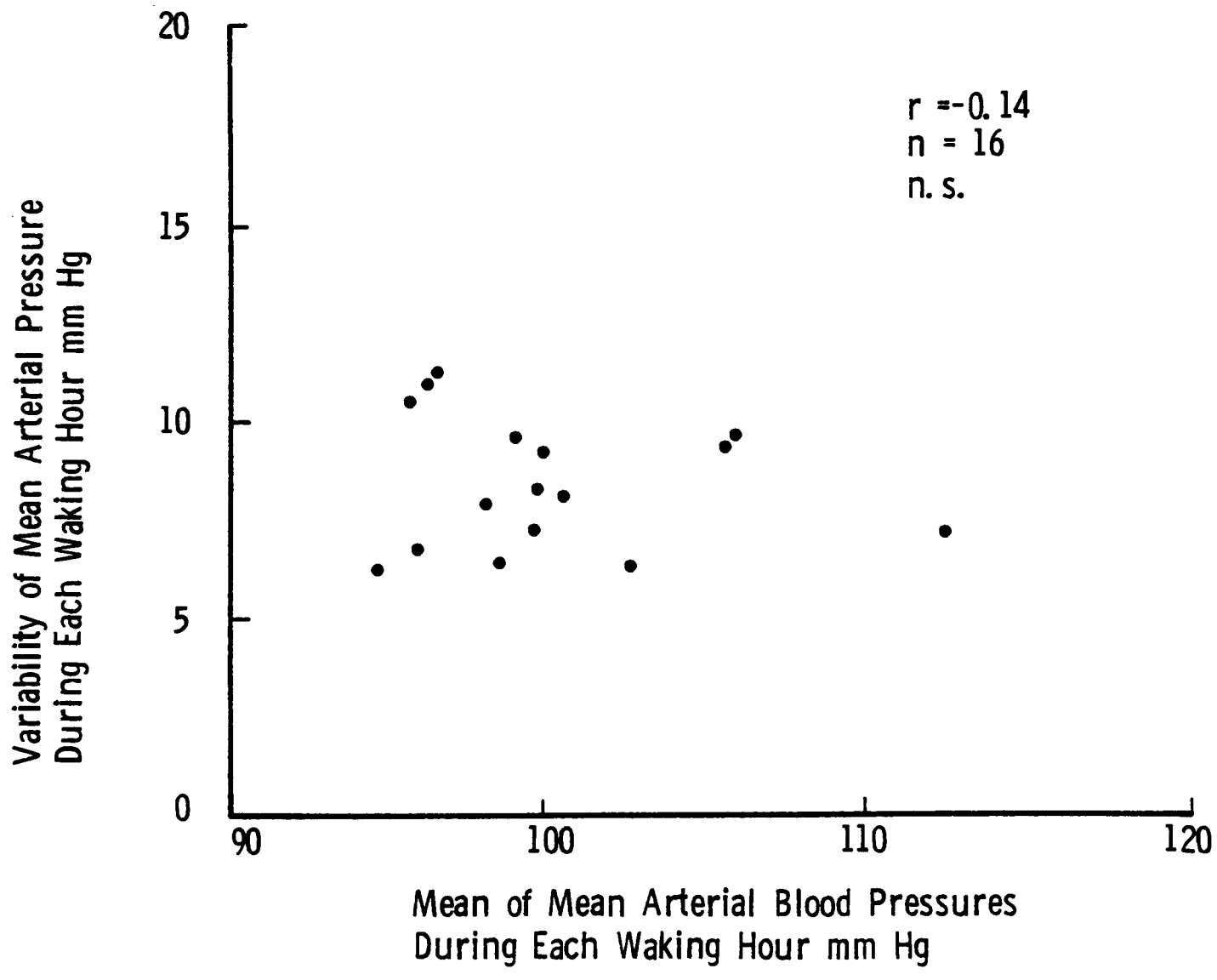

Fig. 5-35 Medium term variability of mean arterial pressure (one subject).

in three of the eight, there was an inverse (not significant) relationship. A significant positive correlation between SBP and VSBP was seen in two patients. There was no relationship between pulse interval and its variability (Table 5-26, Fig. 5-35).

The variation of ambulatory waking mean arterial pressure

The twenty-four hour ambulatory record for each patient was divided into waking and sleeping periods. For each period, frequency histograms describing the mean and standard deviation of systolic, mean, and diastolic pressures, as well as pulse intervals, were calculated from all beats, as described in Chapter 4. The standard deviation of each of these measurements, i.e. the square root of the variance, was used as the index of variability in this study.

Not all of the records were satisfactory. If a particular hour was edited, or had more than 33% of its pulses affected by damping or artefact, it was excluded when the patient's frequency histogram was calculated. Only those 56 subjects whose blood pressure records retained 9 or more hours of acceptable data after this editing were studied. Their personal details are listed in Table 5-27. Baroreflex sensitivity could not be recorded in one of these subjects (H.D.).

The average ambulatory mean arterial pressure in these 56 patients ranged from 89.9 to 159.5 mm Hg, with a mean of 118.3 mm Hg. The variability of their mean arterial pressures (VMAP) while awake ranged from 8.5 mm Hg to 20.5 mm Hg, with a mean of 13.8 mm Hg and a standard deviation of 2.4 mm Hg (Table 5-27). The variability of mean arterial pressure was positively correlated with increasing age ($r=0.32$, $P<0.01$) (Fig. 5-36), mean arterial

Table 5-27

Arterial pressure and its variability (V) and baroreflex sensitivity (LBRS) in all 56 subjects (left-hand columns) and in the 44 subjects in whom plasma noradrenaline concentrations (PNA) were obtained at rest, and during exercise (right-hand columns).

	Mean	S.D.	Mean	S.D.
Age	45.8	11.1	45.4	10.6
MAP (mm Hg)	118.3	17.9	119.0	18.5
VMAP (mm Hg)	13.8	2.4	13.5	2.3
SBP (mm Hg)	162.9	27.1	163.9	28.6
VSBP (mm Hg)	19.8	3.6	19.4	3.4
DBP (mm Hg)	91.4	13.6	92.1	13.5
VDBP (mm Hg)	11.8	1.8	11.7	1.8
LBRS	0.78	0.30	0.80	0.30
PNA (rest)	-	-	651.3	228.4
EPNA (bike)	-	-	1111.6	448.2
%ΔPNA (pg/ml)	-	-	81.0	81.2

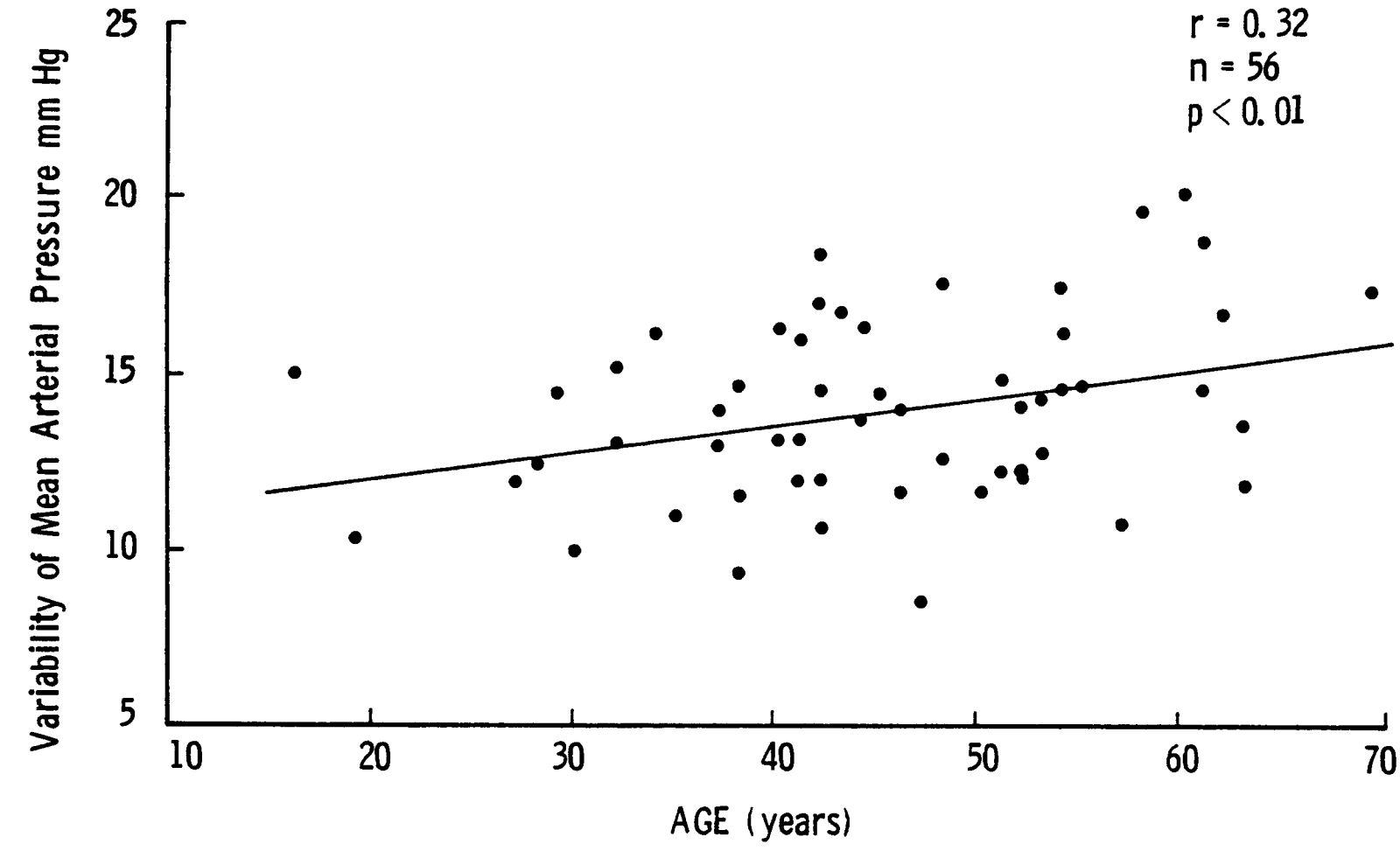

Fig. 5-36 Relationship between the variability of blood pressure and age (n=56).

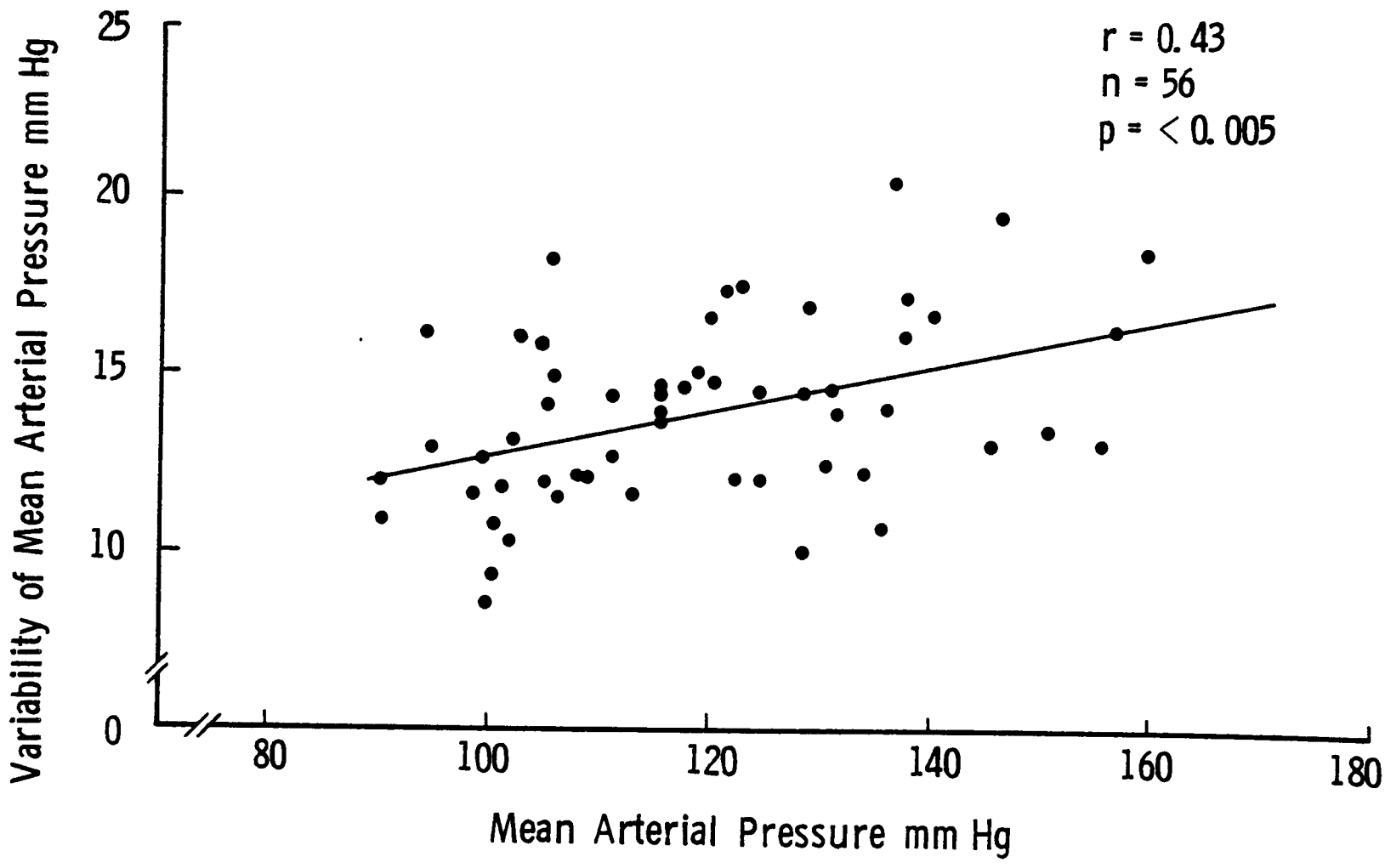

Fig. 5-37 Relationship between the variability of mean arterial pressure and average waking ambulatory mean arterial pressure (n=56).

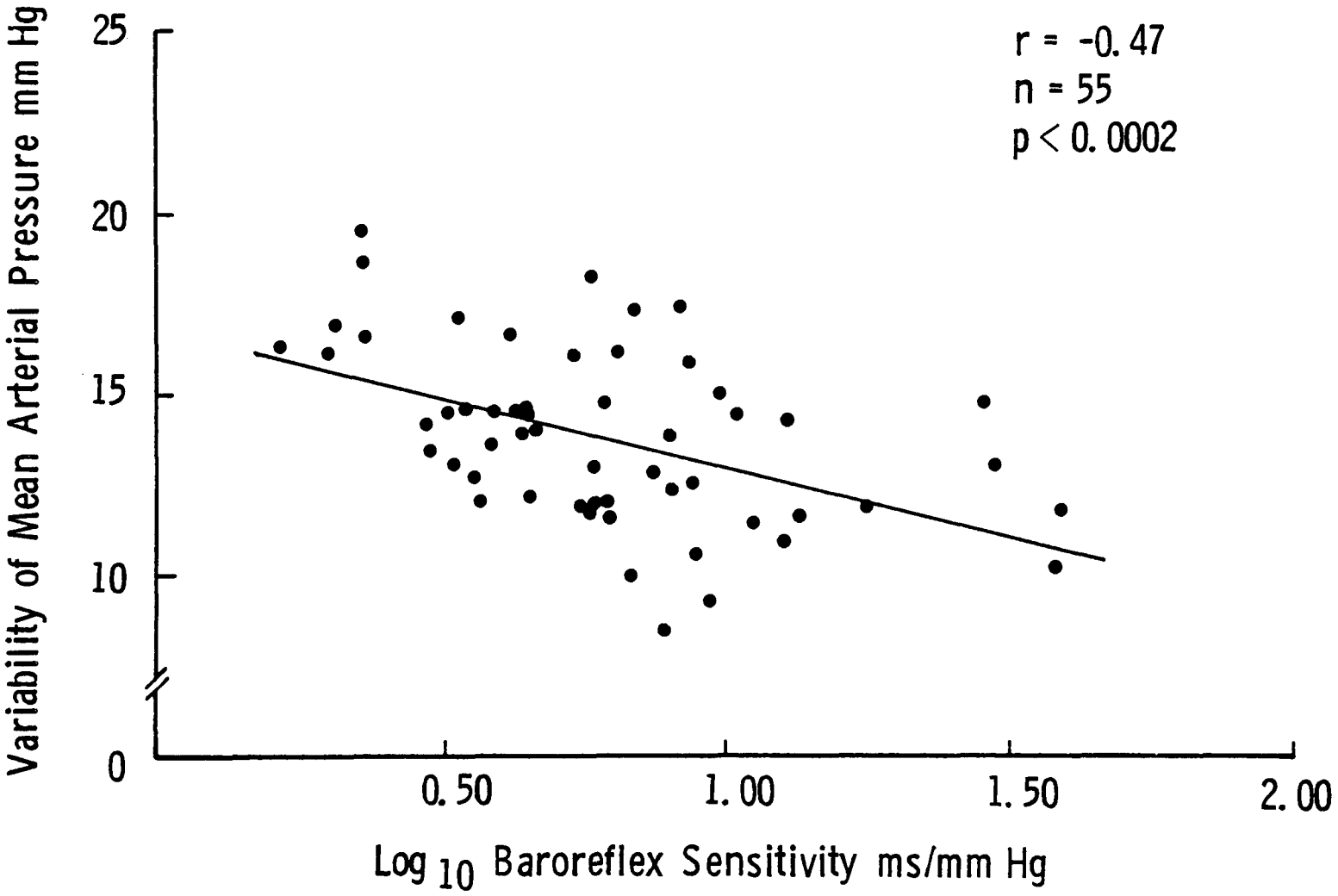

Fig. 5-38 Relationship between the variability of ambulatory waking mean arterial pressure and baroreflex sensitivity.

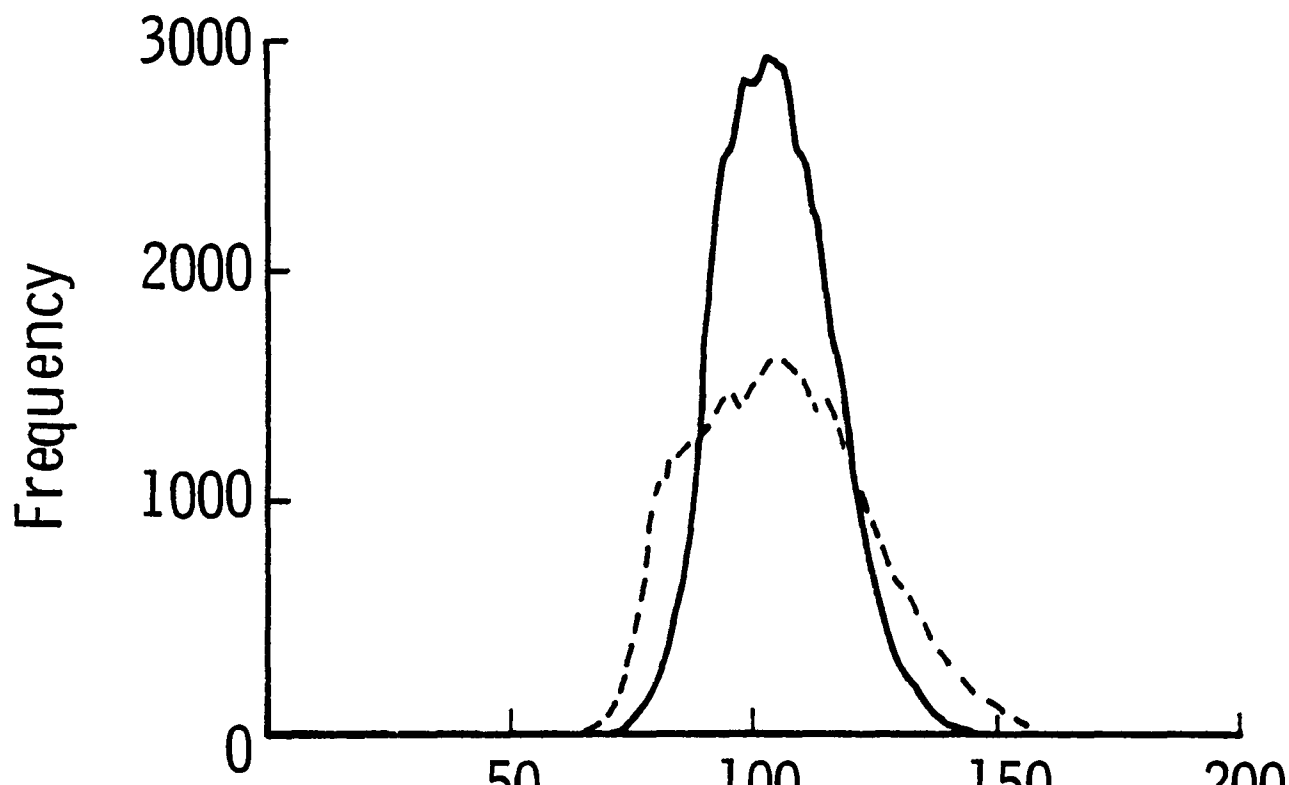

Fig. 5-39 Frequency histograms of ambulatory waking mean arterial pressure in two subjects: B.H. (age 42, MAP 104.2 mm Hg, VMAP 11.9 mm Hg, LBRS 1.024) (solid line), and L.D. (age 42, MAP 105.0 mm Hg, VMAP 18.3 mm Hg, LBRS 0.754) (broken line). The inverse relationship between baroreflex sensitivity and the variability of mean arterial pressure is unrelated to these subjects' ages or blood pressures.

pressure (r=0.43, P<0.0005) (Fig. 5-37) and inversely correlated with LBRS (r=-0.47, P<0.0002) (Fig. 5-38). When multiple regression analysis was performed on the data from these 56 patients, baroreflex sensitivity (LBRS) was found to be the only variable to make a significant contribution (F=15.031, P<0.005) to the regression equation:

$$VMAP = 16.76-3.79\times(LBRS) \qquad (35)$$

with a standard error of the regression coefficient, b_1, of 0.98.

The independent effect of baroreflex sensitivity on blood pressure variability is illustrated in Fig. 5-39, in which the waking frequency histograms of two subjects with similar mean ambulatory MAP and age are superimposed. Poorer LBRS was associated with increased variability of mean arterial pressure; this was also seen in patients L.H. (age 63, MAP 150.4 mm Hg, VMAP 13.5 mm Hg, LBRS 0.477) and J.C. (age 61, MAP 159.5 mm Hg, VMAP 18.6 mm Hg, LBRS 0.355).

Analysis of these data, using partial correlations, was also performed (Table 5-28). The partial correlation between LBRS and VMAP, i.e. excluding the influence of age and MAP, was -0.27 (f=51, P<0.05).

Plasma noradrenaline concentrations were obtained in 44 of these 56 subjects, both at rest and during bicycle exercise. The relative increase in plasma noradrenaline (%ΔPNA) during bicycling was calculated and used as an index of sympathetic nervous activity. Greater relative increases in PNA were seen in subjects with greater variability of arterial pressure (r=0.35, P<0.01) (Fig. 5-40). When multiple regression analysis was performed, examining all four independent variables, only the MAP made a significant independent

Table 5-28

Partial correlation coefficients for the independent effects of mean arterial pressure (MAP), age, baroreflex sensitivity (LBRS), and the relative increase in plasma noradrenaline during exercise (%ΔPNA) on the variability of mean arterial pressure (VMAP) in all 56 subjects (left-hand column) and in the 44 subjects in whom plasma noradrenaline concentrations (PNA) were obtained at rest and during exercise (right-hand column).

	VMAP (mm Hg)	VMAP (mm Hg)
MAP (mm Hg)	0.21	0.32*
Age	0.00	0.10
LBRS	-0.27*	-0.13
%ΔPNA	-	0.20

* $P<0.05$

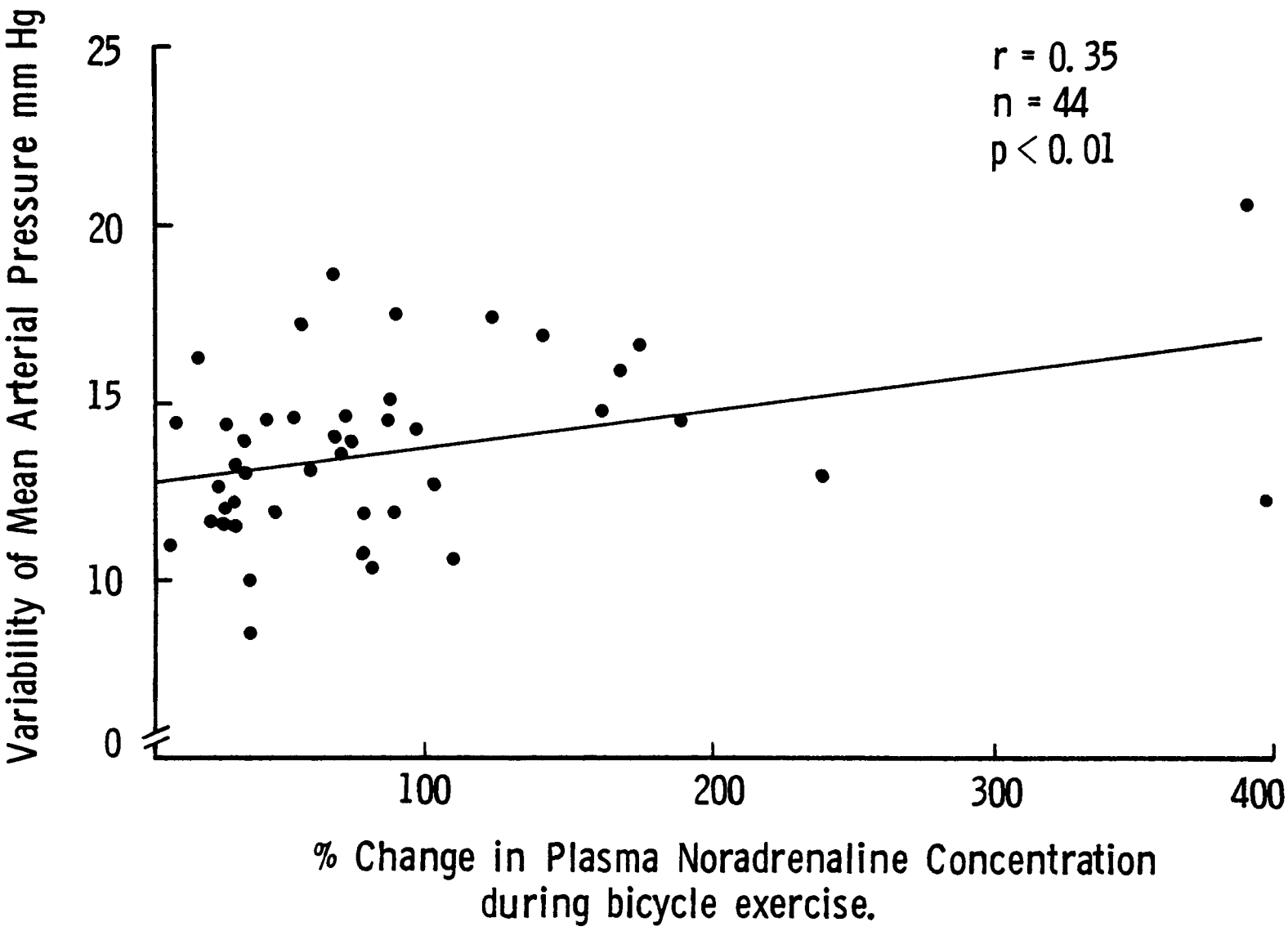

Fig. 5-40 Relationship between the variability of ambulatory waking mean arterial pressure and the relative increase in plasma noradrenaline concentration during bicycle exercise.

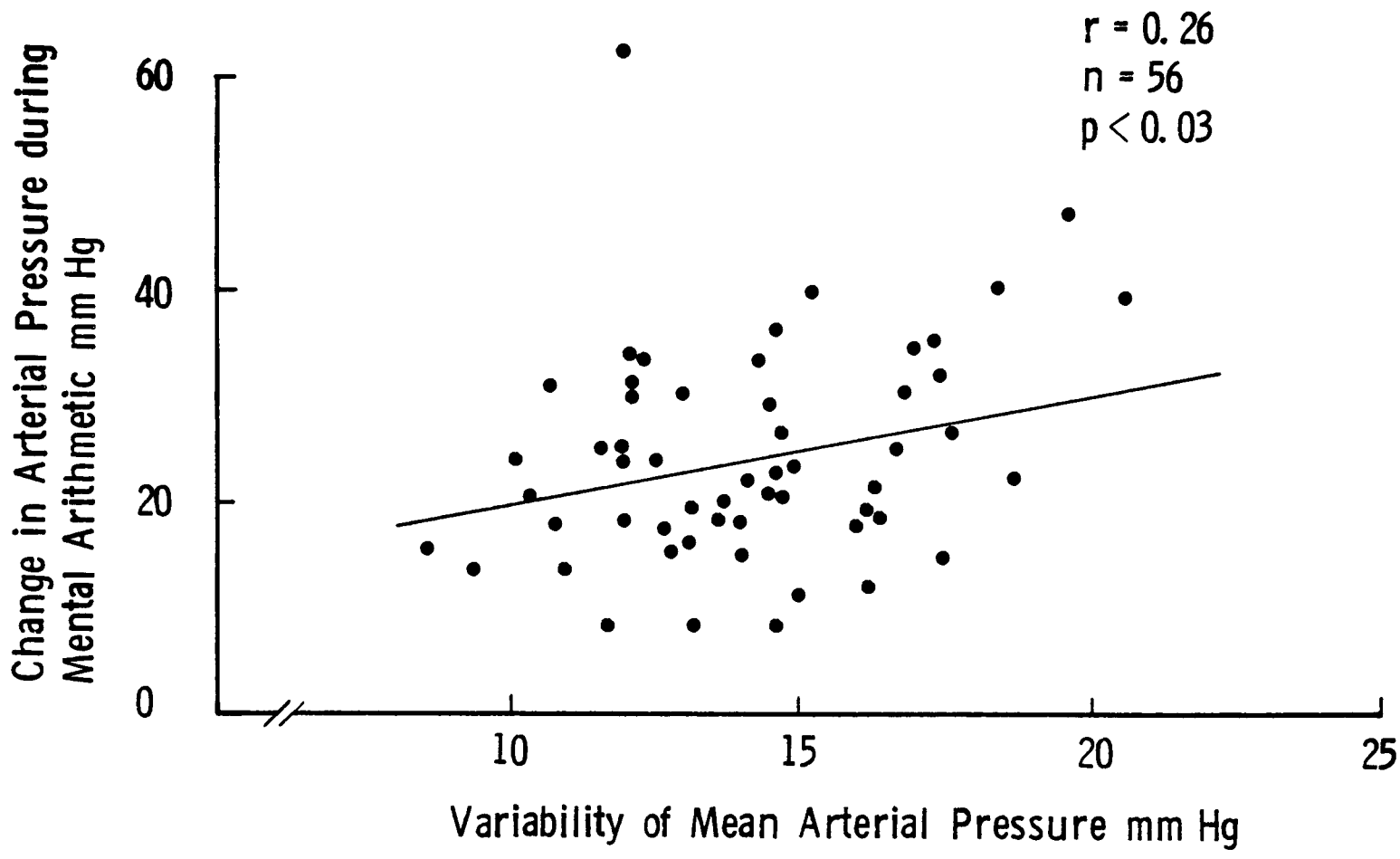

Fig. 5-41 Relationship between the change in mean arterial pressure during mental arithmetic and the variability of ambulatory waking mean arterial pressure in 56 subjects.

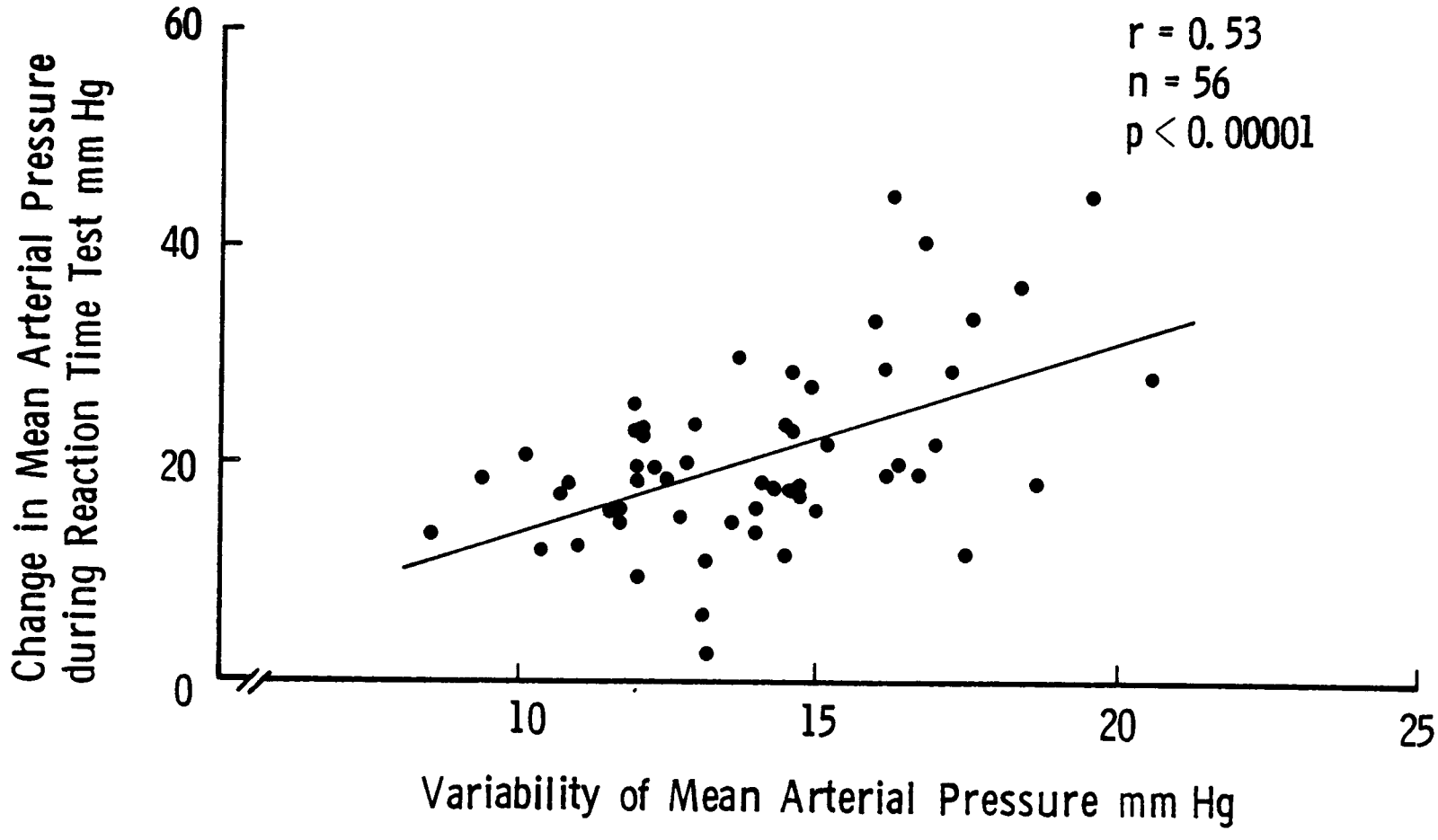

Fig. 5-42 Relationship between the change in mean arterial pressure during the reaction time test and the variability of ambulatory waking mean arterial pressure in 56 subjects.

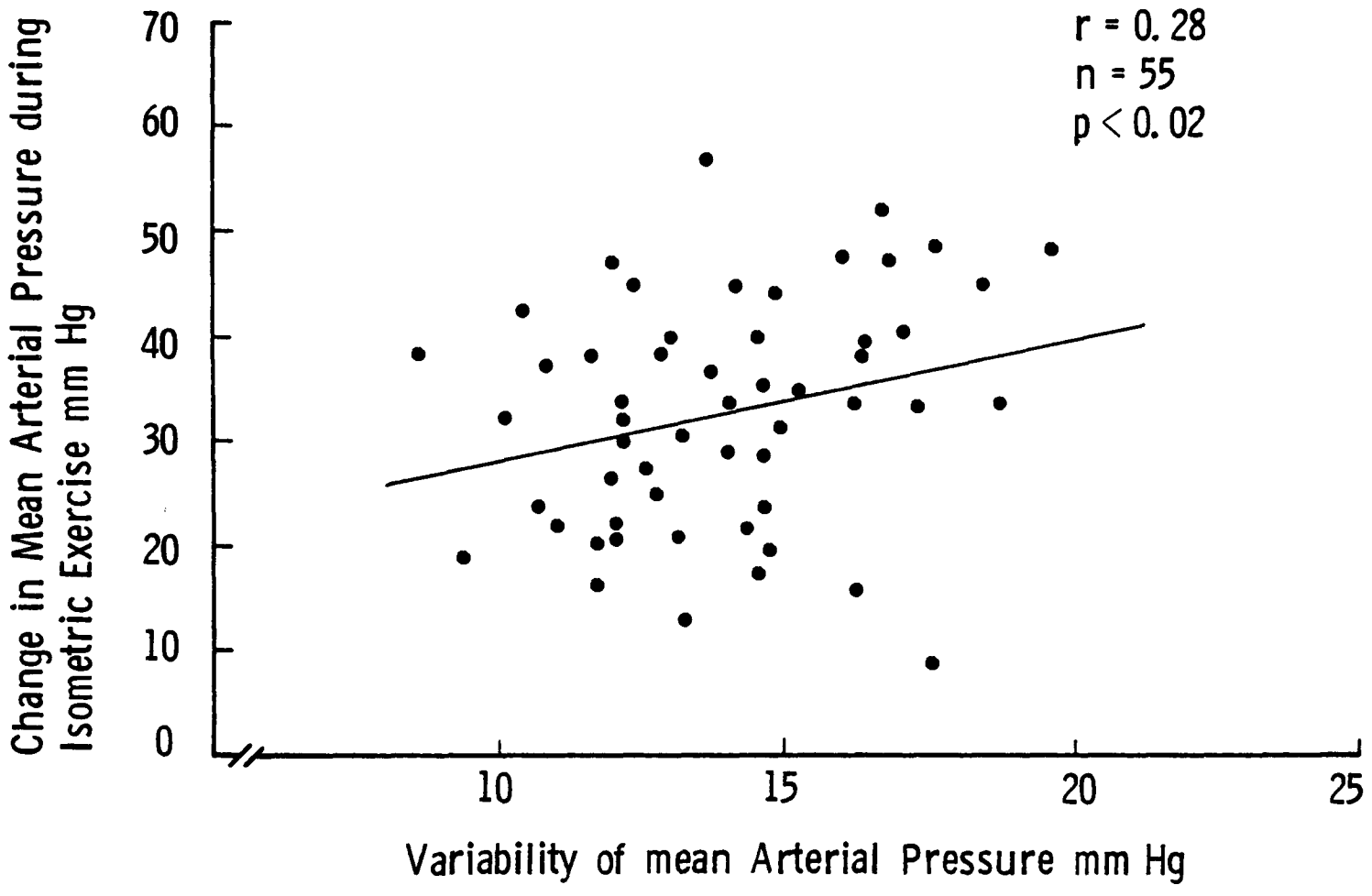

Fig. 5-43 Relationship between the change in mean arterial pressure during isometric exercise and the variability of mean arterial pressure in 55 subjects.

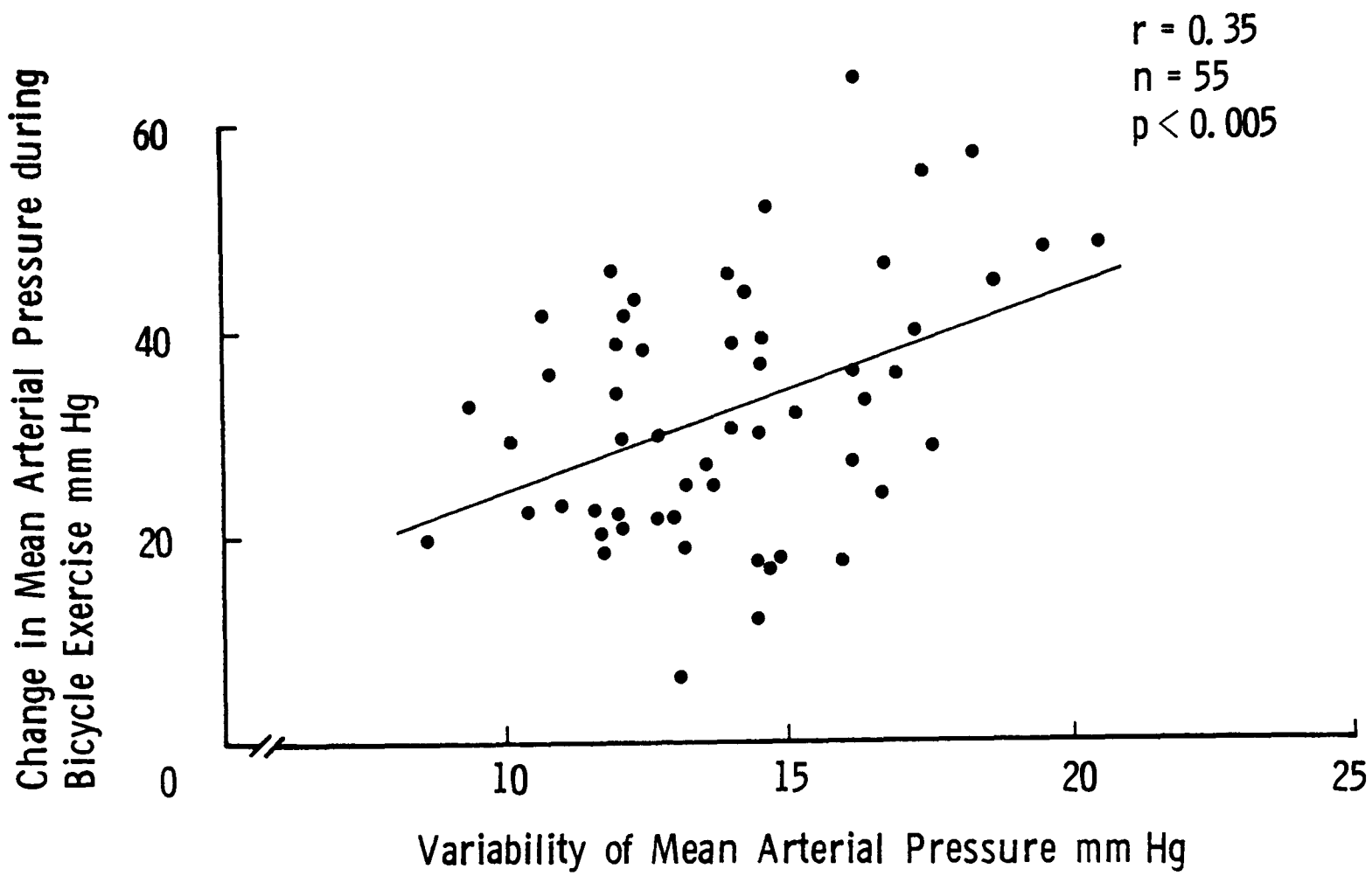

Fig. 5-44 Relationship between the change in mean arterial pressure during bicycle exercise and the variability of mean arterial pressure in 55 subjects.

contribution (F=13.975, P<0.005) to the regression equation:

$$VMAP = 6.136+0.062\times(MAP). \qquad (36)$$

The standard error of the regression coefficient was, in this instance, 0.017.

Partial correlation coefficients of the independent effects of blood pressure, age, baroreflex sensitivity and the relative increase in plasma noradrenaline on exercise are noted in Table 5-28. The significant inverse relationship between LBRS and VMAP in the group as a whole disappear when the smaller number who had plasma noradrenaline concentrations measured in addition were examined on their own.

The variability of mean arterial pressure and haemodynamic changes during mental and physical exercise

In the 56 patients who were included in the calculation of waking blood pressure variability, VMAP was correlated with the absolute increase (ΔMAP) during each of the four exercises. These two variables were significantly related in all of the exercises: mental arithmetic (r=0.26, P<0.03), the reaction time test (r=0.53, P<0.00001), isometric exercise (r=0.28, P<0.02) and bicycle exercise (r=0.35, P<0.005). The response to the reaction time test appeared to be most related to the variability of mean arterial pressure (Figs.5-41 to 5-44).

I Slit open with a Pair of Scissors, from end to end, the Guts of a Dog on that side which was opposite to the Insertion of the mesenterick Arteries and Veins; and having fixed a Tube 4½ Feet high to the descending Aorta a little below the Heart I poured blood warm Water thro' a Funnel into the Tube, which descended thence into the Aorta...This water passed off thro' the Orifices of innumerable small capillary Vessels, which were cut asunder thro' the whole length of the slit Gut....But the Resistance which the Blood meets with in those capillary Passages, may be greatly varied, either by the different Degrees of the Viscidity or Fluidity of the Blood, or by the several Degrees of Constriction or Relaxation of those fine vessels; Instances of which may be seen in Experiments XV (common Brandy), XVI (a strong Decoction of Oak Bark), XVII, XVIII.

- Experiment IX
Stephen Hales (1733)

CHAPTER 6

RESULTS OF EXPERIMENTS IN RATS

Baroreflex sensitivity changes during the development of 2-kidney 1-clip Goldblatt hypertension

Eight animals were studied in each group. After constriction of the left renal artery, changes in mean arterial pressure, and in the ratio of the left ventricular weight to total body weight, expressed as a percentage followed a time-course identical to that observed by Lundgren et al. (1974a)(Figs. 6-1, 6-2). The mean arterial pressure rose from 118.6±2.0 mm Hg (mean±S.E.) in the 0-day control group to 133.1±2.2 mm Hg in the 3-day hypertensive group ($P<0.001$), and to 193.1±14.2 mm Hg in the 25-day hypertensive group ($P<0.001$) but the heart rate did not change (Table 6-1). The left ventricular weight (as a percentage of the body weight) at day 3 (0.25±0.01%) was identical to the weight in 0-day normotensive rats, but had increased significantly by day 7 (0.29±0.01%, $P<0.05$).

The injection of phenylephrine in the normal control rats produced a noticeable bradycardia (Fig. 6-3). Baroreflex sensitivity was 0.950±0.157 ms/mm Hg in the 0-day control group and 0.995±0.199 ms/mm Hg in the 25-day control group (Fig. 6-4). After 3 days of renovascular hypertension, a similar pressure rise continued to reduce the heart rate (Fig. 6-5), but to a markedly diminished degree (0.537±0.105 ms/mm Hg) ($P<0.05$), (Fig. 6-9). This difference between control and experimental rats became greater in those animals

Table 6-1

Rat Groups	Mean Arterial Blood Pressure (mm Hg)	Pulse Interval (ms)	Left Ventricular Weight/Body Weight (%)	Baroreflex Sensitivity (ms/mm Hg)	Body Weight (g)
Normotensive 0-day	118.6±2.0	149.3±5.1	0.25±0.01	0.950±0.157	185.5±3.2
Hypertensive 3-day	133.1±2.2*	141.4±1.0	0.25±0.01	0.537±0.105†	208.0±4.5††
Hypertensive 7-day	164.1±7.6*	147.0±4.1	0.29±0.01†	0.418±0.166†	215.0±5.1*
Hypertensive 14-day	161.8±4.7*	144.8±3.5	0.28±0.01†	0.182±0.039*	246.9±10.8*
Hypertensive 25-day	193.1±14.2*	143.6±5.2	0.33±0.01*	0.299±0.074††	261.1±12.8*
Normotensive 25-day	122.4±2.3	148.8±2.2	0.24±0.01	0.995±0.199	269.8±2.0*

Group data (means S.E.) on mean arterial blood pressure, pulse interval, left ventricular/body weight ratio, baroreflex sensitivity, and body weight in normotensive control rats and renal hypertensive rats after 3, 7, 14 and 25 days (n=8 in all groups; †=P<0.05; ††=P<0.01; *=P<0.001 when compared to normotensive 0-day rats).

Table 6-2

RAT GROUPS	r
Normotensive 0-day	0.26
Hypertensive 3-day	0.55
Hypertensive 7-day	-0.23
Hypertensive 14-day	-0.54
Hypertensive 25-day	-0.63
Normotensive 25-day	-0.20

Group data on correlation (r) between baroreflex sensitivity and mean arterial blood pressure in normotensive control rats and renal hypertensive rats after 3, 7, 14 and 25 days (n=8 in all groups). None of the correlations are significant at the 5% level.

Table 6-3

RAT GROUPS	Mean arterial blood pressure (mm Hg)	t (v. RHR 25)	f	P
Normotensive 25-day	122.4±2.3	---	---	---
Hypertensive 25-day				
baseline	193.1±14.2	---	---	---
initial	177.5±2.5	---	---	---
Declipped 1-day	159.2±2.5	2.461	8.772	<0.05
Declipped 3-day	155.6±3.6	2.775	14	<0.02
Declipped 7-day	157.5±4.4	2.145	14	=0.05
Declipped 14-day	177.4±7.1	0.010	14	n.s.
Declipped 25-day	155.0±4.2	2.749	14	<0.02
Normotensive 50-day	117.7±2.5	---	---	---

Group data on mean arterial pressure (means ±S.D.) in 25- and 50-day normotensive control rats and renal hypertensive rats after 25 days. The latter were assigned to 6 groups, one of which was studied immediately and the others restudied 1, 3, 7, 14 and 25 days after removal of the left renal artery constriction. (n=8 in all groups.)
Baseline and initial mean arterial pressure in the 25-day hypertensive rats are shown. The initial mean arterial pressure in this group is compared to the mean arterial pressures in the other hypertensive rats, before the removal of the renal artery constriction (see text for details).

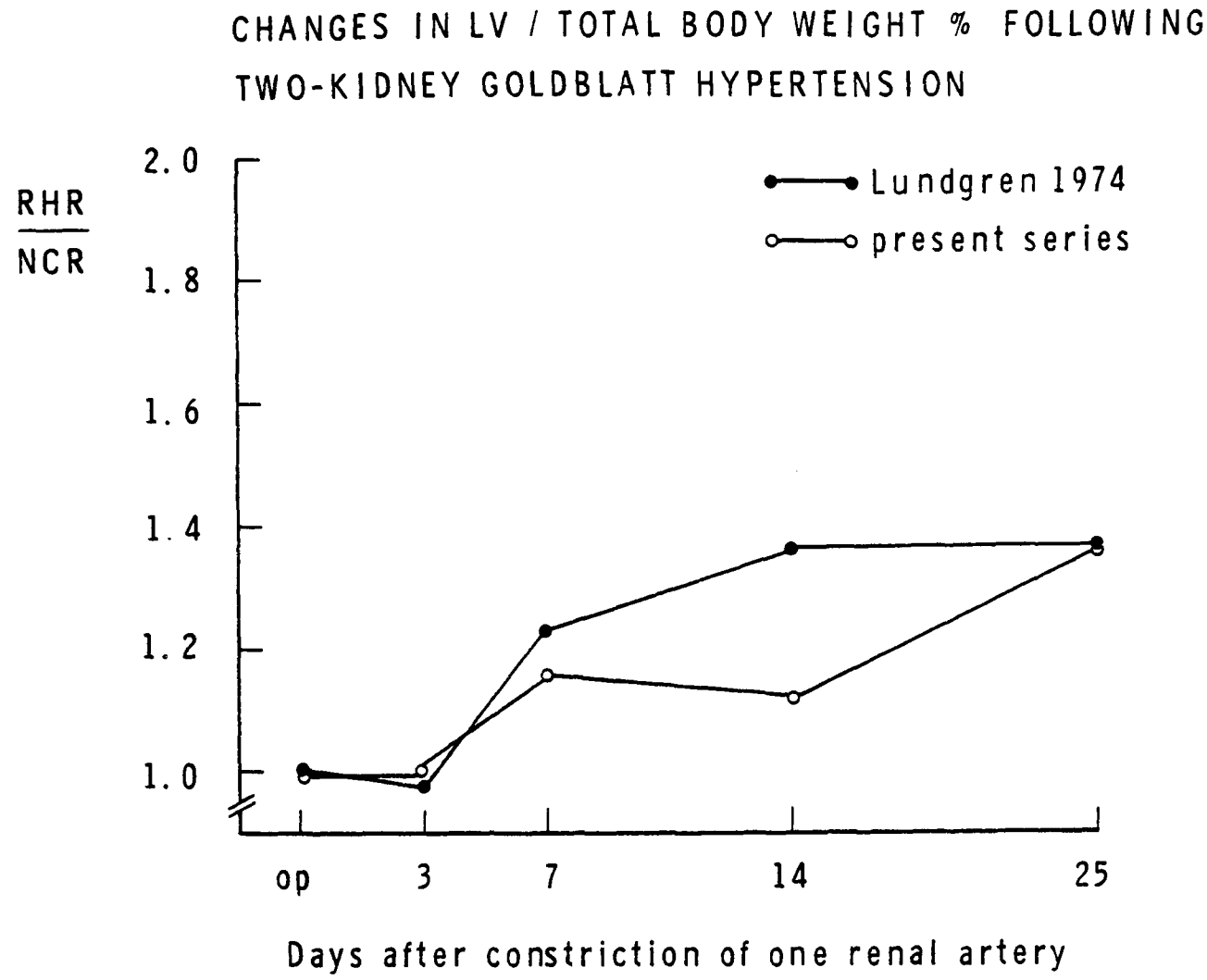

Fig. 6-1 Changes in mean arterial pressure in 2-kidney 1-clip Goldblatt hypertension in the rat expressed as a ratio between renovascular hypertensive (RHR) and normal (NCR) rats: Lundgren (1974) and the present series.

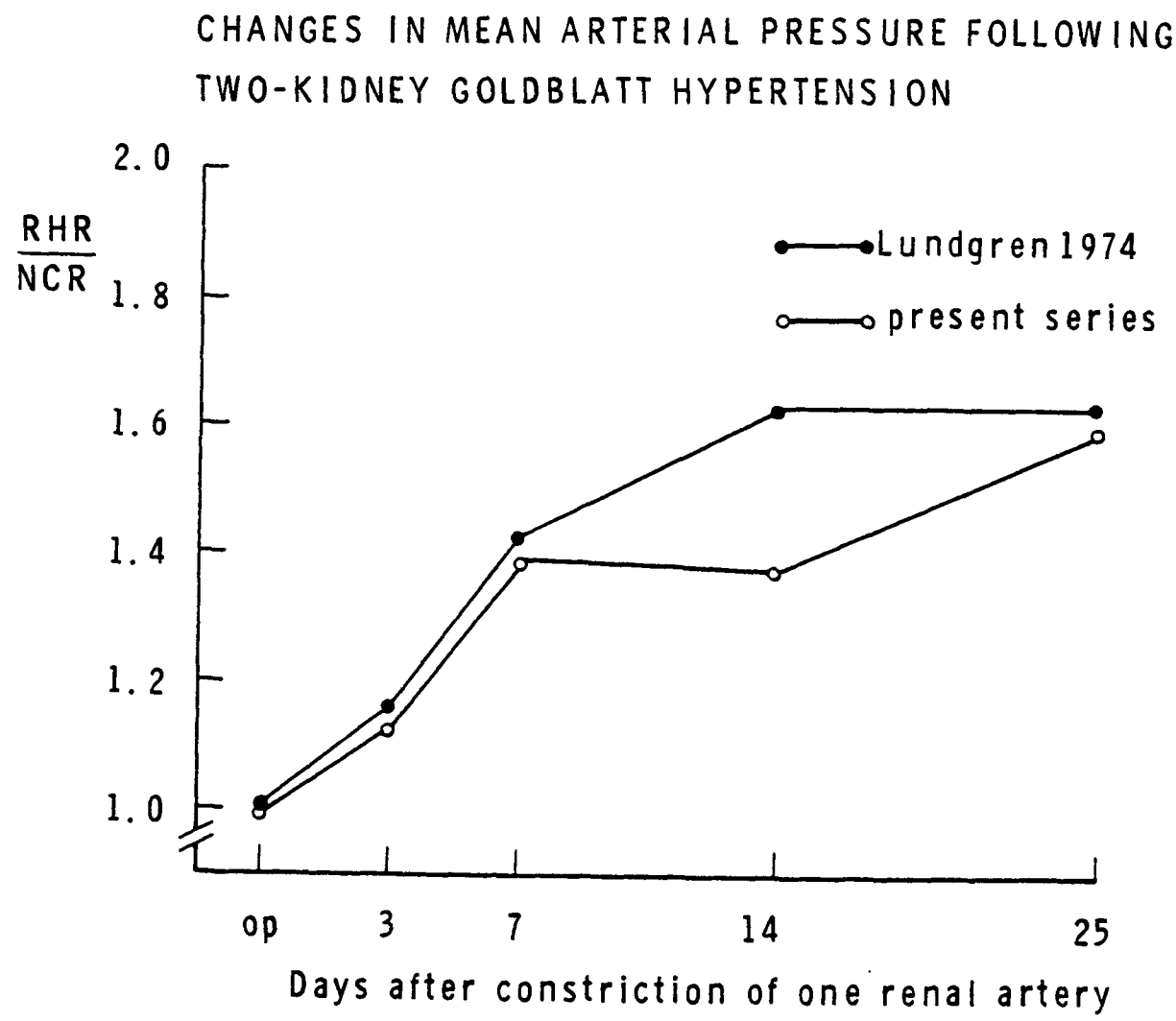

Fig. 6-2 Changes in left ventricular/body weight ratio in 2-kidney 1-clip Goldblatt hypertension in the rat expressed as a ratio between renovascular hypertensive (RHR) and normal (NCR) rats: Lundgren (1974) and the present series.

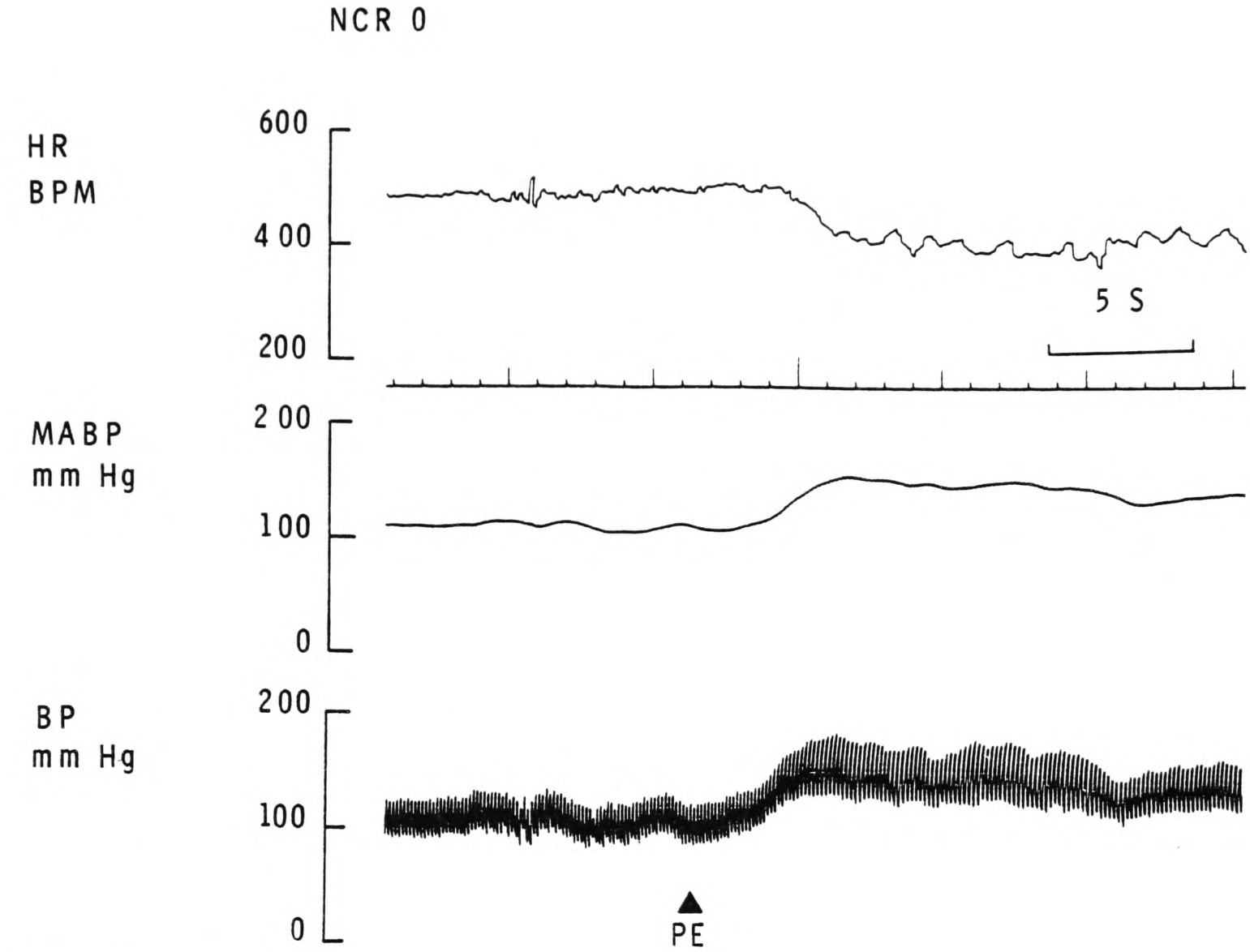

Fig. 6-3 Heart rate (HR), mean arterial pressure (MABP) and pulsatile arterial pressure (BP) in a normotensive control rat (NCR 0). Injection of 1 µg of phenylephrine (PE) causes a rise in blood pressure and a fall in heart rate.

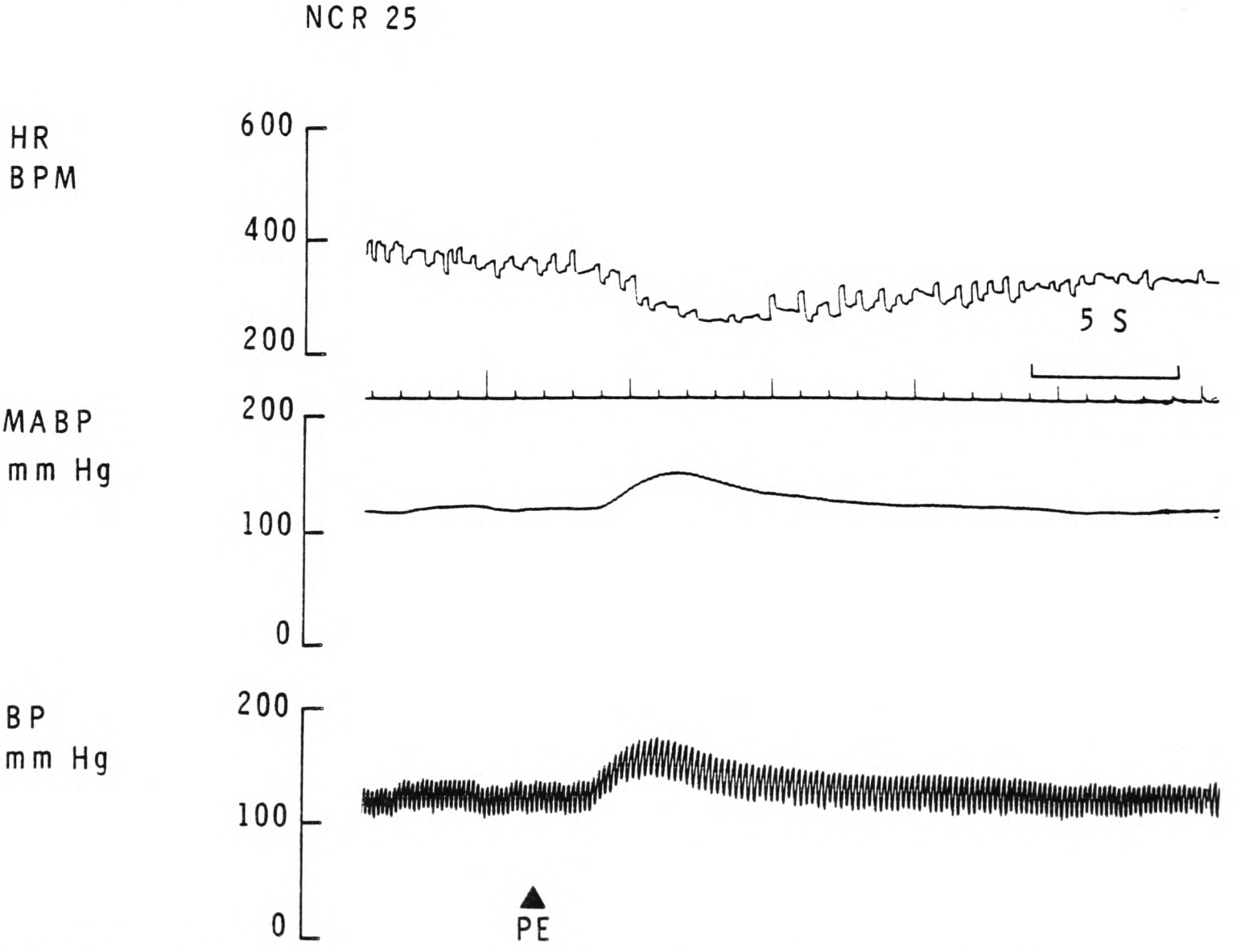

Fig. 6-4 Heart rate (HR), mean arterial pressure (MABP) and pulsatile arterial pressure (BP) in a normotensive control rat 25 days later (NCR 25). Injection of 1 µg of phenylephrine (PE) causes a similar rise in blood pressure and a similar fall in heart rate.

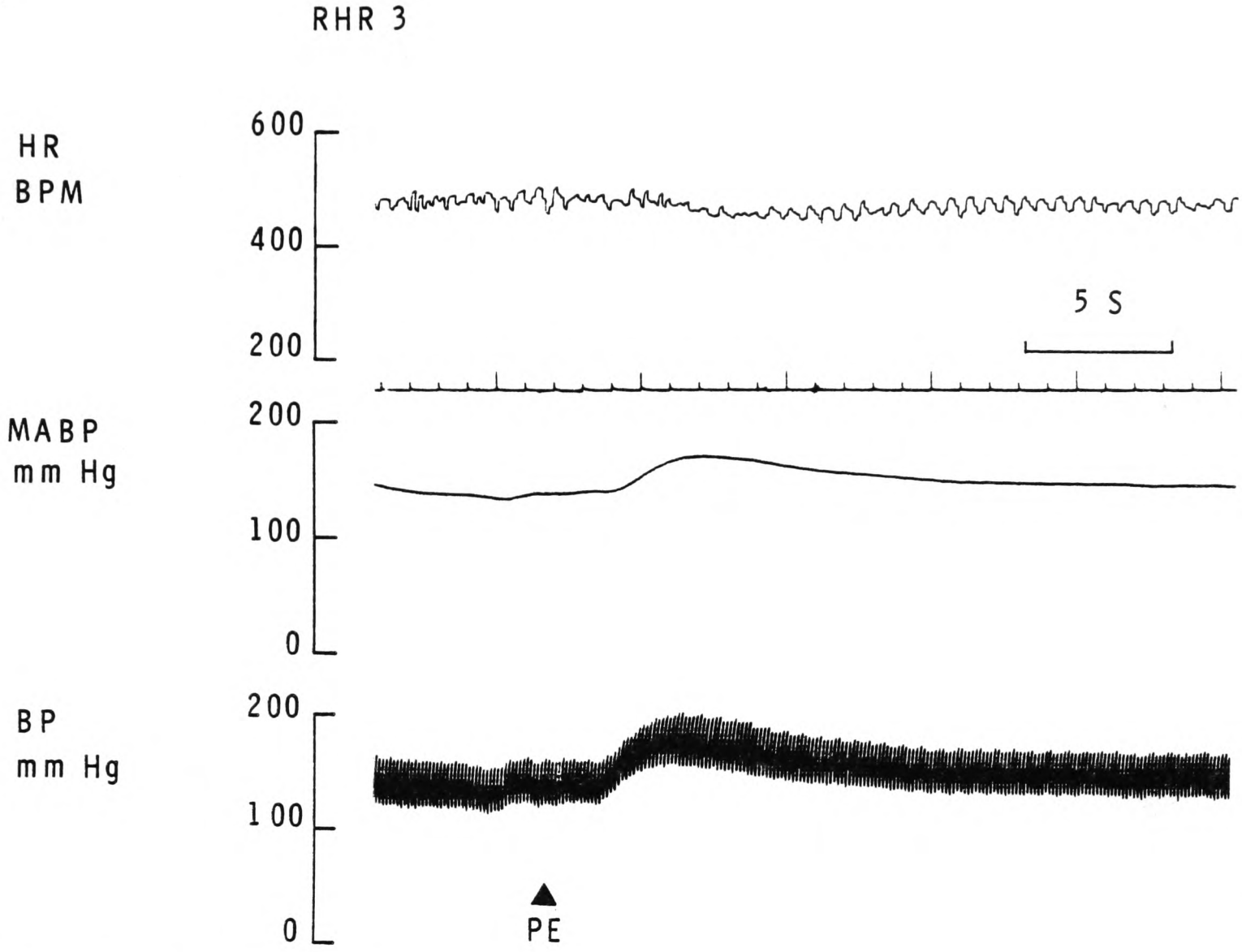

Fig. 6-5 Heart rate (HR), mean arterial pressure (MABP) and pulsatile arterial pressure (BP) in a rat with Goldblatt 2-kidney 1-clip hypertension of 3 days' duration. Injection of 1 µg phenylephrine (PE) causes a rise in pressure and smaller fall in heart rate.

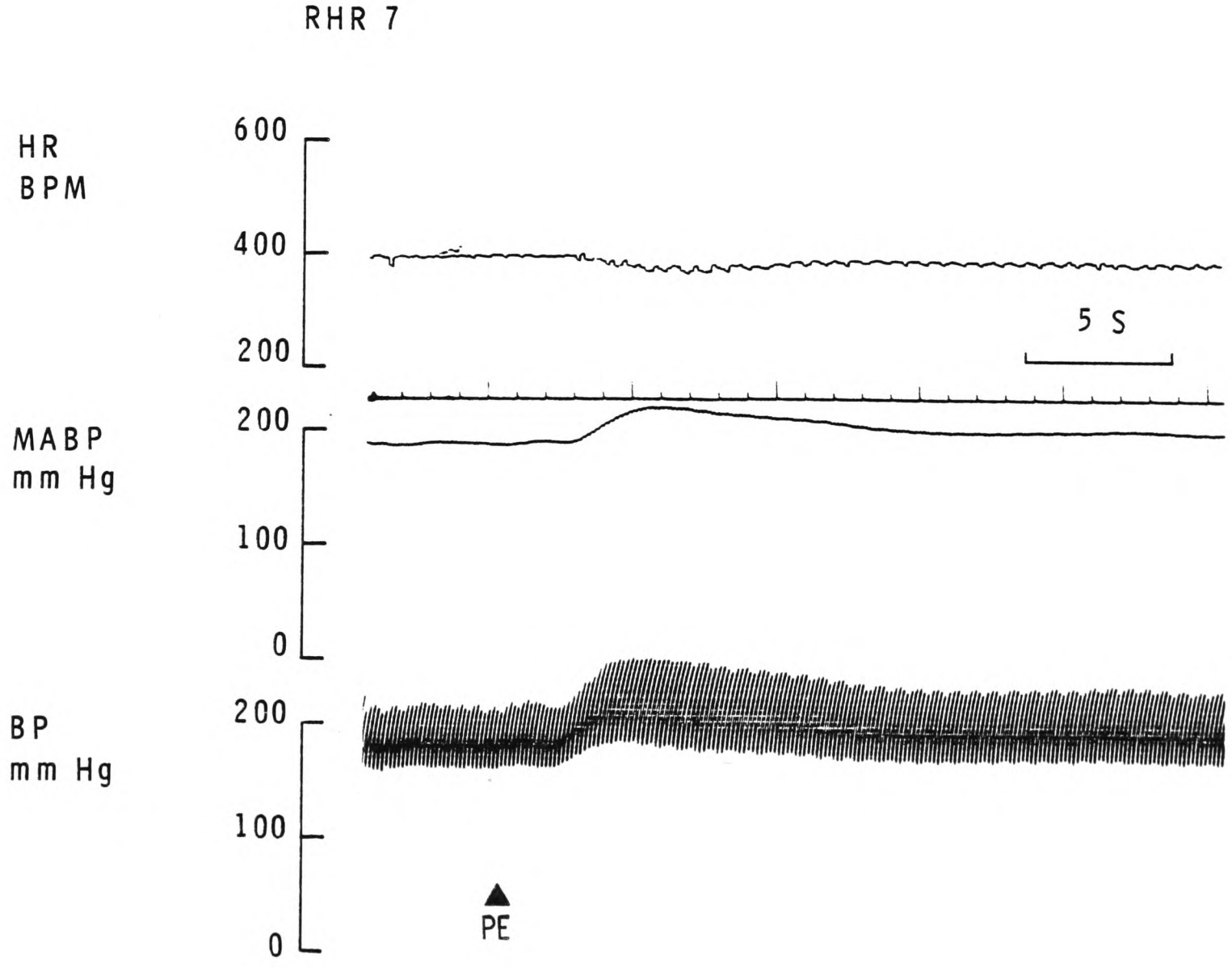

Fig. 6-6 As in Fig. 6-5. Renovascular hypertension of 7 days' duration (RHR 7).

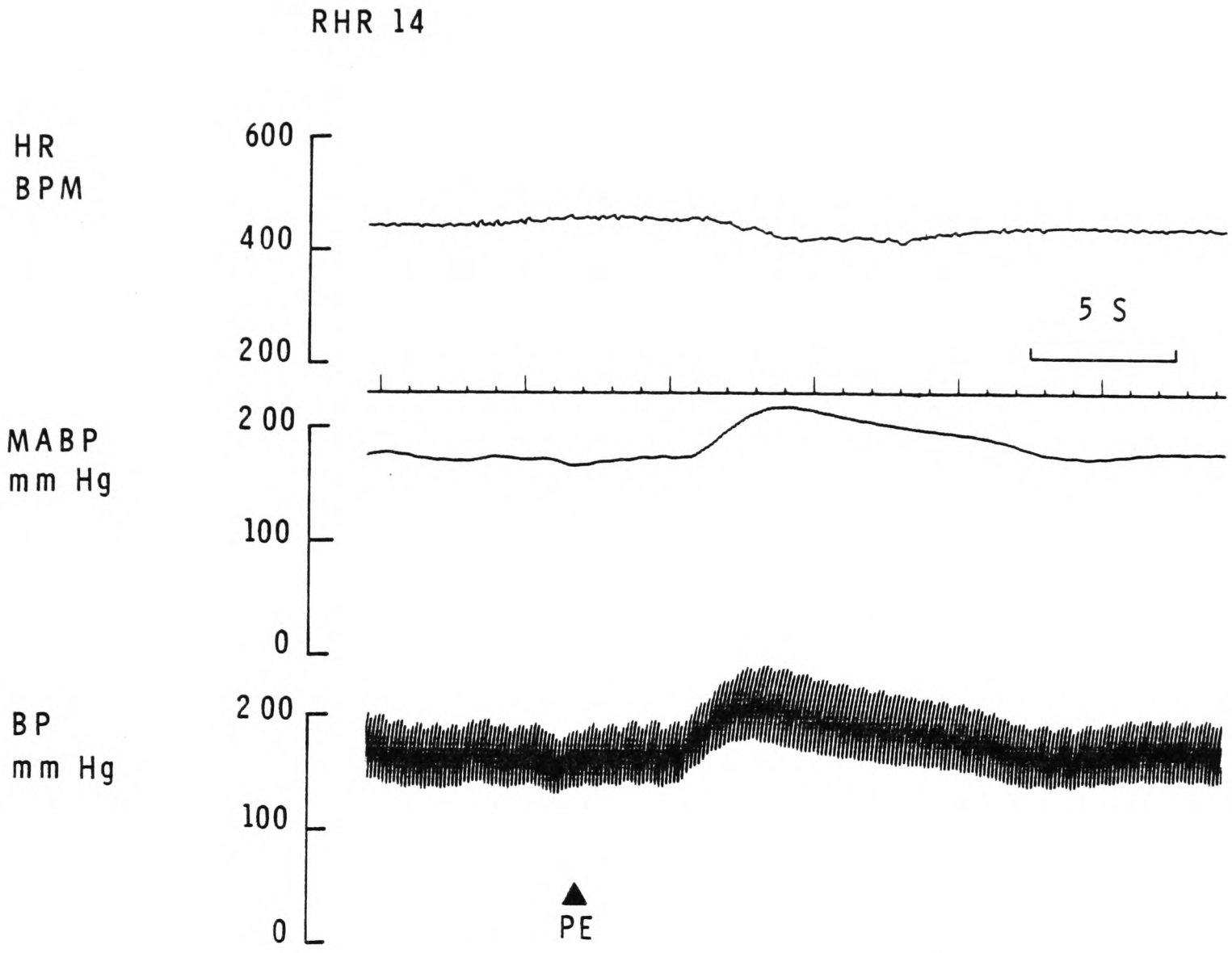

Fig. 6-7 As in Fig. 6-5. Renovascular hypertension of 14 days' duration (RHR 14).

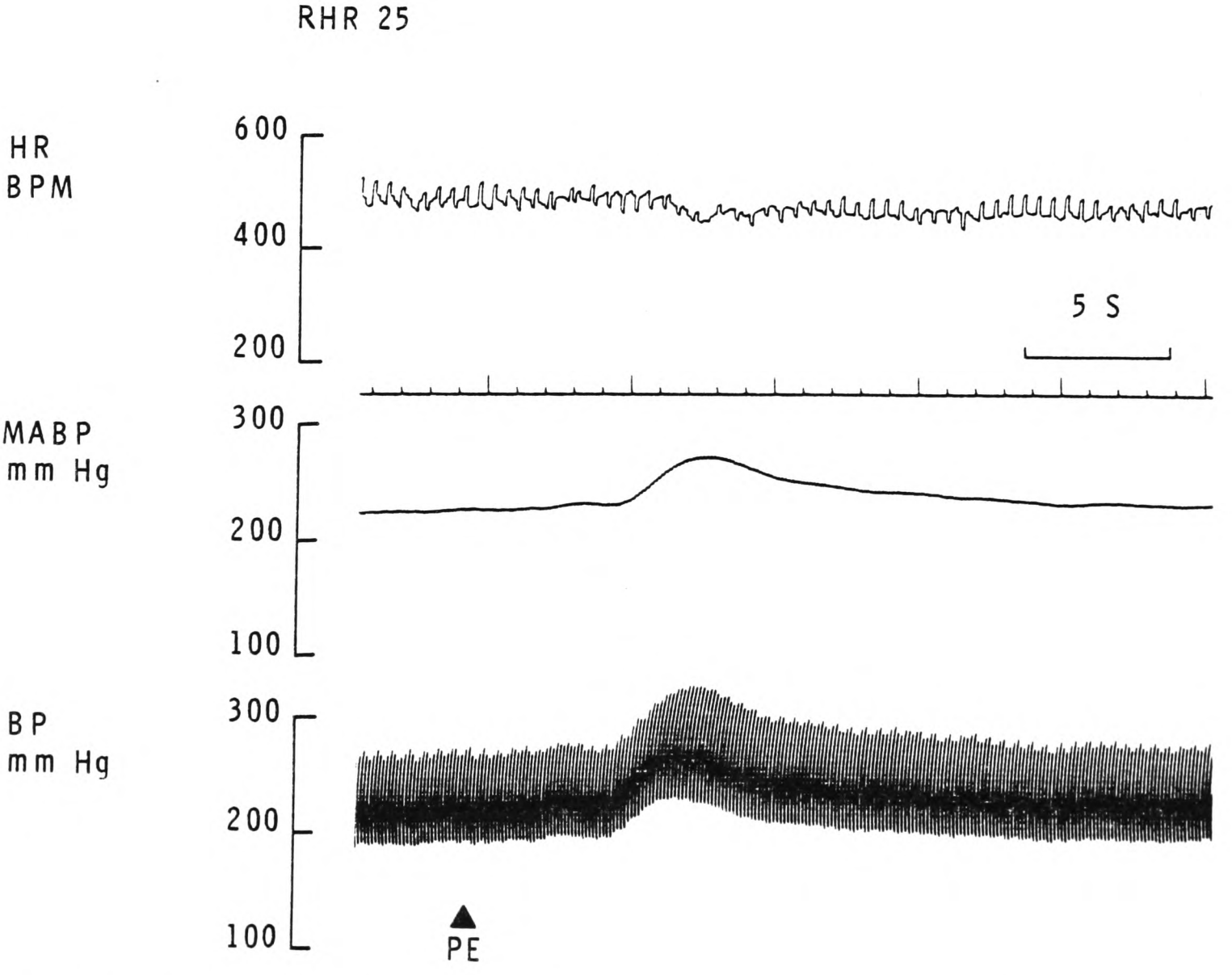

Fig. 6-8 As in Fig. 6-5. Renovascular hypertension of 25 days' duration (RHR 25).

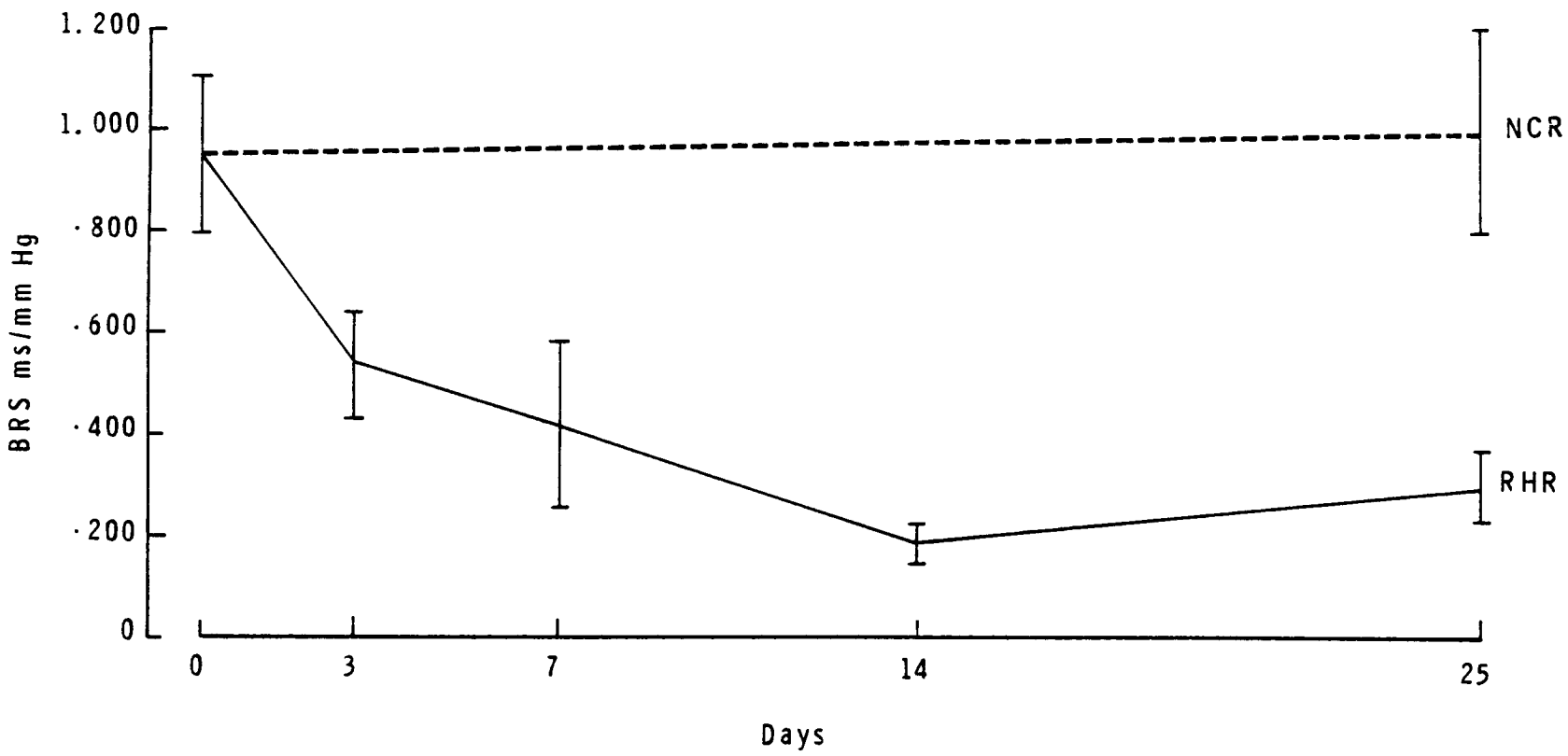

Fig. 6-9 Baroreflex sensitivity (BRS) in normal control rats (NCR) and rats with 2-kidney 1-clip Goldblatt hypertension of 3, 7, 14 and 25 days' duration (n=8 in all groups).

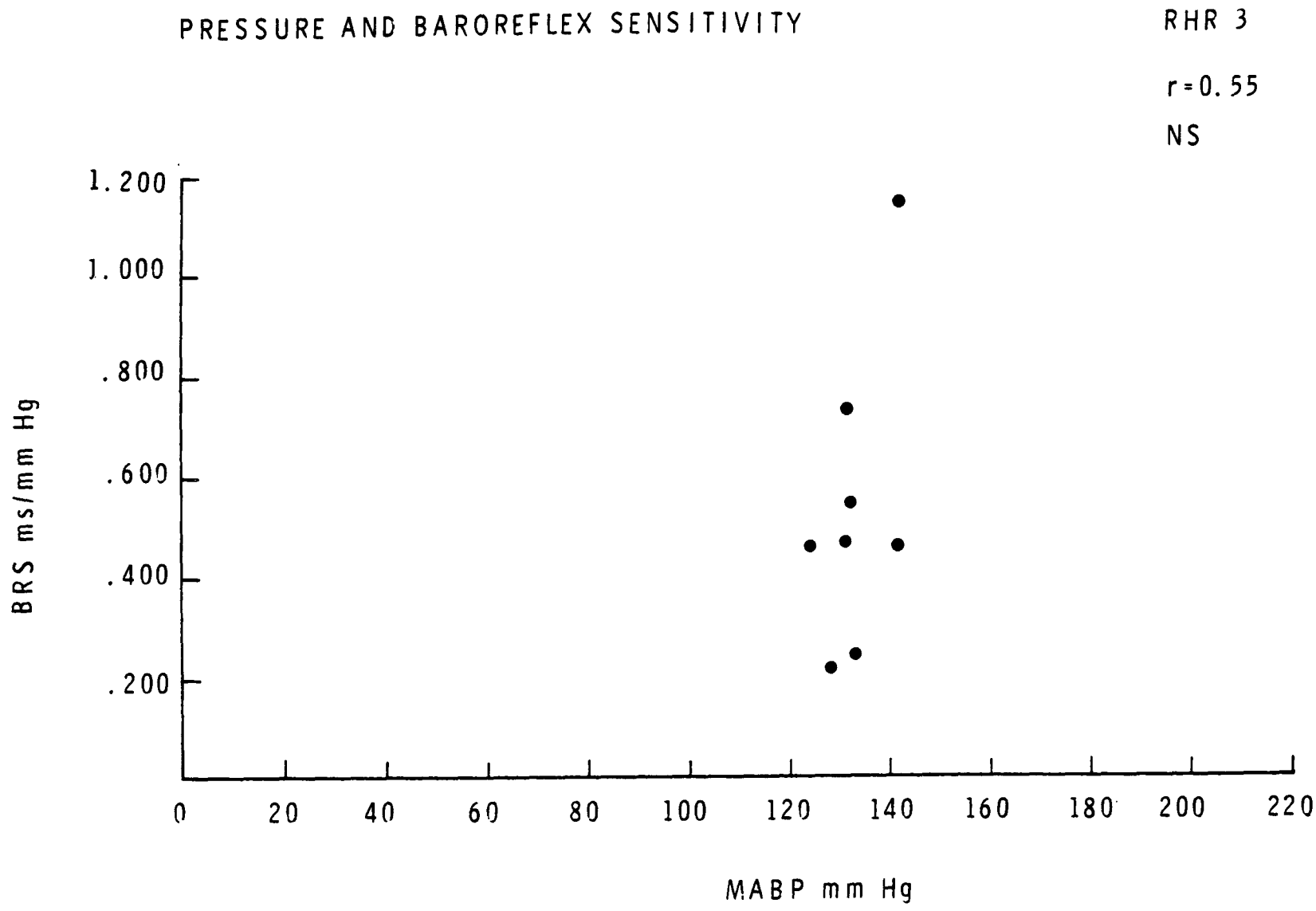

Fig. 6-10 Mean arterial pressure (MABP) and Baroreflex sensitivity (BRS) in 8 rats with 2-kidney 1-clip Goldblatt hypertension of 3 days' duration (RHR 3).

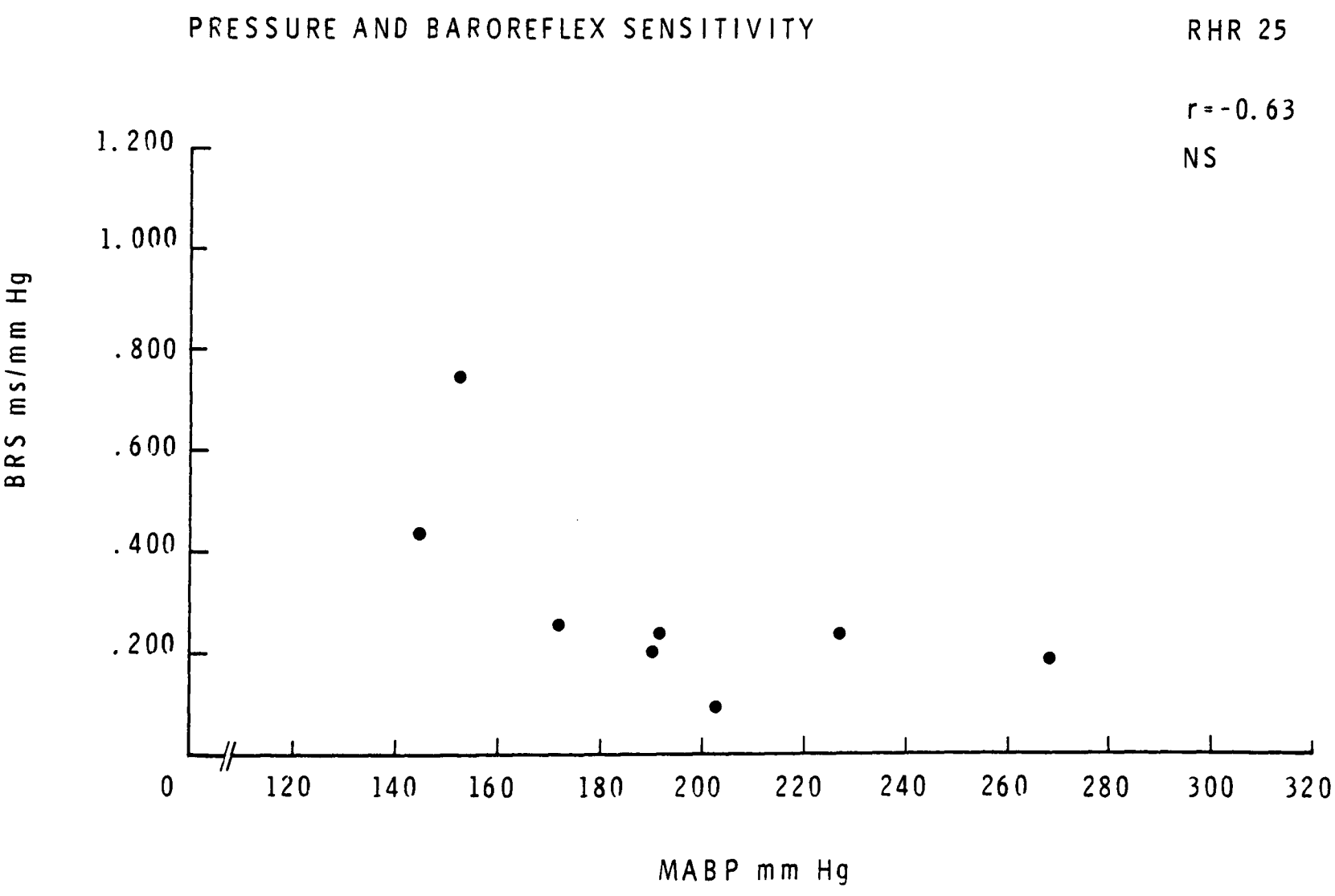

Fig. 6-11 Mean arterial pressure (MABP) and Baroreflex sensitivity (BRS) in 8 rats with 2-kidney 1-clip Goldblatt hypertension of 25 days' duration (RHR 25).

hypertensive for longer periods (Figs. 6-6, 6-7, and 6-8). As can be observed in Fig. 6-9, the baroreflex sensitivity at 14 days was lower than that at 3 days ($P<0.01$); the difference between the 14-day hypertensive rats and the 25-day hypertensive rats was not significant.

There was no relationship between pressure and baroreflex sensitivity in the 3-day hypertensive rats, although higher mean arterial pressures were observed in animals with more sensitive baroreceptors (Fig. 6-10). After 25 days of renovascular hypertension, those animals with higher pressures tended to show less cardiac slowing following the injections of phenylephrine; this trend was not significant (Fig. 6-11) (Table 6-2).

A linear relationship between pulse interval and mean arterial pressure was seen in all groups studied provided that the appropriate delay was selected for each injection. The delay which gave the best correlation between mean arterial pressure, and the succeeding pulse interval for the calculations of baroreflex sensitivity was similar in each group.

Baroreflex sensitivity changes during the reversal of 2-kidney 1-clip Goldblatt hypertension

Mean arterial pressures before removal of the renal artery constriction

Mean arterial pressures in each group of hypertensive rats, before declipping, are noted in Table 6-3, along with the baseline mean arterial pressures of the 25-day hypertensive group, and the two normal control groups, equivalent in age to the 25-day hypertensive rats (normotensive 25 days), and the 25-day declipped rats (normotensive

50 days). Eight animals are included in each group. Arterial pressures in the sets of rats which became the 1-day declipped, 3-day declipped, 7-day declipped, and 25-day declipped groups were virtually identical, but lower than the pressure observed in the 25-day renal hypertensive animals ($P<0.05$, in the case of the D-RHR 3, 7, and 25-day groups, and $0.1>P>0.05$, $t=2.343$, $f=7.432$, in the case of the D-RHR 1 group). Although there was greater variation in the data, the mean arterial pressure before declipping was higher in the 14-day declipped group ($P<0.05$, $t=2.404$, $f=8.7$), and not significantly different from that attained in the RHR 25 group.

Whereas mean arterial pressures were recorded from a cannula inserted in the tail artery of the hypertensive rats to be declipped, immediately on their waking from the ether anaesthetic, the mean arterial pressures tabled for the 25-day hypertensive group represent the baseline blood pressures seen before the injection of phenylephrine, during experimental runs 5 through 8, i.e. 30 to 40 minutes after the animals had awakened from ether. The Grass polygraph records for these 8 animals revealed the mean arterial pressure seen before the first injection, i.e. about 10 minutes after waking from ether, to be 16 mm Hg lower, at 177.5±7.0 mm Hg ($t=1.646$, n.s.), comparable to the initial pressures in the 14-day declipped group, although higher than the pressure in the other groups (Table 6-3).

As the intent of the experiment was to observe changes in baroreflex sensitivity itself during the reversal of renovascular hypertension, this difference might be critical if, within this range, higher mean arterial pressures were directly correlated with lower baroreflex sensitivities. During the previous experiment baseline

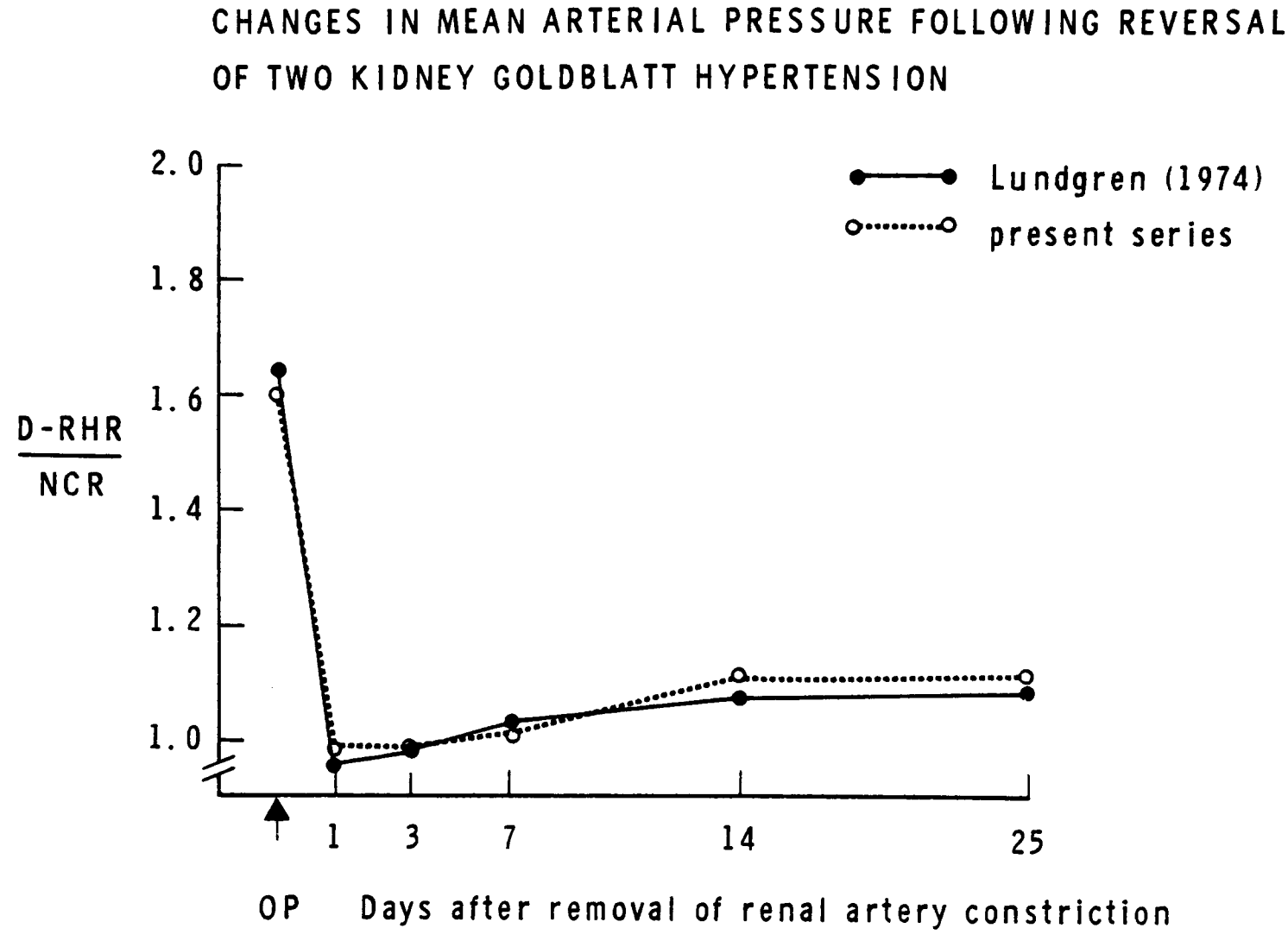

Fig. 6-12 Changes in mean arterial pressure following the reversal of 2-kidney 1-clip Goldblatt hypertension in the rat expressed as a ratio between declipped hypertensive (D-RHR) and normal (NCR) rats: Lundgren (1974) and the present series.

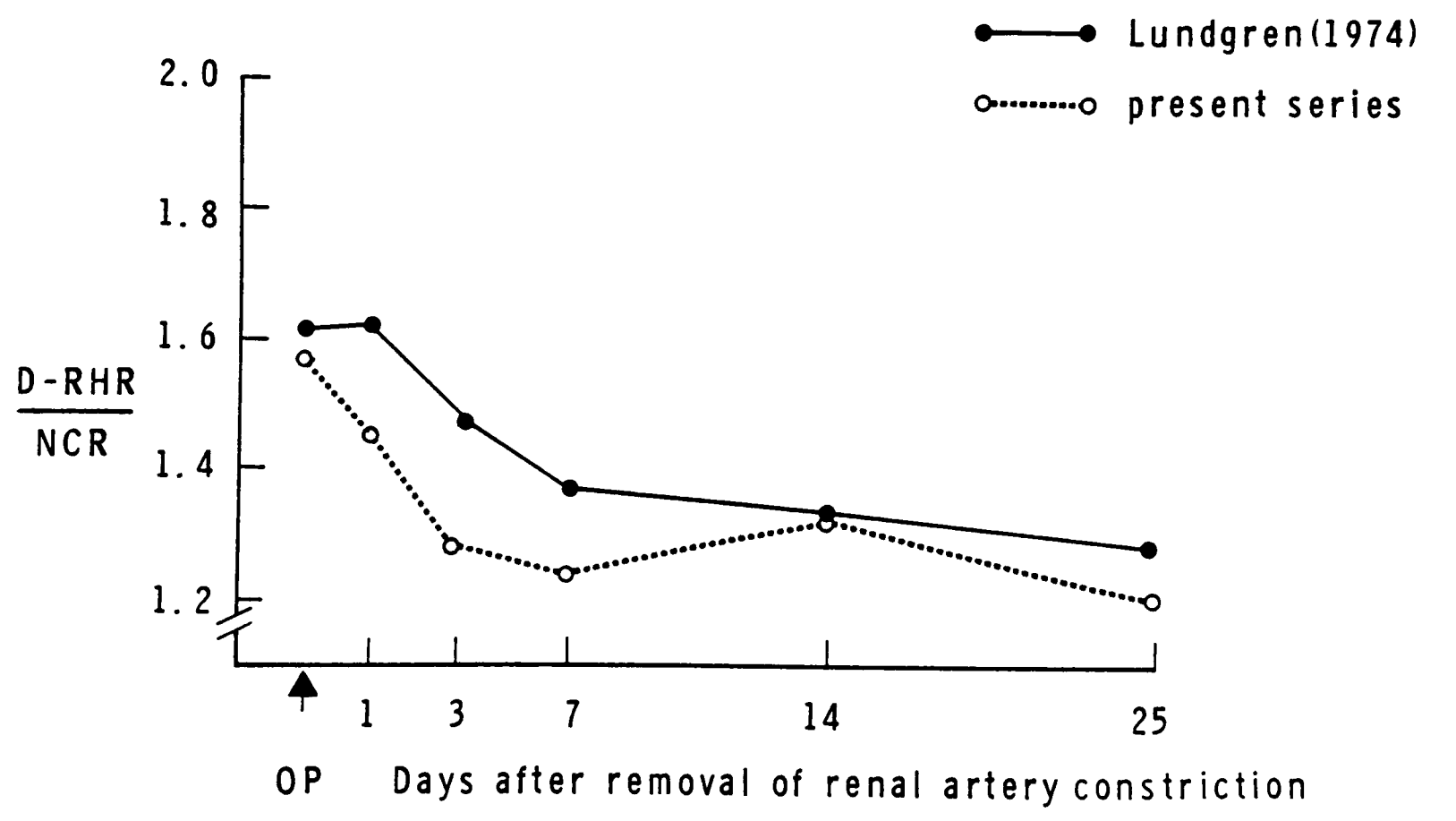

Fig. 6-13 Changes in left ventricular/body weight ratio following the reversal of 2-kidney 1-clip Goldblatt hypertension in the rat expressed as a ratio between declipped hypertensive (D-RHR) and normal (NCR) rats:

Table 6-4

RAT GROUPS	Mean Arterial Blood Pressure (mm Hg)	Pulse Interval (ms)	Left Ventricular Weight/Body Weight (%)	Baroreflex Sensitivity (ms/mm Hg)	Body Weight (g)
Normotensive 25-day	122.4±2.3	148.8±2.2	0.24±0.01	0995±0.199	269.8±2.0
Hypertensive 25-day	193.1±14.2††	143.6±5.2	0.33±0.01†††	0.299±0.072††	261.1±12.8
Declipped 1-day	120.6±3.2***	150.5±4.9	0.30±0.02†	0.657±0.155*	260.6±6.5
Declipped 3-day	121.3±3.2**	155.8±3.9	0.26±0.02**	0.786±0.093**	253.5±15.2
Declipped 7-day	124.2±3.7**	150.0±5.8	0.25±0.01***	1.071±0.211**	313.2±10.9**††
Declipped 14-day	131.1±1.7**††	156.0±3.1	0.28±0.01**†	0.780±0.091***	251.2±5.4 ††
Declipped 25-day	130.9±3.4**	155.5±3.3	0.25±0.01***	0.817±0.056***	369.4±11.4***†††
Normotensive 50-day	117.7±2.5***	159.9±2.6*††	0.25±0.01***	1.237±0.134***	376.9±11.4***†††

Group data (means ±S.E.) on mean arterial blood pressure, pulse interval, left ventricular/body weight ratio, baroreflex sensitivity and body weight in 25- and 50-day normotensive control rats, renal hypertensive rats, after 25 days, and rats whose hypertension was reversed by removal of a left renal artery clip 1, 3, 7, 14 and 25 days earlier. (n=8 in all groups; †=P<0.05; ††=P<0.01; †††=P 0.001 when compared to normotensive 25-day rats; *=P<0.05; **=P<0.01; ***=P<0.001 when compared to hypertensive 25-day rats).

mean arterial pressures of 161.8±4.7 mm Hg in the 14-day hypertensive group (again obtained before experimental runs 5 to 8) were associated with the lowest baroreflex sensitivities, namely, 0.182±0.039 ms/mm Hg.

It is therefore likely that the range of pressures attained in the groups to be declipped was sufficient to depress BRS to a level that was satisfactory for this experiment.

Baroreflex sensitivity and haemodynamic changes following removal of the renal artery constriction

Changes in mean arterial pressure (Fig. 6-12) and in the ratio of the left ventricular weight to total body weight, expressed as a percentage (Fig. 6-13) followed a time course similar to that observed by Lundgren (1974b). (NCR 25 data have been used as controls for the 1, 3, and 7-day declipped groups, and NCR 50 data have been used as controls for the 14- and 25-day declipped groups in these figures.)

Mean arterial pressure fell from 193.1±14.2 mm Hg in the 25-day hypertensive rats to 120.6±3.2 mm Hg ($P<0.001$), on the first day following declipping, and remained at these levels over the first week; pressure then gradually rose, to 130.9±3.4 mm Hg at day 25, which was significantly greater than the pressures seen in the 50-day normotensive controls ($P<0.001$) (Table 6-4). Pulse interval tended to increase with time following the removal of the clip, but in no case was this significant. The difference in pulse interval between the 25-day normotensive control rats (148.8±2.2 ms) and the 50-day normotensive control rats (159.9±2.6 ms) is significant, however

(P<0.01), and may be due to the effect of increasing age in these animals.

The left ventricular weight (as a percentage of body weight), which fell from 0.33±0.01% in the 25-day hypertensive group to 0.30±0.02% in the 1-day declipped group (t=1.342, n.s.), was still significantly greater than the ratio in the 25-day normotensive rats (t=2.683, P<0.02). Except for the 14-day declipped group, whose initial arterial pressure was higher, left ventricular/body weight ratios returned to normal by day 3 of declipping (P<0.01 vs. RHR 25). This was due to a reduction of left ventricular hypertrophy as the body weights themselves remained fairly constant (Table 6-4). Lundgren (1974b) found that the left ventricular weight/body weight ratio did not return to normal until two weeks following the removal of the renal artery clip. Two factors may be responsible for her observation. The higher mean arterial pressure before declipping (around 180 mm Hg) may have produced greater initial left ventricular hypertrophy in her animals. As can be seen in Table 6-1, the rise in pressure from 161.8±4.7 mm Hg in the 14-day hypertensive group to 193.1±14.2 mm Hg in the 25-day hypertensive group was itself associated with an increase in this ratio from 0.28±0.01% to 0.33±0.01% (P<0.01). The rats in her experiment with the highest pressures before declipping, namely, the 14-day declipped group, still showed significant elevation of the left ventricular/body weight ratio when restudied. Secondly, whereas left ventricular weight/body weight ratios in all three groups of our normotensive control animals remained constant, in the range of 0.24-0.25% (Table 6-1), they fell, with time from 0.22% to 0.18%, in the normal paired control rats in Lundgren's

Table 6-5

RAT GROUPS	Body Weight	Left Ventricular Weight/Body Weight Ratio (%)	Ratios: RHR/NCR 25 or D-RHR/NCR 25;50	Body Weight	Left Ventricular Weight/Body Weight Ratio (%)	Ratios: RHR/NCR or D-RHR/NCR	RHR/NCR 25 or D-RHR/NCR 25;50
Hypertensive 25-day	261.1±12.8	0.33±0.01	1.38	217±7	0.307±0.011	1.41	1.41
Normotensive 25-day	269.8±2.0	0.24±0.01		216±8	0.218±0.003		
Declipped 1-day	260.6±6.5	0.30±0.02	1.25	228±7	0.265±0.003	1.42	1.22
Normotensive 26-day	-	-	-	235±7	0.186±0.002		
Declipped 3-day	253.5±15.2	0.26±0.02	1.08	273±8	0.238±0.004	1.27	1.09
Normotensive 28-day	-	-	-	274±10	0.187±0.006		
Declipped 7-day	313.2±10.9	0.25±0.01	1.04	272±6	0.216±0.005	1.17	0.99
Normotensive 32 day	-	-	-	270±7	0.184±0.004		
Declipped 14-day	251.2±5.4	0.28±0.01	1.17	293±5	0.200±0.004	1.12	0.92
Normotensive 34-day	-	-	-	293±5	0.179±0.004		
Declipped 25-day	369.4±11.4	0.25±0.01	1.00	292±5	0.185±0.006	1.06	1.06
Normotensive 50-day	376.9±11.4	0.25±0.01		289±5	0.175±0.004		

Group data (means ±S.E.) on body weight, left ventricular weight/body weight ratio (%), and the ratio of this latter figure between 25-day renal hypertensive rats and 25-day normotensive control rats (RHR/NCR 25) or between declipped rats, 1, 3, 7, 14, and 25 days after removal of the left renal artery constriction and 25- or 50-day normotensive control rats (D-RHR/NCR 25;50) in the present study (left-hand side, n=8 for all groups), and also for matched pairs of rats (RHR/NCR or D-RHR/NCR) in Lundgren's study (right-hand side, n is variable).

experiment (Table 6-5). If this ratio were compared instead to that of the 25-day normotensive group, as we have done (all illustrated in Fig. 6-13), the time course of changes in the left ventricular weight/body weight in both studies would be similar over the first three days, and more rapid over the following two weeks in Lundgren's series (Table 6-8).

The slight bradycardia which occurred when phenylephrine was injected into the 25-day hypertensive rats (on the average 0.299±0.072 ms/mm Hg) is illustrated in Fig. 6-14. One day after the removal of the renal artery clip, baroreflex sensitivity increased to 0.657±0.155 ms/mm Hg) (Fig. 6-15) ($P<0.07$, unpaired t-test, $P<0.05$, Wilcoxon rank sum test) not significantly different from the BRS of the 25-day normotensive control animals (0.995±0.199 ms/mm Hg) (Figs. 6-4 and 6-21). A further increase in BRS was seen over the following 6 days (Figs. 6-17, 6-21). Figures 6-16, 6-17, 6-18 and 6-19 illustrate the effect of similar injections into animals whose constrictions had been removed 3, 7, 14 and 25 days previously, whereas Fig. 6-20 is from a 50-day normotensive control animal. The increase in baroreflex sensitivity was clearly significant by day 3. None of the declipped animals had baroreflex sensitivities which differed significantly from the normotensive 25-day values.

With the exception of the 1-day declipped group, which showed a significant inverse correlation between BRS and mean arterial pressure ($r=-0.76$, $P<0.05$; Fig. 6-22), there appeared to be no relationship between MAP and BRS within each group (Table 6-6) or in the declipped animals as a whole (Fig. 6-23). The delay which gave the best correlation between mean arterial pressure and the succeeding pulse interval was similar in each group.

Table 6-6

RAT GROUPS	*r*
Normotensive 25-day	-0.20
Hypertensive 25-day	-0.63*
Declipped 1-day	-0.76**
Declipped 3-day	-0.44
Declipped 7-day	-0.33
Declipped 14-day	-0.22
Declipped 25-day	-0.15
Normotensive 50-day	-0.04
Declipped Rats (1 to 25 days)	-0.10

Group data on correlation (r) between baroreflex sensitivity and mean arterial blood pressure in 25- and 50-day normotensive control rats, renal hypertensive rats after 25 days, and rats whose hypertension was reversed by removal of a left renal artery clip 1, 3, 7, 14 and 25 days earlier (n=8 in all groups, except for the declipped 1-25 day group, in which n=40; *=P<0.10; **=P<0.05).

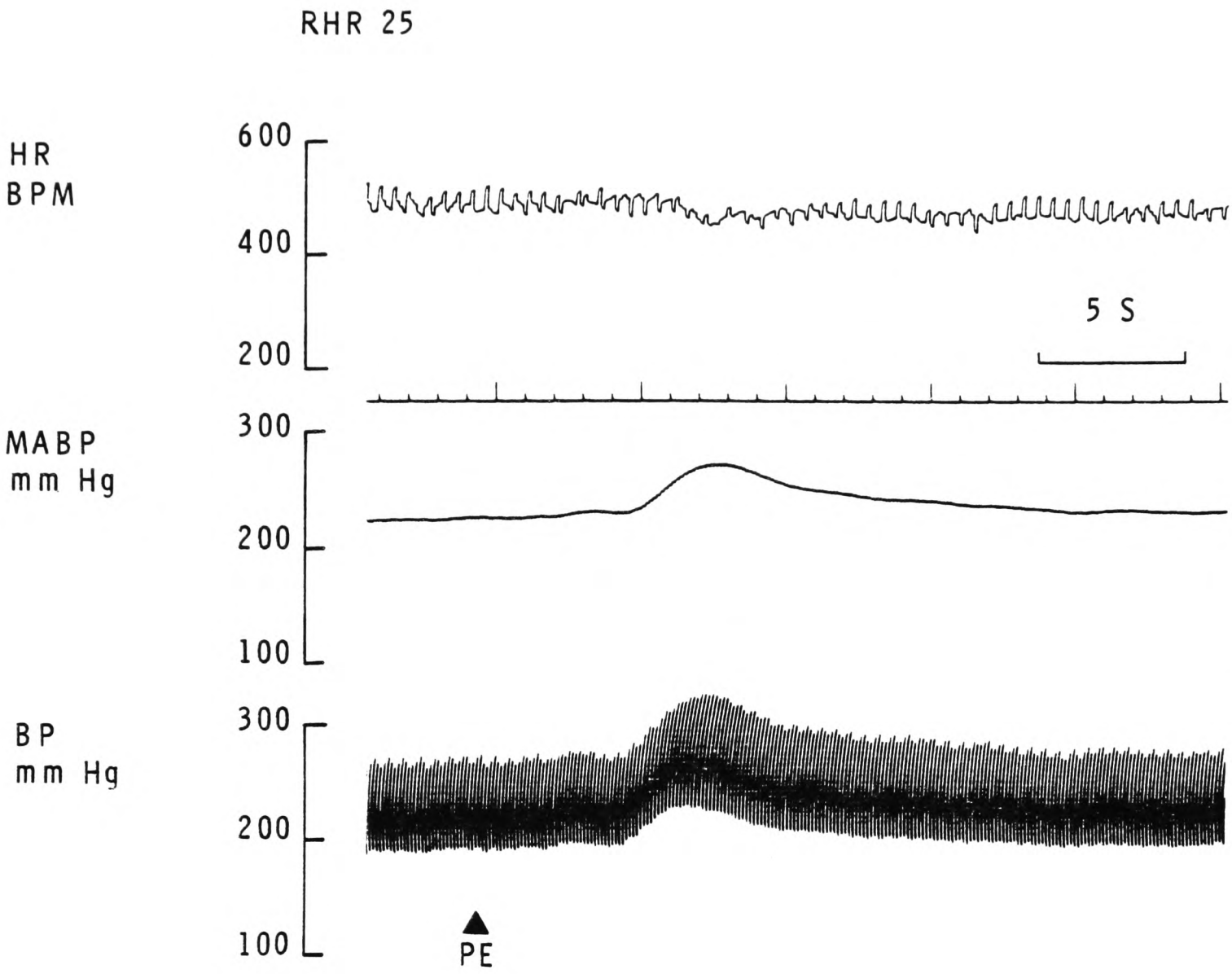

Fig. 6-14 Heart rate (HR), mean arterial pressure (MABP) and pulsatile arterial pressure (BP) in a rat with renovascular hypertension of 25 days' duration (RHR 25). Injection of 1 µg of phenylephrine (PE) causes a rise in blood pressure and a fall in heart rate.

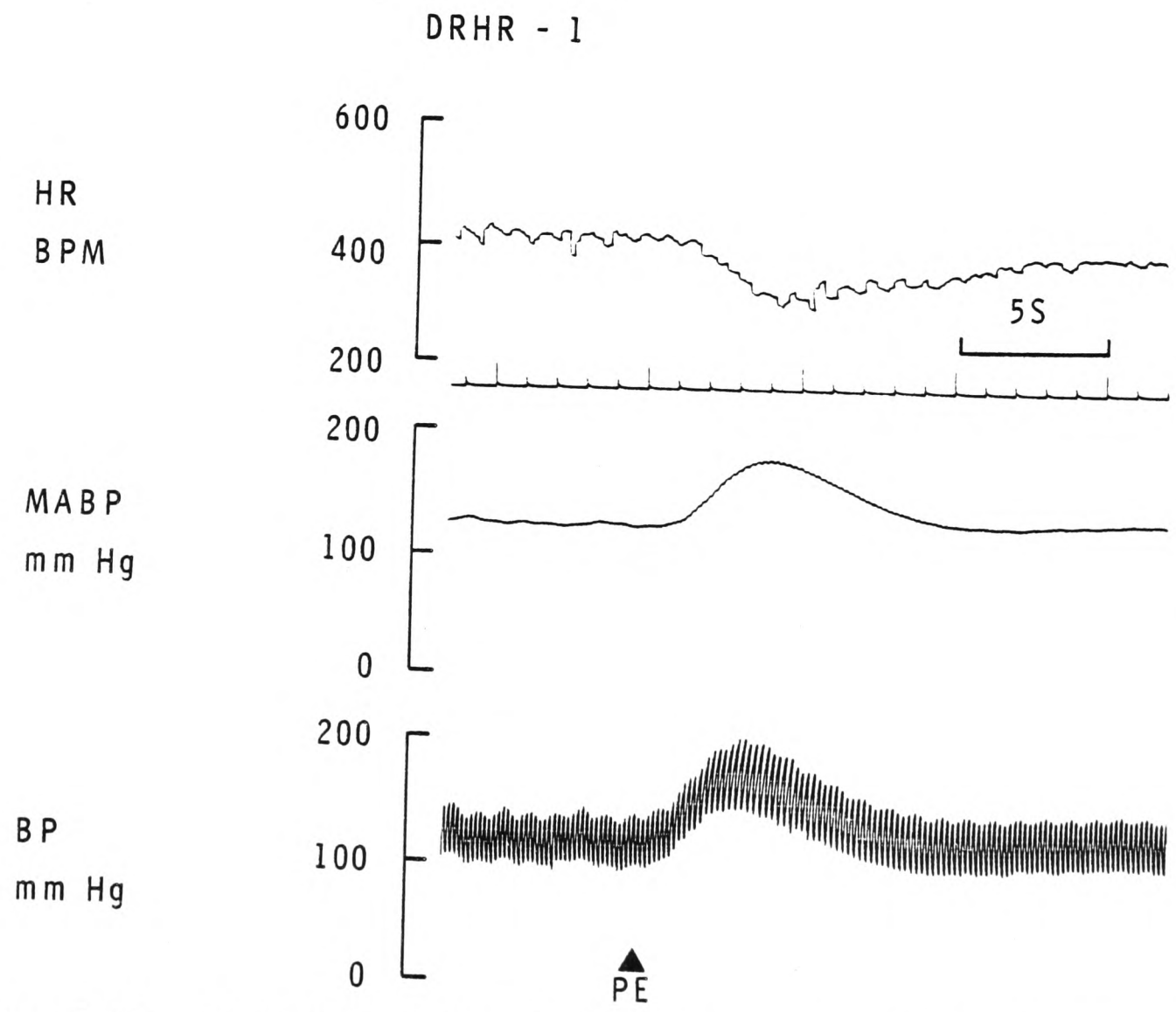

Fig. 6-15 As in Fig. 6-14. One day after the removal of the renal artery constriction (DRHR-1), pressure has fallen and the same dose of phenylephrine produces a relatively greater fall in heart rate.

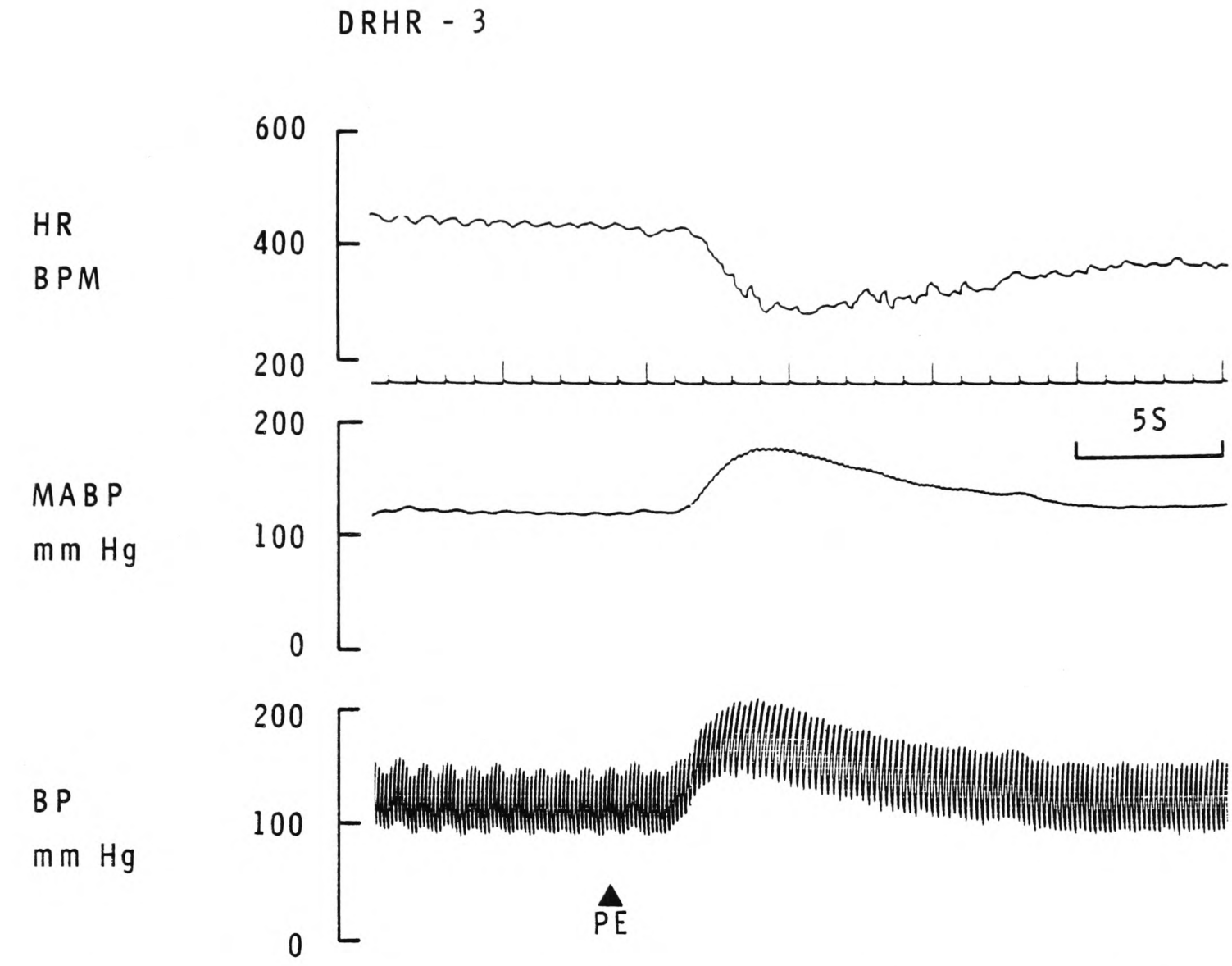

Fig. 6-16 As in Fig. 6-14. Three days after the removal of the renal artery constriction (DRHR-3).

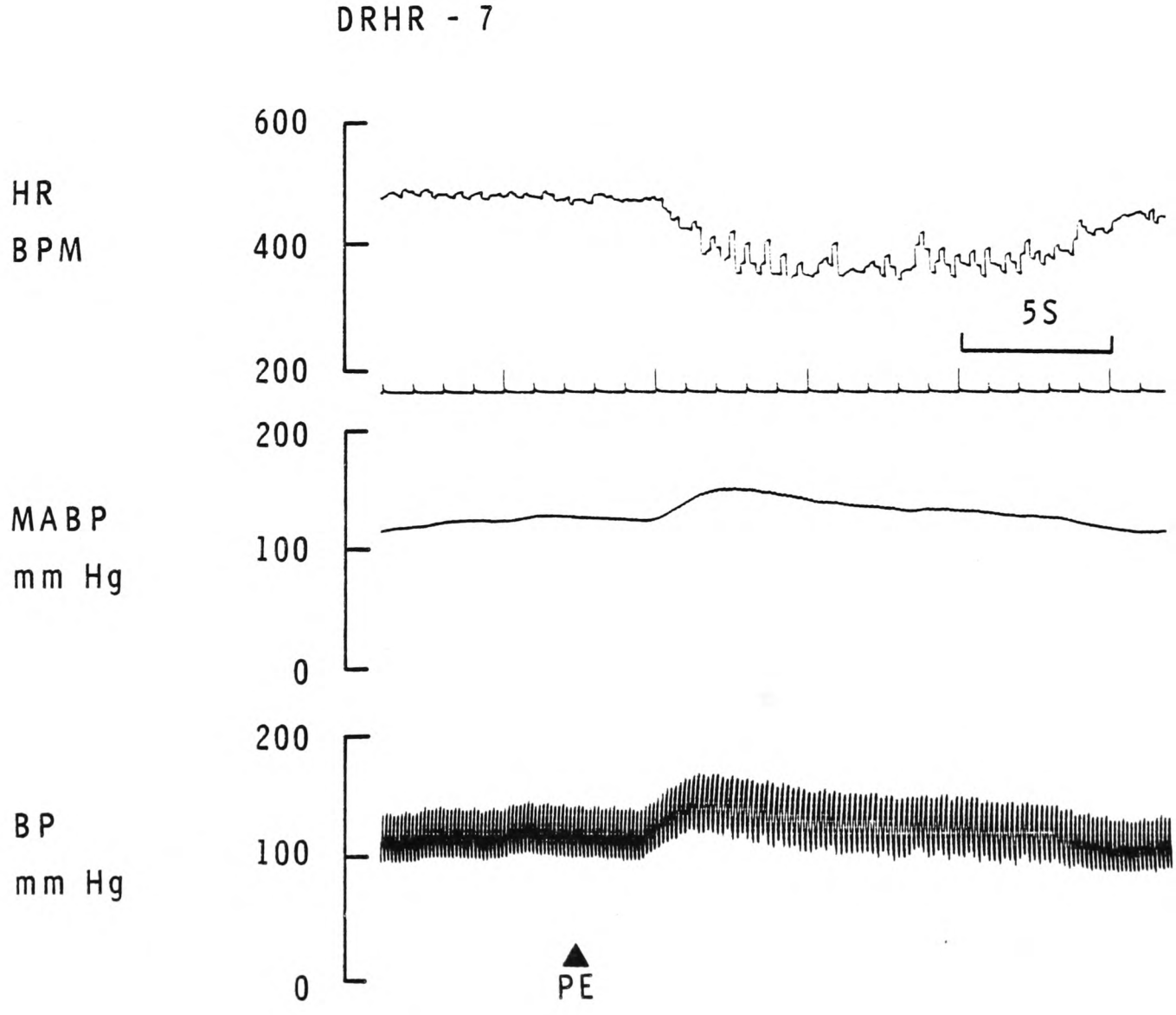

Fig. 6-17 As in Fig. 6-14. Seven days after the removal of the renal artery constriction (DRHR-7).

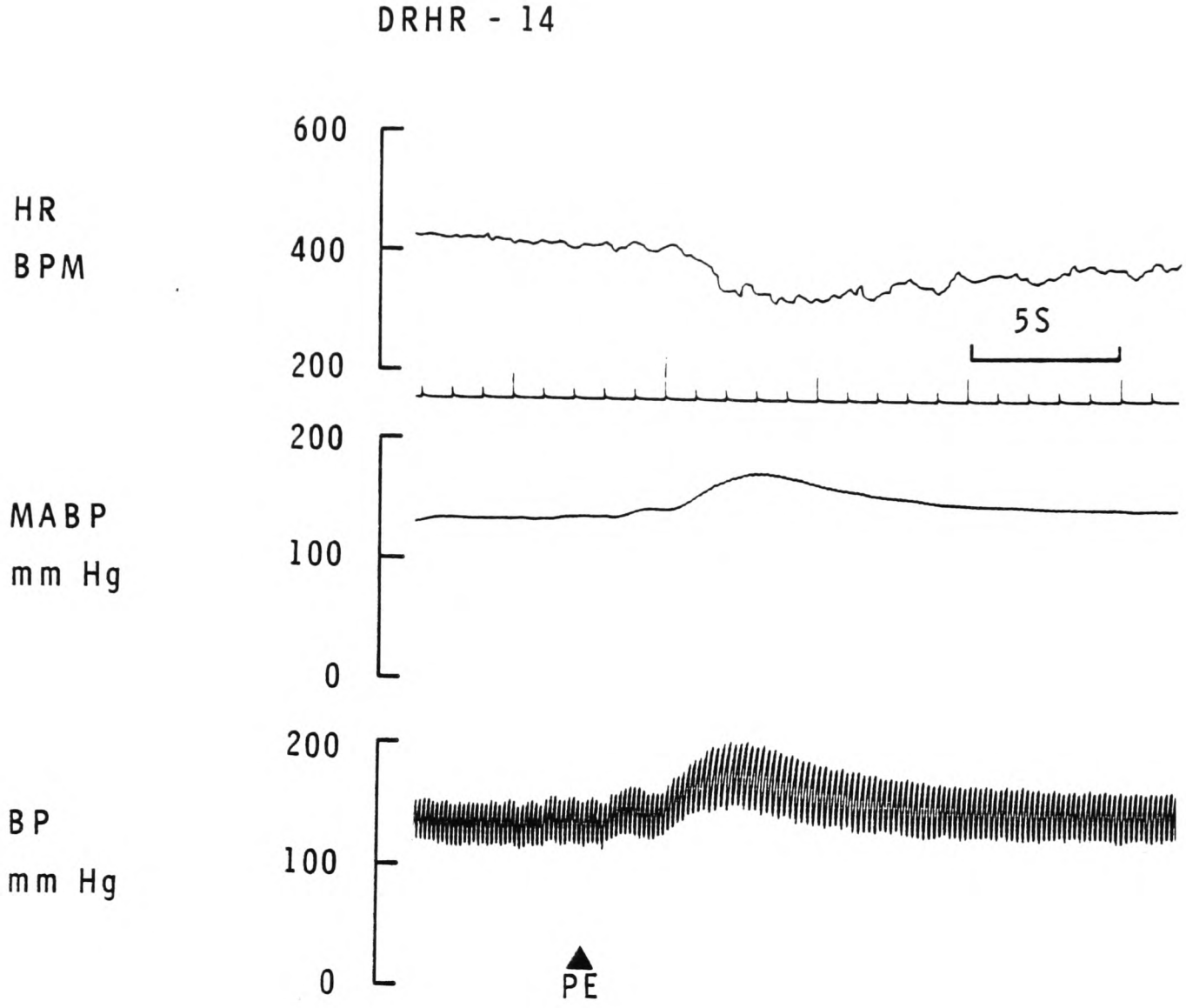

Fig. 6-18 As in Fig. 6-14. Fourteen days after the renal artery constriction has been removed (DRHR-14).

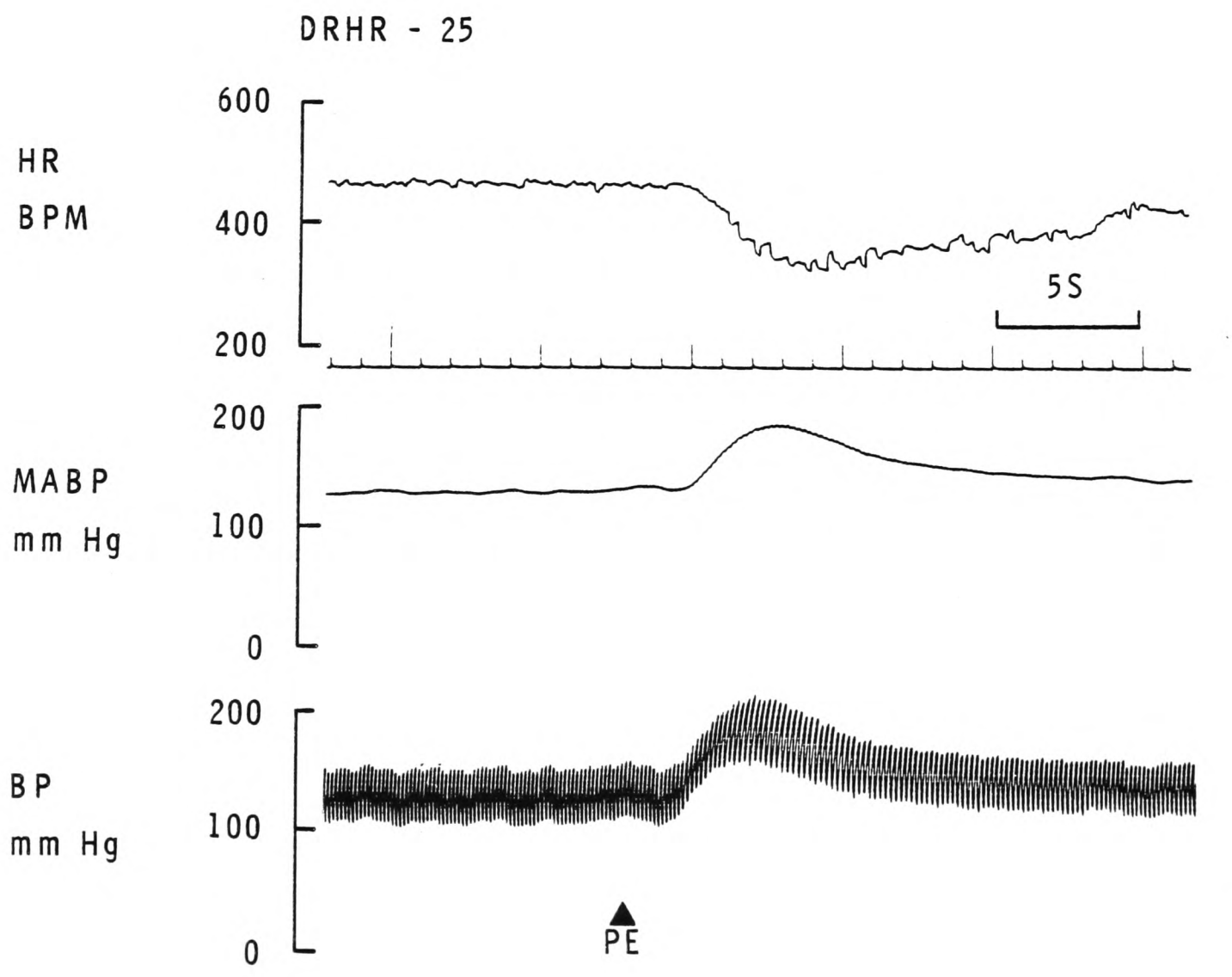

Fig. 6-19 As in Fig. 6-14. Twenty five days after the renal artery constriction has been removed. The injection of 1 µg of phenylephrine (PE) produces a rise in blood pressure and a reflex bradycardia.

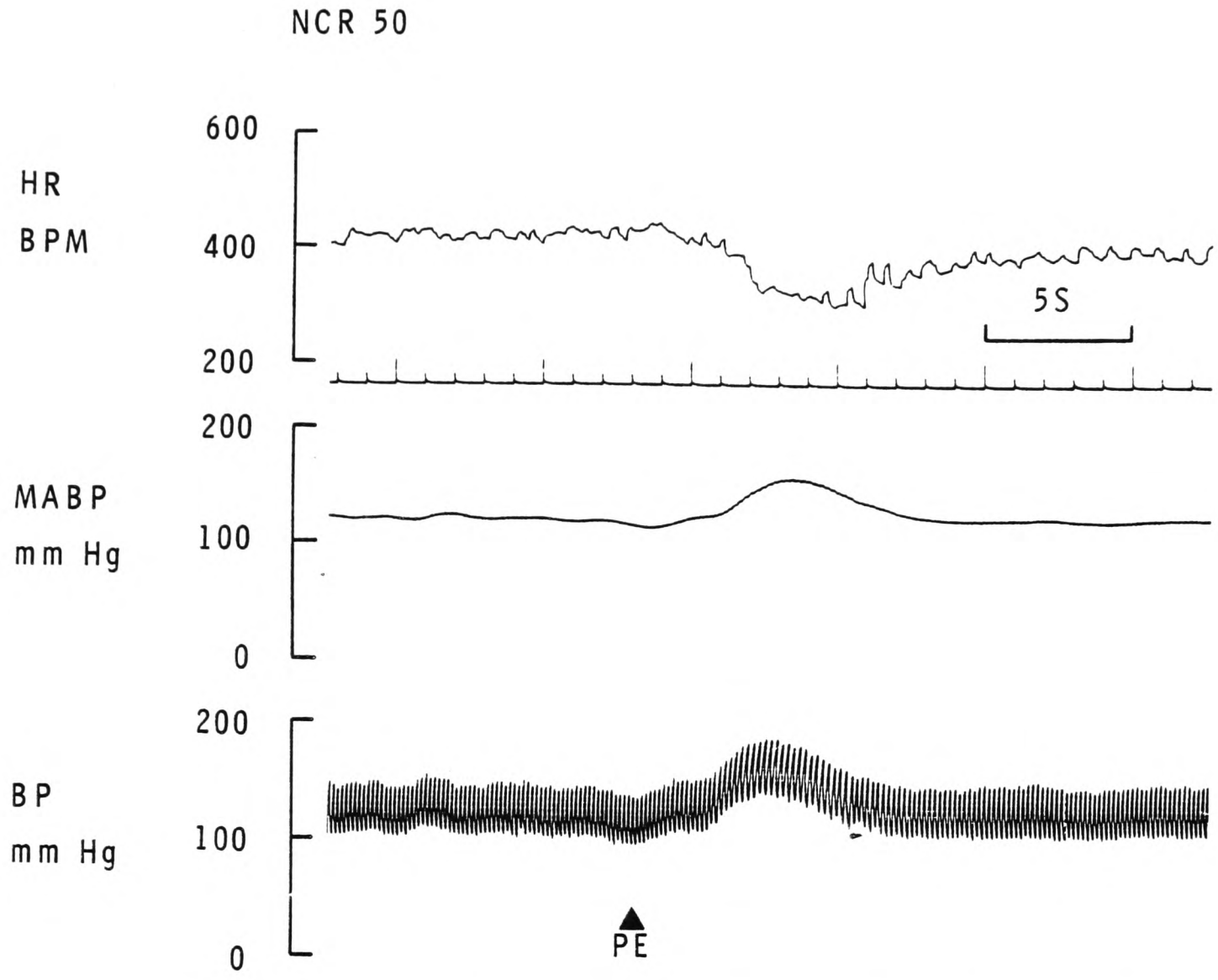

Fig. 6-20 As in Fig. 6-4. Normal control rat (NCR 50) similar in age to rats studied 25 days after removal of the renal artery constriction (D-RHR 25).

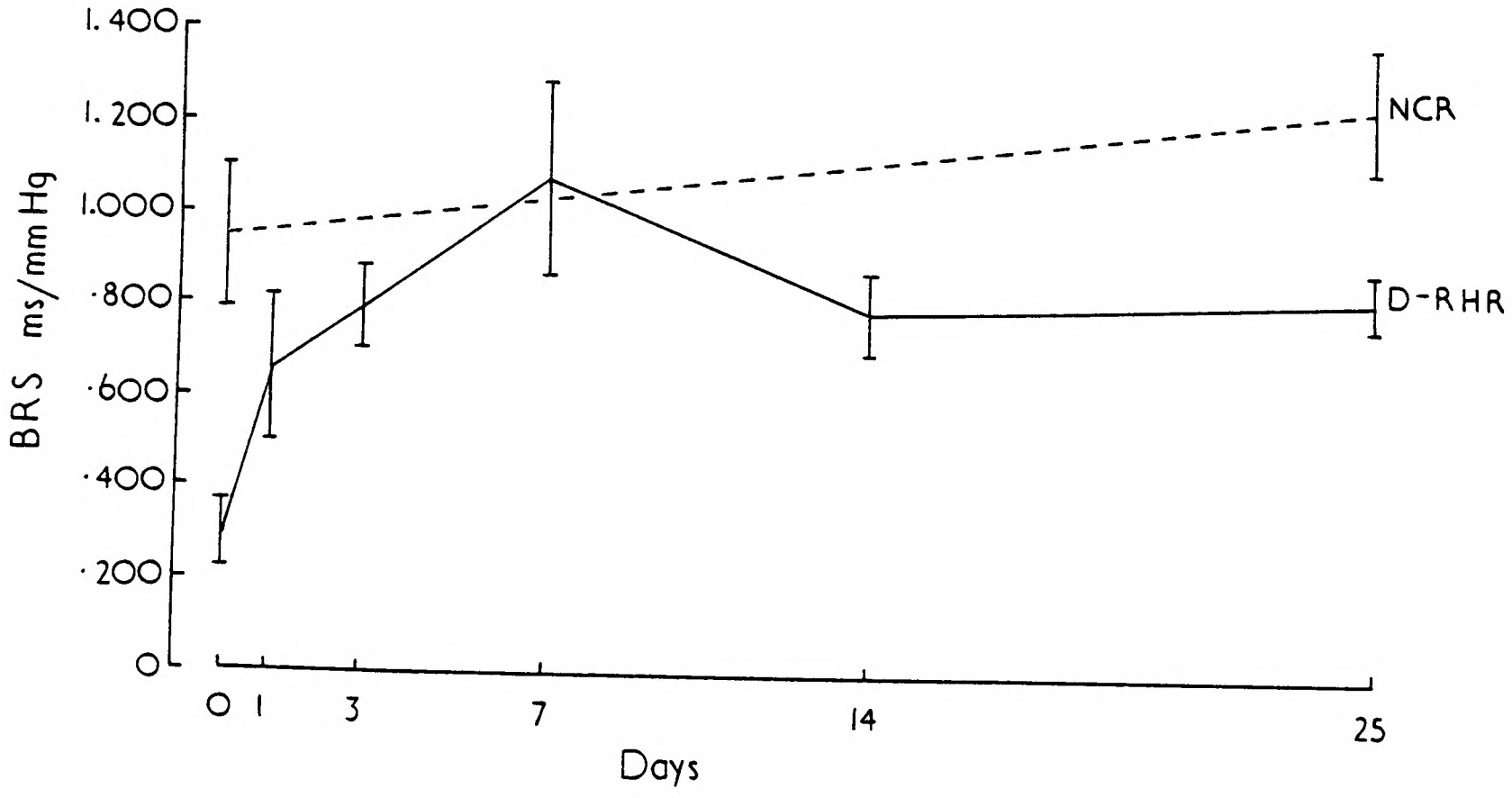

Fig. 6-21 Baroreflex sensitivity (BRS) in normal control rats (NCR) and rats with 2-kidney 1-clip Goldblatt hypertension of 25 days' duration, before (Day 0), and 1, 3, 7, 14, and 25 days after removal of the renal artery constriction (n=8 in all groups).

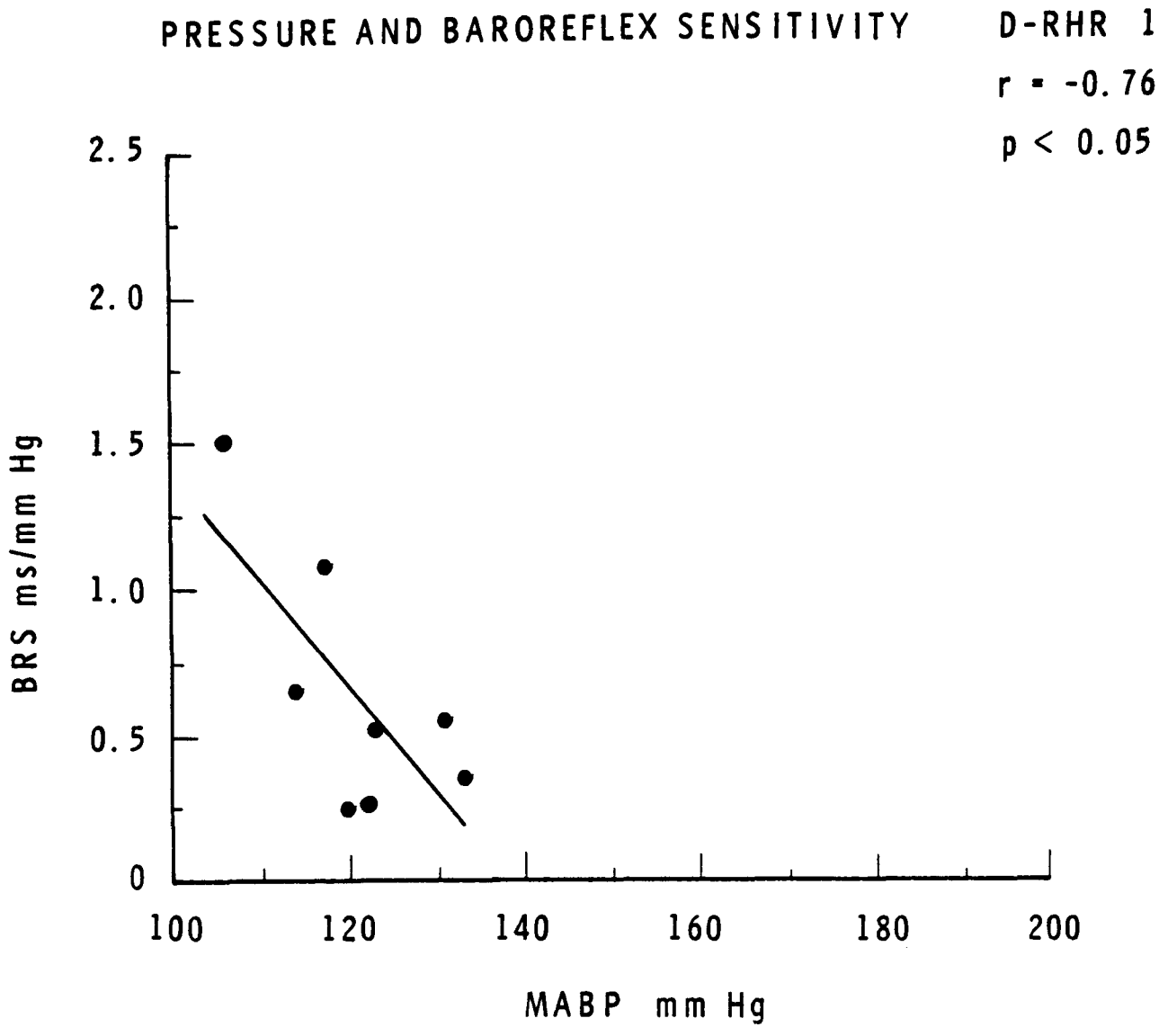

Fig. 6-22 Relationship between mean arterial pressure (MABP) and Baroreflex sensitivity (BRS) in 8 rats studied 1 day after the reversal of 2-kidney 1-clip Goldblatt hypertension of 25 days' duration.

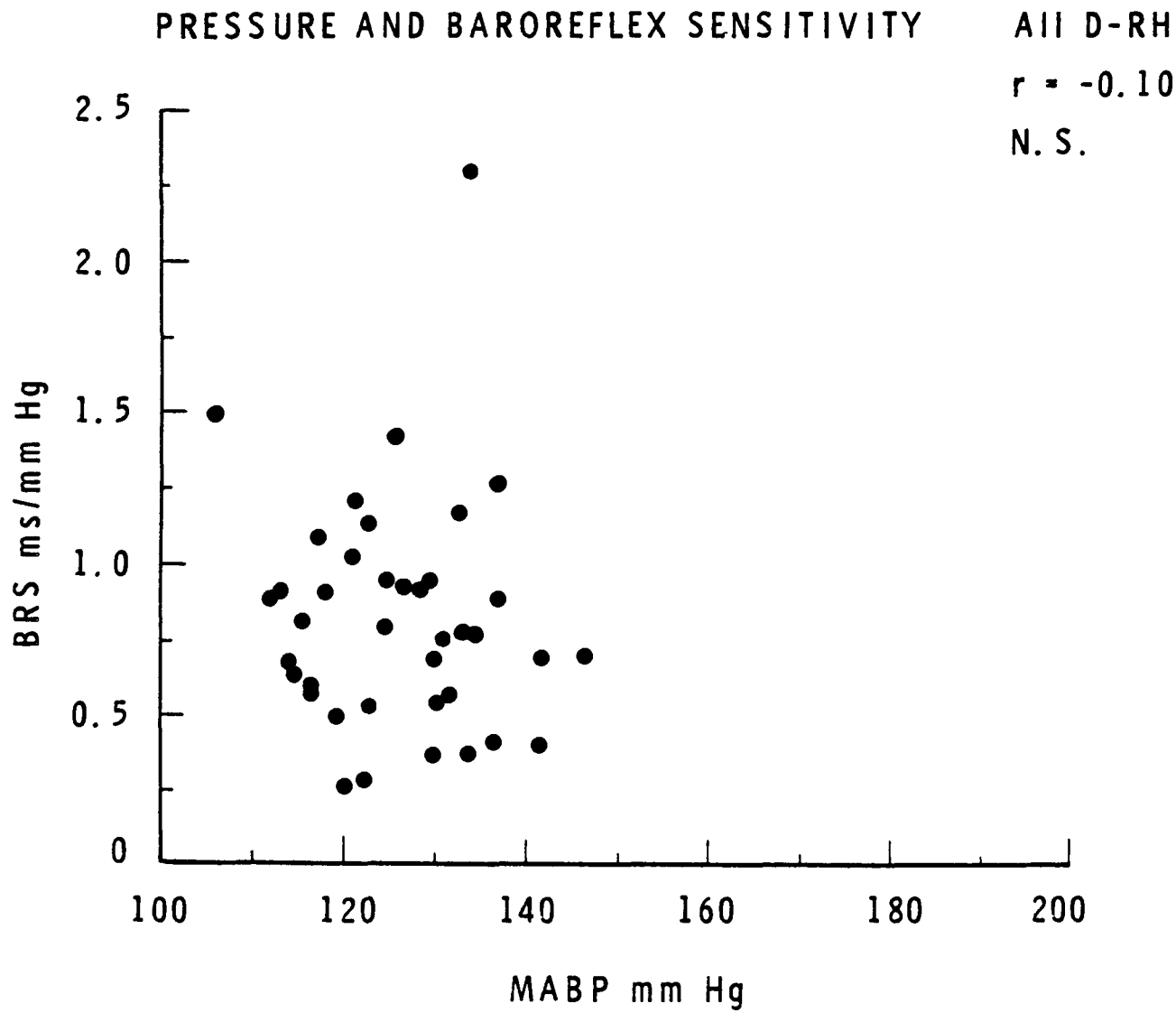

Fig. 6-23 Relationship between mean arterial pressure (MABP) and Baroreflex sensitivity (BRS) in all rats following the reversal of 2-kidney 1-clip Goldblatt hypertension of 25 days' duration. (See text and Table 6-6 for details)

DISCUSSION

And as the State of the Blood or Blood vessels are in these Respects continually varying from divers Causes, as Motion, Rest, Food, Evacuations, Heat, Cold &c. so as probably never to be exactly the same, any two Minutes, during the whole Life of an Animal, so nature has wisely provided, that a considerable Variation in these, shall not greatly disturb the healthy State of the Animal.

- Experiment IX
Stephen Hales (1733)

CHAPTER 7

DISCUSSION

The present investigations had two aims. One was to study, in subjects with essential hypertension, the effect that reduced baroreflex sensitivity might have on several indirect indices of sympathetic nervous activity. The second aim was to define the time course and extent of changes in baroreflex sensitivity in rats, in relation to changes in the heart and (by inference from the work of Lundgren (1974a,b)) the peripheral vasculature, during the development and reversal of 2-kidney 1-clip Goldblatt hypertension.

Essential hypertension

A direct comparison of heart rate, blood pressure and its variability, and plasma noradrenaline concentrations between normal and hypertensive subjects was not possible. Instead, multiple regression analysis and partial correlation coefficients were used to examine the independent effect that age, blood pressure and baroreflex sensitivity might exert over each of these indices of sympathetic nervous activity in subjects being investigated for hypertension. The range of ages (16-69 years), blood pressures (139/80 mm Hg to 213/137 mm Hg by cuff), and baroreflex sensitivities (1.607 ms/mm Hg to 38.130 ms/mm Hg) of these subjects was high, thereby improving the likelihood of detecting any effect of these variables, if such an effect were present.

Some of these subjects, diagnosed as having borderline or mild hypertension on the basis of conventional criteria, using casual cuff measurements, may not have had persistently elevated blood pressure. As may be seen in Fig. 5-37, about 20 individuals had average ambulatory mean arterial pressures of less than 107 mm Hg (i.e. comparable to 140/90 mm Hg). The difference between cuff and average ambulatory mean arterial pressure, which averaged 10 mm Hg overall, tended to be greatest in those subjects who were free of detectable end-organ damage (Floras, Jones, Hassan, Osikowska, Sever and Sleight, 1981). Similar observations were made by Sokolow et al. (1966) and Watson, Stallard, Flinn and Littler (1980).

Despite their 'normal' average ambulatory mean arterial pressures, these 20 subjects could not be properly considered normotensive. Ordinarily, they would have been presumed to be hypertensive on the basis of their elevated cuff pressures, and treated. Moreover, any dividing line between 'normal' and 'high' blood pressure, on the basis of these direct records, would be entirely arbitrary, and there is, as yet, no evidence to suggest that the long-term prognosis of these patients is improved by virtue of their lower ambulatory pressures. Given the present experimental design, any division of these subjects into categories of 'normal' and 'high' blood pressure subsequent to the analysis of the ambulatory blood pressure record would have exposed any comparison of these two groups to the statistical criticism of 'subset selection'. The continuous distribution of blood pressure within the population (Pickering, 1968) suggests that it is preferable to examine the independent effect of blood pressure on the indices of sympathetic nervous activity under investigation, rather than to

divide these subjects into arbitrary 'normal' and 'hypertensive' groups.

Baroreflex sensitivity

Baroreflex sensitivities in these patients were consistent with their ages and mean arterial pressures (eqn. 6) (Pickering, 1970; Gribbin et al., 1971). The use of weighted mean slopes narrowed the confidence limits about these estimates without significantly altering their magnitude (Chapter 4). These narrowed confidence limits, in turn, may have assisted the statistical handling of the data, in view of the number of subjects of similar ages and mean arterial pressures, who could be predicted, on this basis, to have similar slopes.

The distribution of slopes in these investigations was skewed; linear relationships between baroreflex sensitivity, age and systolic blood pressure could be obtained by log-transformation of the data. When this was done, baroreflex sensitivity was found to be independent of resting heart rate (eqn. 7). This confirmed the findings of Gribbin et al. (1971).

The relationship between baroreflex sensitivity and sympathetic nervous activity

The activity of the sympathetic nervous system was assessed indirectly in these 62 patients in three ways: by recording changes in heart rate and blood pressure during mental and physical exercise, by measuring plasma noradrenaline concentrations at rest, and on exercise, and by examining the variability of mean arterial pressure during the waking day.

Changes in blood pressure and heart rate during mental and physical exercise

All four exercises elicited significant increases in mean arterial pressure, physical exercise (28%) more than mental exercise (20%) (Fig. 5-20). Isometric and bicycle exercise increased mean arterial pressure to a similar extent, as noted by Brorson et al. (1978), but a much greater increase in heart rate and systolic blood pressure occurred during bicycling. The increase in diastolic pressure was least with this exercise.

The reaction time test (Obrist, 1976) produced similar increases in mean arterial pressure to those in previous reports, but was the least effective pressor stimulus. Nor was blood pressure increased purely through a rise in heart rate and systolic pressure, contrary to the literature; the increase in diastolic pressure was greater than the systolic, and the heart rate response was the smallest of the four exercises (Tables 5-2 to 5-5). The haemodynamic response to the reaction time test appeared to resemble mental arithmetic, but in a weaker fashion.

The maximum mean arterial pressure achieved during each of the four exercises was significantly related to the mean arterial pressure at rest. This could have been due to similar, or greater increases in mean arterial pressure in patients with higher, as compared to lower, resting pressures. The absolute and relative increases in blood pressure during each exercise were therefore calculated. Gombos, Hulet, Bopp, Goldring, Baldwin and Chasis (1962) suggested that the altered vascular design in hypertension should lead to greater absolute changes in blood pressure, following pharmacologic or physiologic stimulation. Folkow (Folkow, Grimby

and Thulesius, 1958; Folkow, 1978) has provided the theoretical groundwork for this suggestion. However, the absolute increase in mean arterial pressure was independent of the resting blood pressure in each exercise, even when the influence of age was excluded by partial correlation coefficients (Tables 5-8, 5-10, 5-12, 5-14); and the relative increase in mean arterial pressure tended to be less in the subjects with higher resting pressures. Similar findings in borderline and persistent hypertensive, and normal subjects have been reported by Hjemdahl and Eliasson (1979) during mental arithmetic and tilt, and Sannerstedt (1966), Sannerstedt and Julius (1972) and Brorson et al. (1978) during physical exercise. On the other hand, Brod et al. (1959) noted larger increases in blood pressure in hypertensive patients during mental arithmetic, as did Lamid and Wolff (1973) and Nyberg (1976) during isometric exercise; Sannerstedt (1966) found that blood pressure rose to a greater extent during bicycle exercise in subjects with WHO Stage II or III disease.

It might be concluded from this that structural vascular adaptations, which lead to increased pressor responses to supra-threshold doses of noradrenaline, are not in themselves haemodynamically important in the conscious subject. Moreover, rats with renovascular hypertension respond to alerting stimuli with similar changes in blood pressure as do normal rats, despite the presence of these vascular alterations in the former group. Young 'pre-hypertensive' SHR and older SHR respond with much greater increases in blood pressure, even though the development of structural changes in the heart and resistance vessels is incipient in the younger group (Hallback and Folkow, 1974; Folkow and Hallback, 1977).

Structural changes may therefore require an environment of increased neurogenic activity, before they are able to amplify the pressor response to activation of the sympathetic nervous system. If haemodynamic changes were purely a function of structural changes, one would expect hypertensives of similar age and mean arterial pressures to have roughly similar increases in blood pressure during mental and physical exercise in this study. This is not the case, as can be seen in Figures 5-5, 5-9, 5-13, and 5-18. An additional, neurogenic, component is evidently present in some subjects.

Baroreflex regulation of blood pressure and heart rate during exercise

Baroreflex sensitivity was inversely related to mean arterial pressure at rest, and to the maximum mean arterial pressure during each of the four exercises (Figs. 5-4, 5-8, 5-12, 5-17). The absolute changes in blood pressure were used to detect whether subjects with more sensitive baroreflexes were better able to buffer the acute increases in blood pressure with each exercise. The results did not, on the whole, support this contention (Figs. 5-6, 5-10, 5-14, 5-19). Neither zero-order, nor partial correlation coefficients revealed baroreflex sensitivity to have any bearing on the absolute or relative increases in mean arterial pressure during mental arithmetic, the reaction time test, or isometric exercise (Tables 5-8, 5-10, 5-12, 5-14). However, the change in blood pressure during bicycle exercise was significantly, and inversely, related to baroreflex sensitivity (Fig. 5-19). Multiple regression analysis and calculation of partial correlation coefficients revealed this to be an age-related effect (eqn. 28); the absolute

increase on bicycling was greater in subjects whose BRS was reduced on account of age (Table 5-14). Julius et al. (1967) also noted that changes in systolic blood pressure, and systemic vascular resistance during bicycle exercise were greater at all levels of exertion in older subjects.

Koch's "Blutdruck-Herzfrequenz-Charakteristic" curve (1931) no longer applies when subjects are alerted, stressed, or exercised (Smyth, 1967; Bristow, Brown, Cunningham, Howson, Strange Petersen, Pickering and Sleight, 1971; Sleight et al., 1978).

The lack of relationship between baroreflex sensitivity and changes in blood pressure in three of the four exercises might be explained if (1) the baroreflex control of peripheral resistance, as well, was acutely altered, or (2) baroreflex mediated withdrawal of sympathetic efferent activity was amplified in hypertensive subjects whose resistance vessels had increased their wall to lumen ratio (as suggested by Angell-James and George, 1980). Bicycle exercise may differ in that the activation of somatic afferents from muscle may override the effect of both factors.

The extrapolation of a demonstrable reduction in the reflex control of heart rate to the inferred reduction in the baroreflex control of peripheral resistance in exercising hypertensive patients is based on three assumptions: (1) that the baroreflex control of blood pressure and heart rate are normally of similar magnitude; (2) that the baroreflex remains intact, or only partially blunted during mental and physical exercise, and (3) that the resetting of baroreceptor afferent discharge with increasing age and blood pressure affects efferent control of heart rate and peripheral resistance to the same extent.

Schmidt et al. (1971) noted that changes in carotid sinus perfusion pressure in anaesthetised dogs led to falls in both heart rate and peripheral resistance. However, an inverse, rather than a linear relationship between these two variables was detected. When Faris et al. (1980), using an isolated carotid sinus preparation, examined this question in the conscious resting rabbit, static pressure changes produced heart rate and blood pressure responses that were similar in direction and in magnitude, but clearly capable of dissociation by autonomic blockade. A similar dissociation can be effected by medullary lesions (Humphrey, 1967; Miura and Reis, 1969; Talman et al., 1980).

Inactivation of the baroreceptors during exercise could occur through peripheral, central, or even efferent means, e.g. the accumulation of vasoactive metabolites.

Increased sympathetic tone during exercise might make the baroreceptors less susceptible to mechanical deformation; however, experimental evidence suggests that sympathetic stimulation or the local application and infusion of sympathomimetic compounds has the opposite effect (Heymans and van den Heuvel Heymans, 1950; Landgren et al., 1952; Koizumi and Sato, 1969; Sampson and Miles, 1970; Bergel et al., 1980; Peveler et al., 1980). Marx, Powell, Conn, Bruce and Kusumi (1967) pointed out that the lateral distending pressure in arteries, which exerts strain upon the mechanoreceptors, may be considerably less than the kinetic energy of the blood, i.e. the value measured when an ordinary catheter is inserted into a peripheral artery. Thus, the actual stimulus to the baroreceptors during exercise may be less than is thought. Astrand and Rodahl (1977) recommended that a cannula with side holes be used to measure the

effect of lateral distending pressure on baroreceptors during exercise.

The lack of relationship between LBRS and the change in blood pressure during mental arithmetic and reaction time test may be due to the activation of a defence-like reaction which overrides the baroreflex control of blood pressure. Hilton (1963; 1966) demonstrated that the baroreflex control of heart rate could be diminished by hypothalamic stimulation; the reflex control of peripheral resistance was felt by others to be minimally suppressed, or even enhanced (Djojosugito et al., 1970; Gebber and Snyder, 1970; Humphreys and Joels, 1972; Kumada, Schramm, Altmansberger and Sagawa, 1975). However, Coote et al. (1979) found that the reflex response to hypothalamic stimulation was dependent upon its location: both efferent arcs could be acutely altered by stimulation within the hypothalamic defence area, whereas stimulation slightly outside this region only altered the heart rate response to carotid sinus nerve stimulation. The physiological response to mental arithmetic is thought to resemble this defence reaction (Brod et al., 1959; Brod, 1963) but the similarity of this response in man to hypothalamic stimulation in animals can only be a subject of speculation. Interestingly, sympathetic discharge in muscle nerve fascicles is inhibited during mental arithmetic, as would be expected if the baroreflex continued to function (Delius et al., 1972b).

Isometric exercise does not appear to interfere with the pressor and depressor responses to positive and negative neck pressure. On the other hand, 'central command' appears to inactivate the baroreflex regulation of heart rate almost immediately in both isometric and bicycle exercise; it is through changes in cardiac

output that the rise in blood pressure is mediated in the former exercise. Interestingly, the increases in heart rate during mental arithmetic and isometric exercise were of similar magnitude in this series, although the increase in blood pressure was significantly greater during handgrip (Tables 5-2 to 5-5); thus the reflex regulation of heart rate may not be completely abolished during this manoeuvre.

In this, and other studies, the rise in blood pressure in normal, labile and hypertensive subjects appears to be similar when 30% of maximum voluntary contraction is exerted. These haemodynamic changes may be sufficient to ensure adequate blood flow to the contracting muscle, with baroreflex regulation of the circulation inhibited only insofar as needed to meet these requirements (Freyschuss, 1970a,b; McCloskey and Mitchell, 1972; Sannerstedt and Julius, 1972; Chrysant, 1978; Ludbrook et al., 1978; Mancia et al., 1978; Robertson, Shand, Hillifield, Nies, Frolich and Oates, 1979; Duncan et al., 1981). Sympathetic discharge to the muscle nerves increases during this exercise, but Delius et al. (1972b) continued to observe the normal rhythmic inverse relationship between sympathetic bursts and variations in diastolic blood pressure during handgrip.

The only significant inverse relationship between baroreflex sensitivity and the change in mean arterial pressure was seen during bicycle exercise. There are several possible explanations for this.

The baroreflex regulation of resistance may remain selectively intact, e.g. mediating splanchnic vasoconstriction and peripheral venoconstriction in order to sustain arterial pressure during exercise. Bevegard and Shepherd (1966) observed similar falls in blood pressure at rest and during dynamic exercise when the carotid

sinus was stimulated by negative suction, and concluded that the baroreceptors continued to oppose the rise in blood pressure during this activity. Geis and Wurster (1980) have recently shown that the reflex response to carotid sinus occlusion and hypertension persists, albeit in a reduced fashion, in exercising dogs.

Secondly, bicycle exercise, which increased systolic pressure by 36% on average (Table 5-4), may have provided a stronger stimulus to the baroreceptors. Thirdly, the haemodynamic changes during bicycle exercise which were due to large increases in cardiac output and selective vasodilation in the resistance vessels of muscle (Vatner and Pagani, 1976) may have been more amenable to baroreflex regulation. Beiser et al. (1970) showed that stimulation of the carotid sinus baroreceptors with neck suction led to a reflex reduction in skin and muscle vascular resistance in subjects at rest, and animal studies suggest that the effect of baroreceptor stimulation is most marked in the skeletal muscle bed (Vatner et al., 1970; Kendrick et al., 1972; Cox and Bagshaw, 1975). The difference in cardiac output between borderline and normal subjects disappears on exercise, and at moderate workloads the increase in blood pressure in the former group is mediated by a higher vascular resistance (Amery et al., 1967). This could be due to the presence of structural changes, or due to a greater inhibition of baroreceptor mediated vasodilation during exercise in hypertensive subjects (Donald et al., 1970; Vatner et al., 1970). This factor may be more important at rest than during exercise, which tends to induce maximal vasodilation. However, Abboud and his colleagues (1979) contend that cardiopulmonary reflexes have a greater influence than baroreceptor reflexes over the resistance vessels in skeletal muscle.

Warner and Topham (1967) have shown that exercise tachycardia can be prevented if peripheral resistance is kept constant with an aortic cuff. If the tachycardia of bicycle exercise remains under baroreflex control, another discrepancy between bicycling and the previous three exercises may be explained, namely the lack of relationship between changes in mean arterial pressure and changes in heart rate (eqns. 11, 18, 24, 31). The tachycardia in the other three exercises may be an important determinant of the extent to which blood pressure rises; heart rate may be released from baroreflex control by input from supramedullary centres to a greater extent in mental arithmetic and isometric exercise than in bicycle exercise.

The combined activation of 'central command', and somatic and cardiopulmonary reflexes, is greatest during bicycle exercise. These systems may have synergistic or opposing effects on the baroreflex which can contribute to the rise in blood pressure and heart rate and not be buffered entirely by the sinoaortic baroreflex arc (Freyschuss, 1970a,b; McCloskey and Mitchell, 1972; Bevegard, Castenfors and Lindblad, 1977; Mitchell et al., 1977; Abboud, 1979). Abboud (1979) has suggested that the reduction in baroreflex sensitivity in hypertension may be associated with an increase in sympathetic outflow to blood vessels when somatic afferents are activated; the principal difference between isometric and bicycle exercise, as suggested by the work of Duncan et al. (1981), in patients with sensory neuropathies, and Streatfield et al. (1977) in anaesthetised dogs, may in fact be the relative unimportance of somatic afferent activation during handgrip. The observation that reduced baroreflex sensitivity was reflected in greater absolute increases in blood pressure, and higher plasma noradrenaline concentrations during bicycling, alone, is consistent with this suggestion.

Given that there is some evidence for retention of baroreflex control of resistance in mental exercises and handgrip, can there be an alternative explanation for the lack of relation between exercises? The maximum gain of curves relating increases in carotid sinus transmural pressure (CSTMP) to changes in systemic blood pressure appeared to be increased, whereas those relating increases in CSTMP to changes in heart rate were decreased, when hypertensive subjects (Mancia et al., 1978) and rabbits (Angell-James and George, 1980) were studied about their resting mean arterial pressures. The latter authors suggested that a withdrawal of efferent sympathetic activity should produce a larger fall in peripheral resistance in the presence of the increased wall to lumen ratio thought to occur in the resistance vessels in hypertension (Folkow, 1978).

The net effect of this process might be a similar buffering of blood pressure rises in normal and hypertensive man under most conditions: the reduced baroreceptor afferent input to the central nervous system may be balanced by the fact that any changes in efferent sympathetic nerve discharge to the resistance vessels would be amplified by these vascular adaptations, provided that the baroreflex remained operative and was not overcome by other neural activity, e.g. somatic input from exercising muscle. This hypothesis might explain why most young borderline hypertensive subjects have similar changes in blood pressure as normal subjects when tilted but would not explain why they have similar changes in blood pressure when exercised (Hoel et al., 1970; Sannerstedt, 1966; Sannerstedt et al., 1971; Sannerstedt and Julius, 1972; Brorson et al., 1978; Robertson, Shand, Hollifield, Nies, Frohlich and Oates, 1979). As the composition and distensibility of the vascular wall alters with age (Roach and Burton, 1959; Learoyd and Taylor, 1966; Wolinsky, 1972),

the resistance vessels may become less responsive to changes in sympathetic discharge, possibly explaining why with advancing age (Julius et al., 1967) or hypertension (Sannerstedt, 1966; Amery et al., 1967) these similarities may disappear. Bicycling was the only exercise in the present series in which older subjects exhibited greater rises in blood pressure (eqn. 28); again, this may be due to the activation of somatic afferents in the presence of reduced baroreflex sensitivity. Maximum heart rate during both physical exercises, and the relative increase in heart rate during bicycling, were reduced in older subjects. These observations are consistent with those of Gerstenblith et al. (1976) and with the suggestion that aging reduces the responsiveness to beta-adrenoceptor stimulation (Conway et al., 1971; Bertel et al., 1980).

Neither the maximum heart rates, nor the change in heart rate during these exercises were related to LBRS, probably because heart rates during exercise tended to decline with age.

Patients with poorer baroreflexes therefore achieved greater maximum arterial pressures during mental and physical exercise, but this was probably due to their higher baseline pressures. Only during bicycle exercise did reduced baroreflex sensitivity appear to be associated with decreased buffering of changes in mean arterial pressure.

Plasma noradrenaline concentrations at rest

Plasma noradrenaline concentrations (PNA) were determined at rest and during exercise in approximately fifty of the subjects. Resting PNA concentrations before mental arithmetic were 25-30%

higher than values obtained by other groups using the PNMT method (Sever, 1980). This may have been due to our waiting 15-20 minutes, as suggested by Sever (1980), rather than 3-4 hours as advised by Brecht and Schoeppe (1978), or may have been a result of sampling a smaller number of patients. Resting PNA before isometric and bicycle exercise, when patients were seated, were slightly, but not significantly, higher than the supine figures; these resting values are similar to those obtained by others with patients seated (Lake et.al., 1976).

Resting PNA in this study was normally distributed, as has been reported by Hofman et al. (1979) in a smaller number of patients, but not by Sever (1978) and Brecht and Schoeppe (1978) in a larger group. The data were not transformed logarithmically, as had been proposed by these, and other authors (Watson, Hamilton, Reid and Littler, 1979). The resting values were unrelated to age, any measure of blood pressure, heart rate, or indeed, baroreflex sensitivity. In this respect they are in keeping with studies by Sever et al. (1977), Miura et al. (1978) and Ibsen et al. (1979), who found no relationship between PNA and blood pressure, and Lake et al. (1977a), Sever et al. (1977), and Miura et al. (1978), who were unable to detect age related increases in plasma noradrenaline in a hypertensive population, but inconsistent with Louis et al. (1973), Brecht and Schoeppe (1978), Hofman et al. (1979) and Kiowski et al. (1981) who showed a relationship between arterial pressure and plasma noradrenaline and Brecht and Schoeppe (1978), who reported that PNA increased with age in a hypertensive population.

These data might imply that certain young borderline hypertensives exhibit increased PNA, while their normal age-matched counterparts do

not, as suggested by some authors (Sever et al., 1977; Sever, 1978; Miura et al., 1978; Hofman et al., 1979) but not by others (Lutold et al., 1976; Henquet et al., 1981); this disagreement cannot be resolved by the present investigations.

Possible reasons for the lack of a relationship between resting plasma noradrenaline concentrations and these variables have been discussed in Chapter 3. Inter-individual variations in noradrenaline kinetics (Reid et al., 1980), possible alterations in PNA by other factors, such as sodium intake (Robertson, Johnson, Robertson, Nies, Shand and Oates, 1979), and individual differences in the vascular response to noradrenaline, or in the density of adrenoceptor sites in the smooth muscle of hypertensive subjects (Philipp et al., 1978) may make comparisons of resting PNA between subjects unhelpful. Wallin et al. (1981) have convincingly demonstrated a relationship between PNA and sympathetic discharge to the muscle nerves; this discharge increases with age (Sundlof and Wallin, 1977, 1978). The diastolic pressure at which sympathetic discharge is inhibited is reset to a higher level in hypertensive subjects, which may be a consequence of baroreceptor afferent resetting, but there is no quantitative relationship between burst frequency and the level of arterial pressure (Wallin and Sundlof, 1979); this may also serve to explain the lack of relationship between resting arterial pressure and PNA, and resting PNA and baroreflex sensitivity.

It would therefore seem that the sympathetic discharge to large skeletal muscles is not increased in hypertension. If, on the other hand, sympathetic nervous activity to the heart, renal and splanchnic vessels were increased, this might not be evidenced by an increase in PNA, as the extent of noradrenergic innervation to these vascular

beds is small when compared with that to the skeletal muscles. Furthermore, noradrenaline released into the splanchnic and renal vascular beds may be cleared by the liver (Jones et al., 1980), and not be detected in the peripheral circulation. It is possible that selective activation of the sympathetic nervous innervation to these beds alone could produce haemodynamically significant changes, and at the same time evoke a reflex withdrawal of sympathetic tone to the resistance vessels in skeletal muscle; the net result might be a reduced, rather than elevated PNA during the early stages of essential hypertension.

Plasma noradrenaline concentrations during exercise

Mental arithmetic, isometric exercise, and bicycle exercise all produced significant rises in mean arterial blood pressure (18%, 29%, and 28% respectively) and heart rate (35%, 25%, and 65% respectively). Although the means by which these haemodynamic changes were effected in each instance differed, all these exercises had their desired effect, namely, activating the sympathetic nervous system.

The observation that only bicycle exercise increased PNA was an unexpected finding in these investigations. It was thought that both mental arithmetic (Nestel, 1969; Lorimer et al., 1971; Falkner et al., 1979; Januszewicz et al., 1979) and isometric exercise (Kozlowski et al., 1973, 1976; Lake et al., 1977; Hansen et al., 1978; Vecht et al., 1978; Robertson, Johnson, Robertson, Nies, Shand and Oates, 1979) would increase PNA, although in more recent work a small, or insignificant increase in this catecholamine has been found during these exercises (McDermott et al., 1974; Hjemdahl and Eliasson, 1979; Watson, Littler and Eriksson, 1980). The observations of

Vecht et al. (1978) may have been affected by the inclusion of patients with impaired left ventricular function in their series.

These observations are, however, consistent with the different haemodynamic changes known to occur in each of these exercises. Mental arithmetic is associated with an increase in heart rate, renal, epidermal and, by inference, splanchnic vascular resistance. Vasodilation, however, occurs in skeletal muscles (Brod et al., 1959), and sympathetic nerve discharge to these vessels is reduced (Delius et al., 1972b). This may, in fact, explain the progressive, but not significant, fall in PNA from baseline to recovery values.

Handgrip, at the level of exertion in this study, increases cardiac output through parasympathetic withdrawal and modest sympathetic activation. Vascular resistance does not increase in normal subjects (Laird et al., 1979) or those with 'labile' or 'fixed' hypertension (Chrysant, 1978), but it is possible that peripheral resistance may increase in older subjects (Kino et al., 1975) and some hypertensive subjects with left ventricular hypertrophy (Ewing et al., 1973) or ischaemic heart disease (Hansen et al., 1978). A mild increase in muscle sympathetic nerve discharge is seen in some subjects, no change, or a decrease, in others (Delius et al., 1972b). In this study, PNA increased in 23 patients, did not change in 9, and decreased in 18, but there seemed to be no way of predicting the individual responses. Again, the progressive, but not significant, increase in PNA from baseline through exercise to recovery might be explained by this mild increase in sympathetic nerve discharge.

In bicycle exercise, peripheral resistance falls, and sympathetic nerve discharge to the heart, nonactive vasculature and the capacitance

vessels is increased (Shepherd, 1966; Krasney et al., 1974; Galbo et al., 1975; Vatner and Pagani, 1976; Laird et al., 1979). Thus selective activation of the sympathetic nervous system can produce significant haemodynamic changes that may not be reflected by increases in PNA if restricted to the cardiac, splanchnic or renal sympathetic nerves, and not complemented by activation of noradrenergic discharge to the resistance and capacitance vessels of the skeletal muscles, i.e. the predominant source of noradrenaline overflow into the plasma. Some authors (Philipp et al., 1978) have stated that the activation of cardiac sympathetics is the primary source of circulating PNA, and Christensen and Brandesborg (1973) and Lutold et al. (1976) noted a strong positive relationship between the increase in PNA and the increase in heart rate during bicycle exercise. No such relationship was observed in the present study; moreover, isometric exercise and mental arithmetic increased heart rate significantly without affecting plasma noradrenaline concentrations. By way of contrast, tilting, which produces much smaller changes in heart rate and blood pressure, but activates sympathetic discharge to resistance vessels in the lower extremities (Shepherd, 1966), increases plasma noradrenaline (Hjemdahl and Eliasson, 1979). Positive neck pressure, which increases heart rate and systemic blood pressure (if only modestly) (Mancia et al., 1979), and appears to reduce sympathetic nerve discharge to the muscles (Eckberg, 1981, personal communication), does not.

It is clear, from this discussion, that the log-linear relationship between PNA and systolic blood pressure reported by Watson, Hamilton, Reid and Littler (1979), only applies in selected instances; PNA appears to be a relatively insensitive index of sympathetic nerve activity.

Plasma adrenaline concentrations were not measured, but they do not appear to increase during mental arithmetic (Hjemdahl and Eliasson, 1979), isometric exercise, in younger subjects (McDermott et al., 1974) or with mild to moderate bicycle exercise (Galbo et al., 1975).

The changes in plasma noradrenaline in mental arithmetic were unrelated to age, baroreflex sensitivity, or changes in heart rate and blood pressure, although the small number of subjects (n=10) may have prevented any significant relationships from emerging.

A larger number of subjects (n=50) was studied during isometric exercise; here again, the maximum PNA was unrelated to any of the other variables, save for resting PNA, and the relative increase in PNA was not related to changes in blood pressure, heart rate, and not related to age or baroreflex sensitivity, reflecting the overall similarity between resting and exercising PNA during handgrip. The relative increase in PNA was in fact lower in patients with larger initial values, and the change in PNA during isometric exercise bore no relation to age, as seen earlier by McDermott et al., 1974.

PNA rose 78% during bicycle exercise; this was a smaller relative increase than noted by others, who either found resting PNA to be lower, or exercised their subjects for a longer time, or at a heavier workload (Lutold et al., 1976; Philipp et al., 1978; Bertel et al., 1980; Henquet et al., 1981).

There was a significant relationship between exercise mean arterial pressure and plasma noradrenaline concentration during bicycling that was not present at rest (Fig. 5-29). This has not been noted previously. Moreover, patients with poorer baroreflexes tended to have higher PNA, suggesting that the activation of somatic

afferents during this exercise may have revealed a reduced ability, by the baroreflex, to inhibit sympathetic nerve discharge to resistance vessels. Unfortunately, the latter tendency, which would have provided support for this thesis, was not quite statistically significant ($P<0.06$), perhaps, in part, owing to inter-individual differences in the vascular reactivity to noradrenaline (Philipp et al., 1978).

The absolute increase in PNA during bicycle exercise was greater in those subjects with lower resting blood pressures; however, the relative increase in PNA was independent of the resting mean arterial pressure (Table 5-23). This might suggest that borderline hypertensives did in fact have evidence of increased sympathetic nerve activity at rest and during exercise, as suggested by Robertson, Shand, Hollifield, Nies, Frolich and Oates (1979). On the other hand, some 'normal' subjects may have been inadvertently included in the study; Bertel et al. (1980) in fact found greater increases in their normals, rather than their age-matched borderline hypertensive subjects, although plasma noradrenaline concentrations are similar in both borderline hypertensive and normal subjects during heavy exercise (Henquet et al., 1981).

In any event, the greater absolute increase in these subjects with lower blood pressures undoubtedly contributed to the lack of relation between LBRS and PNA during this exercise (Table 5-23); it would be of interest to compare these two variables in young borderline and age-matched normotensive subjects at some future stage.

The higher absolute and relative increases in PNA seen by Bertel et al. (1981) in his older subjects was not confirmed by this study. Zero-order correlations between these values and age

were greater than the partial correlation coefficients (Table 5-23), implying that the colinearity of age and mean arterial pressure may have contributed to the relationship they described.

Three minutes after the end of bicycle exercise, heart rate and plasma noradrenaline concentration remained significantly elevated, while the increase in mean arterial pressure over the baseline figure was small. The persistence of PNA in the circulation at this time, despite its half-life of about 1.5 minutes, may be due to continued overflow from sympathetic nerves, decreased clearance, or both. Hepatic uptake of noradrenaline (Jones et al., 1980) probably diminishes during exercise, as stimulation of splanchnic sympathetics, or the infusion of noradrenaline into the hepatic artery or portal vein lowers hepatic blood flow by 50% (Hirsch, Ayabe and Glick, 1976).

Sever (personal communication, 1980), who studied the clearance of noradrenaline following its infusion into young healthy adults at rest and after bicycle exercise, noted that "noradrenaline elimination following exercise appears to be multiphasic. The half-life and elimination rate constant for the first phase are similar to that following cessation of infusion. However, there appears to be a number of bursts of sympathetic activity which continue for up to 15 minutes or more at the end of exercise, as indicated by a transient rise in the noradrenaline, and I think it is more likely that this reflects increased release of noradrenaline, rather than haemodynamic response altering clearance". Since blood pressure plummets at the end of bicycle exercise, these bursts may be due to a fall in baroreceptor afferent discharge, until short-term resetting of the viscoelastic properties of the baroreceptor-arterial wall coupling (Coleridge et al., 1981) returns to normal.

It would appear that rather than being a determinant of resting blood pressure and heart rate, plasma noradrenaline concentrations reflect changes in sympathetic nervous activity, but only in some forms of circulatory stress. When the sympathetic nervous system was activated by bicycle exercise there was a tendency for patients with poorer baroreflexes to release more noradrenaline into the plasma and achieve higher mean arterial pressures (Figs. 5-19, 5-29, 5-30, 5-31).

The variability of blood pressure

The variability of mean arterial pressure, defined as the standard deviation about the average waking ambulatory mean arterial pressure, was directly related to age and mean arterial pressure in these 56 'free-ranging' subjects. Apart from Clement (1977), most previous authors have not observed a relationship between the level of blood pressure and its variability (Diehl, 1929; Sokolow et al., 1966; Horan et al., 1981). This may have been because the methods of recording blood pressure in these investigations had two limitations: they were indirect and discontinuous, and they required the subjects studied to restrict their activities. Watson, Stallard, Flinn and Littler (1980) found a direct correlation between systolic pressure and its variability (but not between diastolic and its variability) in 26 subjects studied with direct ambulatory monitoring. The variability of systolic pressure also increased with age, but this did not appear to be independent of the colinearity of blood pressure and age. Here again, subjects were confined to hospital and limited to a standard protocol of rest and exercise. Diet, as well, was standardized. Mancia et al. (1980) found that the variability of

blood pressure increased with the progression of hypertension, but they examined the fluctuations of blood pressure over small intervals of time, rather than its beat-to-beat variability. Pessina et al. (1980) compared the variability of blood pressure in borderline and persistent hypertensives in a small series, but did not report the ages of their subjects. The present investigations have therefore come closest to examining these variables under conditions as near as possible to the subjects' daily activities.

Although a wide range of variability was seen in subjects with average mean arterial pressures around 100 mm Hg (i.e. borderline hypertensives) (Fig. 5-37), on the whole, borderline hypertensives did not exhibit increased lability of their blood pressure; the converse in fact appeared to be the case, consistent with the findings of Mancia et al. (1980), Pessina et al. (1980), and Watson, Stallard, Flinn and Littler (1980). These observations fit with the hypothesis that diminished baroreflex sensitivity impairs the short-term buffering of fluctuations in blood pressure.

This was confirmed by the present investigations. The variability of mean arterial pressure was inversely related to baroreflex sensitivity in these 56 subjects (Fig. 5-38). When multiple regression analysis was performed on these data, only baroreflex sensitivity was found to have a significant independent effect on blood pressure variability (eqn. 35). This was confirmed by partial correlation coefficients (Table 5-28).

There is good evidence from animal and human investigations to support this hypothesis. Denervation of the sinoaortic baroreceptors in rats and dogs consistently leads to an increase in the beat-to-beat variation in blood pressure when these animals are stimulated (Cowley

et al., 1973; Jones and Hallback, 1978; Ito and Scher, 1979). Central interruption of the baroreflex by lesions to the nucleus tractus solitarii (NTS) produces marked hypertension, sustained tachycardia, and increases in blood pressure variability (Nathan and Reis, 1977), whereas the selective removal of the noradrenergic innervation to this nucleus (Snyder et al., 1978) or lesions to the A2 catecholamine region of the rat brain (Talman et al., 1980) increase blood pressure lability without inducing hypertension. Snyder et al. (1978) showed that the increase in variability was of similar magnitude as the decrease in the baroreflex control of heart rate.

Watson, Stallard, Flinn and Littler (1980) have found a significant inverse relationship between the variability of systolic blood pressure and baroreflex sensitivity in 23 patients. This correlation was also found to be independent of both age and the level of systolic blood pressure. Mancia et al. (1980) used three indices of baroreflex sensitivity to examine the same question: (1) the bradycardia following phenylephrine, (2) the tachycardia following trinitroglycerine, and (3) the bradycardia following neck suction. Only in the first instance did they note a significant inverse relationship between blood pressure variability and baroreflex sensitivity. The independence of this relationship from the effect of age and blood pressure, and the beat-to-beat variability, were not calculated.

Under the 'free-ranging' conditions in this study, blood pressure variability appeared to be a useful index of sympathetic nervous activity, and correlated well with the relative increase in plasma noradrenaline during bicycle exertion (Fig. 5-39), and with the absolute change in mean arterial pressure during each of the four

exercises (Figs. 5-41 to 5-44). The strongest correlation, interestingly enough, was with the change in blood pressure during the reaction time test, which was the mildest stimulus to blood pressure and heart rate in this series, but which may be the closest to the normal response to social interactions over the routine waking day.

Clement, Bogaert, Moerman and de Schaepdryver (1978) failed to observe a relationship between plasma noradrenaline and the coefficient of variation of blood pressure, and de Leeuw, Wester, Stientra and Birkenhager (1979) in fact noted an inverse relationship between PNA and the index of variability used by his group. However, these were resting concentrations of PNA, and blood pressure in these studies was measured by ultrasound.

Watson, Stallard, Flinn and Littler (1980), who recorded blood pressure directly, did not observe a relationship between the variability of either systolic and diastolic blood pressure and resting or exercising catecholamines. They did not study the relative increase in noradrenaline with bicycling. These authors noted a relationship between blood pressure variability and the increase in systolic pressure during immersion of the hand and forearm in cold water, but not with the rise in blood pressure during isometric or bicycle exercise. It is not clear as to why the results in the present study differed from the observations of Watson and his colleagues. This may have been due to their comparison of systolic rather than mean arterial pressures or their use of a more strenuous bicycle exercise.

The direct relationship between blood pressure and its variability has prompted several authors to argue that the coefficient of variation

(i.e. the standard deviation divided by the mean), rather than the variability of blood pressure itself, be studied. The coefficient of variation is useful when a change in the conditions under which measurements are made alters the standard deviation in the same proportion as it alters the mean, as it then remains constant (Armitage, 1971). The coefficient of variation is not needed in the present circumstances. As seen in Chapter 5 (Figs. 5-34, 5-35; Tables 5-25, 5-26), changes in blood pressure variability are not invariably related to changes in arterial pressure per se. Watson, Stallard, Flinn and Littler (1980) found that systolic pressure and its variability were significantly related in individual patients when many 10-minute periods throughout the 24-hour day were studied; this finding may have been due to their combining waking and sleeping periods in their analysis. The same authors (Watson, Stallard and Littler, 1979a) found that beta-adrenoceptor blockade could lower blood pressure significantly at rest, and during sleep, without altering its variability. Evidence from experimental hypertension further suggests that the mechanisms which regulate blood pressure variability can be dissected free from those which control its absolute level (Cowley et al., 1973; Jones and Hallback, 1978; Snyder et al., 1978; Talman et al., 1980).

The interaction between the renin-angiotensin system and the central regulation of blood pressure (Severs and Daniels-Severs, 1973; Dickinson, 1981) suggests that increased activity of this system may enhance the lability of arterial pressure, as has been observed following chronic angiotensin infusion into experimental animals (Forsyth, Hofbrand and Melmon, 1971; Cowley and deClue, 1976). As intervertebral infusions of angiotensin reduce both parasympathetic

efferent activity, and the cardiovagal response to phenylephrine induced pressure rises (Lumbers, McCloskey and Potter, 1979), it is possible that a third mechanism, such as angiotensin, may be responsible for both the decrease in baroreflex sensitivity and the increase in blood pressure variability in some of these patients. A relationship between supine plasma renin activity, corrected for age, and beat-to-beat blood pressure variability, was in fact observed by Watson, Stallard, Flinn and Littler (1980), and Birkenhager, Van Es, Honwing, Lamers and Mulder (1968), and Schalekamp, Schalekamp-Kuyken and Birkenhager (1970) noted that the range of blood pressure, measured with an oscillometric device, correlated with resting cardiac output and plasma renin concentrations. The influence of angiotensin on baroreflex sensitivity was not studied in the present experiments, but in view of the findings in rats, could form the basis of future investigations.

Summary

The decrease in baroreflex sensitivity in hypertension was associated with indirect evidence of increased sympathetic activity in some, but not all, of the instances examined. The maximum mean arterial pressure during all four mental and physical exercises was greater in patients with poor baroreflexes, but the change in mean arterial pressure from baseline values was inversely related to baroreflex sensitivity in the case of bicycling only.

Plasma noradrenaline concentrations, at rest, bore no relationship to baroreflex sensitivity, blood pressure, or heart rate, but there was a tendency for the plasma noradrenaline concentrations during bicycle exercise to be lower in subjects with better baroreflexes.

Plasma noradrenaline, which did not change during mental arithmetic, or isometric exercise, was on the whole a less sensitive index of sympathetic nervous activity than either the changes in blood pressure and heart rate during exercise or the variability of blood pressure.

An inverse relationship with sympathetic function was clearest when baroreflex sensitivity was compared with the variability of mean arterial pressure. This occurred in that part of the study which allowed the subjects the greatest freedom of movement. This would suggest that the reduction in baroreflex sensitivity in hypertension is of considerable physiological significance in man. The demonstration, in this study, of a diminution in the ability to buffer acute fluctuations in blood pressure under situations as near as possible to a routine daily activity is of greater interest than the lack of inverse relationship between baroreflex sensitivity and the increase in mean arterial pressure during mental arithmetic or the reaction time test.

Most human activity (certainly most of the activity recorded during the ambulatory monitoring of waking blood pressure) has a component of muscular activity which would activate somatic afferents. It would therefore seem reasonable to expect to find evidence of increased sympathetic activity in patients with reduced baroreflex sensitivity under those conditions which (1) excite somatic afferent activity, and (2) lead to a significant overflow of sympathetic neurotransmitter into plasma.

Experimental hypertension

Lundgren et al. (1974) have studied the time course of the blood pressure rise and its relationship to hypertrophy of the left ventricle and changes in the perfused hindquarter bed of the rat during the development of renovascular hypertension. Left ventricular hypertrophy was not present 3 days after clipping the renal artery, but was present by 1 week. Changes in the hindquarter vascular bed were not apparent after 1 week of renovascular hypertension, but were fully developed after 2 weeks. As both the left ventricle and the vessels of the hindquarters, including the aorta and larger arteries, are affected by the rising pressure in a similar fashion (Folkow, 1978), it would not be unreasonable to assume that adaptive changes occur simultaneously in the forequarters, including the baroreceptor regions of the aortic arch and carotid arteries. In support of this, the time course of changes in the threshold for carotid sinus activation during the development of renovascular hypertension has been studied in the same model (Jones, 1977). Only slight changes were observed at 1 week, but the baroreceptor threshold had fully reset at 14 days. This paralleled the development of structural vascular changes and appeared to be secondary to these adaptations. Although the threshold for carotid sinus baroreceptor activation does not appear to be altered early in the development of hypertension, it would appear that the peripheral arterial baroreceptors are less sensitive during this period, for the rise in arterial pressure is not accompanied by a reflex bradycardia. The heart rate was higher, in fact (but not significantly), on the third day of renovascular hypertension.

In the present study, a significant diminution of baroreflex sensitivity was present within 3 days of clipping the left renal artery, at a time when neither left ventricular hypertrophy nor changes in the peripheral vasculature are present in this model. Although the hindquarters were not perfused in the present experiments, the left ventricles were dissected out and there was no evidence of hypertrophy at 3 days. By one week, when left ventricular hypertrophy was evident, baroreflex sensitivity had fallen to 0.418±0.166 ms/mm Hg.

Krieger (1970) in studies on individual receptors, rather than on the baroreflex arc, showed resetting of the aortic arch baroreceptors within 48 hours of clamping the aorta, findings that are not consistent with structural vascular adaptations. Most other studies were performed rather later in the development of hypertension than were the present experiments, and in different models. In hypertensive rabbits, Angell-James and George (1976) found that the reduction of baroreflex sensitivity (as determined by the phenylephrine technique and by direct nerve-fibre recordings) was directly correlated with the duration of hypertension, more so than to the level of blood pressure achieved. Reduction in baroreflex sensitivity was directly related to the reduction in the distensibility of the isolated perfused aortic arch. Resetting of both single fibres and whole nerve preparations was not seen in dogs with renovascular hypertension unless the blood pressure of these animals had been elevated for more than five days or one week (Sleight et al., 1977; Peveler, 1980). In these studies, resetting in these dogs was related to the severity of hypertension, rather than its duration. The time course of changes in baroreflex sensitivity during the

initial phases of hypertension has not been studied.

There is good evidence that the sensitivity of the baroreflex arc as a whole can be modified acutely by mechanisms that are not purely structural. This has been observed during sleep (Smyth et al., 1969), in which the baroreflex appears in some cases to be more sensitive, exercise (Bristow, Brown, Cunningham, Howson, Strange Petersen, Pickering and Sleight, 1971), and mental arithmetic (Sleight et al., 1978) which renders it less sensitive. When animals are alerted defence reactions occur which can alter the reflex (Hilton, 1963; Klystra and Lisander, 1970).

These results support the possibility that a non-structural mechanism may be operative in the early stages of renovascular hypertension, rendering the baroreflexes less sensitive to the rising pressure. If this loss of sensitivity was due simply to progression from the linear to the flatter portion of Koch's (1931) sigmoid pressure-frequency curve, then one would have expected rats with the highest pressures to have the poorest baroreflexes. In fact no such relationship was present at day 3, and if anything a trend towards the converse was seen (Fig. 6-10).

The stimulus to hypertension in the 2-kidney 1-clip model of Goldblatt hypertension is the activation of the renin-angiotensin system. Plasma noradrenaline is not increased, and pre-treatment with 6-OHDA, which depletes central noradrenergic neurones, does not prevent the development of hypertension (Dargie, Davies, Dean, Dollery, Maling and Reid, 1977) as it does in the 1-kidney 1-clip Goldblatt (Dargie, Franklin and Reid, 1977) or the DOCA-salt models of experimental hypertension (Reid et al., 1975).

Kezdi (1967) studied afferent baroreceptor activity of carotid sinus nerve preparations in hypertensive dogs in which one sinus was protected from the pressure rise by means of an arteriovenous fistula. He could find no alteration in baroreceptor characteristics in these sinuses, as would be expected if some humoral mechanism, acting peripherally, was responsible. Nevertheless, the early alteration in baroreflex sensitivity noted in this study may well be mediated instead through the central actions of an agent such as angiotensin, which can stimulate sympathetic activity by a direct action on the vasomotor centres (Joy, 1975). Angiotensin, when infused into the vertebral arteries of anaesthetised dogs, in quantities insufficient to raise peripheral arterial pressure, inhibits baroreceptor mediated reflex vasodilatation (Sweet and Brody, 1970) and reduces the bradycardia and depressor responses to stimulation of the carotid sinus nerve (Fukiyama, 1973; Marker, Miles and Scroop, 1980). Lumbers, McCloskey and Potter (1979) also showed that angiotensin II did not affect discharge frequency in single carotid baroreceptor fibres, although it did inhibit vagal discharge evoked by stimulation of the arterial baroreceptors.

Alterations in plasma volume, which might occur during the early phase of two-kidney one-clip Goldblatt hypertension, do not appear to alter baroreflex sensitivity (Tomiyama et al., 1980; Ludbrook et al., 1981).

Vascular changes, secondary to the rising blood pressure, may further influence and reduce baroreflex sensitivity later in the development of hypertension. Baroreflex sensitivity was observed to be significantly less at days 14 and 25 than at days 3 and 7.

Gradual changes in the vasculature, not detectable by the hindquarter perfusion technique, might be developing after the initiation of renovascular hypertension. Increased endothelial cell turnover has been shown to occur in the renal vein, periureteric arteries and epithelial cells of the ureter within 24 hours of renal artery clipping in rats (Ilich, Hollenberg, Williams and Abrams, 1979); it is unlikely that such subtle changes, if they occurred elsewhere, could be responsible for the significant reduction of baroreflex sensitivity at a time when the threshold for baroreceptor activation is barely altered. If an increase in baroreflex sensitivity was observed following declipping, when these structural alterations were still present, this possibility would appear to be even more remote.

Removal of the renal artery clip in 2-kidney 1-clip Goldblatt hypertension results in an almost immediate fall in blood pressure to normal or subnormal levels, due to a fall in peripheral resistance (Hallback-Nordlander et al., 1979). According to Lundgren (1974b), however, adaptive changes in the blood vessels which have developed in response to the high blood pressure can be detected up to three weeks following declipping. Therefore, vascular hypertrophy, which may be important in determining sensitivity to vasoactive agents such as noradrenaline, does not in itself maintain hypertension (Thurston et al., 1980).

In order to achieve normal or subnormal peripheral resistance in the presence of increased flow resistance, tonic smooth muscle activity must be subnormal. Both the fall in peripheral resistance and lack of reflex tachycardia after declipping have been attributed by Hallback-Nordlander et al. (1979) to a direct suppression of central

sympathetic control. This, in turn, they suggest is due to the sudden withdrawal of a sustained renal excitatory influence, or due to the release of vasodilators from the ischaemic kidney on declipping. It is of interest that Muirhead (1980) and his co-workers have isolated from renomedullary-interstitial cells a polar lipid which reduces mean arterial pressure acutely by lowering peripheral vascular resistance without producing a tachycardia.

Salgado and Krieger (1973) observed a rapid downward shift of the pressure levels at which aortic arch baroreceptors both ceased firing, or attained continuous firing, in the first few hours after unclipping the renal artery of rats with 2-kidney 1-clip Goldblatt hypertension of 2 months' duration. They concluded that the resetting lagged behind the fall in pressure, presumably, before the reversal of structural changes. Interpretation of their results is complicated, however, by their use of haemorrhage to study the range and threshold of neural discharge in some of the rats.

In the present experiments, the sensitivity of the baroreflex arc as a whole rapidly returned to normal following the reversal of hypertension. It is of interest to speculate as to whether the removal of the substance raising the blood pressure also restored baroreflex sensitivity. There was a significant inverse relationship between mean arterial pressure and baroreflex sensitivity in the 1-day unclipped group. Such a relationship might be seen in this group if a factor, e.g. angiotensin, tending to keep the blood pressure up (and at the same time directly diminishing baroreflex sensitivity) was still present in some of the animals. Plasma renin activity should fall to normal levels after removal of the clip in this model

(Ten Berg, Leenen and deJong, 1979).

Only the parasympathetic efferent limb of the baroreflex appears to be enhanced following declipping; the profound fall in mean arterial pressure is not accompanied by a reflex tachycardia. Suppression of central sympathetic activity, as postulated by Hallback-Nordlander et al. (1979), would tend to cause the parasympathetic regulation of heart rate to predominate (Higgins, Vatner and Braunwald, 1973), explaining our finding of increased baroreflex sensitivity in the declipped rats. A similar effect might be achieved if an excitatory factor, particularly one such as angiotensin, which inhibits the parasympathetic efferent limb of the baroreflex arc, were removed. This would not necessarily enhance the sympathetic response, i.e. the reflex tachycardia following the fall in blood pressure.

Bengis and Coleman (1979) studied the antihypertensive effect of captopril, a converting enzyme inhibitor, on 2-kidney 1-clip Goldblatt hypertension in rats. Both malignant hypertension, with elevated levels of renin and angiotensin, and benign hypertension, in which the renin-angiotensin system has little role to play, were produced. When captopril, which blocks the conversion of angiotensin I to angiotensin II, was given to the rats with malignant hypertension, blood pressure fell dramatically, but heart rate did not change; in the group with mild hypertension, captopril produced a small fall in blood pressure, yet a significant tachycardia. The authors did not discuss these findings, analogous to the present series of experiments, wherein the influence of angiotensin was removed by declipping, blood pressure fell, but heart rate did not change.

It is unlikely that a reduction in plasma volume was responsible for the change in baroreflex sensitivity following declipping. Although it was not measured in these experiments, other authors report either no change (Liard and Peters, 1973; Gulati, Carrotero, Morino and Oza, 1976; Ten Berg et al., 1979) or a slight increase (Thurston et al., 1980) following declipping.

In the present series, there was a subsequent rise in mean arterial pressure and a fall in baroreflex sensitivity at 14 and 25 days following declipping. A similar rise in blood pressure was noted by Thurston et al. (1980) in their animals with chronic hypertension. This increase may be a result of renoprival changes in the non-ischaemic kidney, induced by the renovascular hypertension (Carrotero and Romero, 1977); the lowering of baroreflex sensitivity may be due to the lingering presence of structural vascular adaptation. However, there was no significant difference in baroreflex sensitivity between these two groups and the 7-day declipped and 25-day normotensive groups. It was only in comparison to the 50-day normotensive control group, which had the highest baroreflex sensitivity, that a significant difference emerged. There may have been a relationship between the subsequent reappearance of modest hypertension, and the tendency towards diminished baroreflex sensitivity in these later groups which could not be elucidated further by this study.

Subsequent to the completion of this work, Coleridge et al. (1981) described short-term resetting of aortic baroreceptor pressure-firing curves when aortic pressure was either increased or decreased, then held for 20 minutes. The threshold for nerve firing did not appear to be changed. This phenomenon may be explained by a progressive lengthening, or creep, of the viscous elements in the arterial wall,

during which the force transmitted to the baroreceptor may be reduced. These authors suggested that short-term resetting may occur acutely in the conscious animal during fluctuations in arterial pressure. These findings may offer an alternative explanation for the present findings in rats.

Summary and conclusions

The experiments in rats suggest that 'non-structural' factors are capable of altering baroreflex sensitivity during the early stages of hypertension. The nature of these factors has yet to be determined, but clearly, in the 2-kidney 1-clip Goldblatt model, a humoral agent, such as angiotensin, with its effects upon sympathetic nervous outflow, would be a likely candidate. Once acute central or 'autonomic' alteration has occurred, the less sensitive baroreflex may facilitate the development of hypertension by not opposing the rising pressure with a fall in heart rate and cardiac output. Cardiac output may in fact increase in the early stages of renovascular hypertension in the dog (Ferrario, Page and McCubbin, 1970). Later, as the left ventricle and peripheral vasculature adapt to the rising pressure, and the viscoelastic-receptor coupling alters, a secondary, 'structural' resetting may compound this process. More than one 'non-structural' factor may be capable of altering baroreflex sensitivity in experimental hypertension. In the spontaneously hypertensive rat, a primary 'neurogenic' hypertension appears to be followed, at 10 to 15 weeks of age, by aortic baroreceptor resetting that is not due entirely to structural changes. Following this, the baroreflex and the enhanced sympathetic drive exert synergistic effects and these animals exhibit greater pressor responses to alerting

stimuli than do normal rats (Hollback and Folkow, 1974; Brown et al., 1976; Folkow and Hallback, 1977; Judy and Farrell, 1979).

Most authors have considered the decline in baroreflex sensitivity in man with increasing age and mean arterial pressure to be due to a progressive decrease in the compliance of the aortic arch and carotid vessels (Downing, 1979). However, vascular alterations, which may explain the 'resetting' of baroreceptors, alone may not account for the altered baroreflex sensitivity: 'non-structural' factors may again be important. Pickering, Gribbin and Oliver (1972) found that baroreflex sensitivity in uraemic patients on long-term haemodialysis was about 50% of that found in other subjects of comparable ages and arterial pressures, and concluded that this difference could not be accounted for on the basis of altered vascular compliance alone.

The reduction in parasympathetic, and the relative increase in sympathetic tone in some patients with borderline hypertension may also be due to a 'non-structural' reduction in their baroreflex regulation of heart rate. Takeshita et al. (1978) found that intravenous propranolol improved, but did not restore, baroreflex sensitivity to normal levels in young borderline hypertensive subjects. This could be due either to a persistence of an 'autonomic' component which continued to inhibit parasympathetic efferent activity, or due to the underlying presence of a reduction in BRS on structural changes in the resistance vessels in these subjects (Sannerstedt et al., 1976). Recently, Volpe and his colleagues (Volpe, Trimarco, Ricciardelli, Givorito, de Luca, Rengo and Condorelli, in press) found that baroreflex sensitivity could be restored to normal by intravenous propranolol and neostigmine, and concluded that the decreased baroreflex

sensitivity in borderline hypertension seen by Takeshita et al. (1975) and Eckberg (1979) was entirely central in origin.

Whether the 'non-structural' factor responsible for part of the reduction in baroreflex sensitivity in borderline hypertensive subjects is angiotensin, or a primary increase in central sympathetic outflow,is subject to speculation at the moment. Propranolol could be expected to interfere with both mechanisms; and agents which selectively block the conversion of angiotensin I to angiotensin II have not been applied to this problem as yet. Further work is therefore needed to resolve this question.

These investigations, and those of others (Pickering, 1970; Gribbin, 1974) have consistently revealed the presence of individuals whose baroreflex sensitivity is much less than would be predicted simply on the basis of their age and mean arterial pressure; an additional, 'non-structural' factor may contribute to this further reduction. The standard errors of the regression coefficient relating age and mean arterial pressure to LBRS were about 15% of the regression coefficients themselves (eqn. 7), implying a fair range of distribution of these variables about the regression equation. However, these subjects' behaviour is more in keeping with their baroreflex sensitivity than their age or mean arterial pressure. The present findings, and those of Watson, Stallard, Flinn and Littler (1980) have shown baroreflex sensitivity to have a greater bearing than either age or mean arterial pressure, on the variability of blood pressure (eqn. 35; Fig. 5-39; Table 5-28). This is in keeping with evidence from Folkow's laboratory (Hallback and Folkow, 1974; Folkow and Hallback, 1977) suggesting that the 'neurogenic' factors, rather than changes in the resistance vessels

and heart, in themselves, influence the haemodynamic responses to mental and physical stimuli in hypertensive rats.

These changes may be of clinical significance. In this study, patients with good baroreflex sensitivity tended to have much lower average ambulatory mean arterial pressures than average clinic mean arterial pressures, and may be at less risk of developing the complications of hypertension (Floras et al., 1981). The net effect of an imbalance in the baroreflex regulation of heart rate and peripheral resistance could be an elevated cardiac output and peripheral resistance, increased variability of arterial pressure, and a 'hyperresponsiveness' to exercise or alerting stimuli, i.e. features of the spontaneously hypertensive rat (Hallback and Folkow, 1974), borderline hypertensive patients (Julius and Conway, 1968; Julius, Pascual and London, 1971; Julius Pascual, Sannerstedt and Mitchell, 1971), and in some of these respects, patients with reduced baroreflex sensitivity in this study. The increased variability of blood pressure, and the greater fluctuations in pressure during exercise in these patients, could act as trophic influences on the vasculature of genetically susceptible individuals, leading to structural changes that would promote the development of hypertension, and reset the systemic arterial baroreceptors to sustain blood pressure at a higher level. Schaarschmidt described a similar neurovascular interaction over two hundred years ago when he identified a group of patients which exhibited "vehement agitation" of the circulation and "spastic constriction of the vascular bed" and tended to suffer cerebrovascular haemorrhage (Backer, 1953). However, at the present time there is no good evidence, either from animal work (Jones and Hallback, 1978; Talman et al., 1980), or from limited experience with

man (Sokolow et al., 1966) to suggest that more variable blood pressure induces hypertension.

Longitudinal studies, which might resolve this question, will have to await the development of continuous, yet non-invasive methods of measuring blood pressure.

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