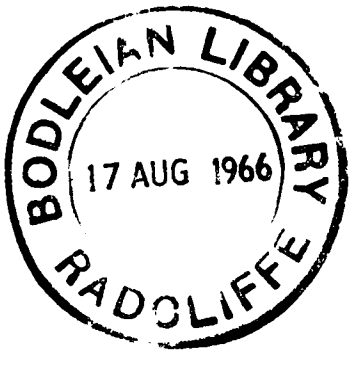
RESPIRATORY DISTURBANCES IN CONGENITAL HEART DISEASE

A dissertation for the
degree of Doctor of Medicine

by

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PREFACE

The work described in this thesis has been carried out over the period 1958-65, having been begun during the tenure of a residency at the University of Colorado, Denver, U.S.A. At this time, surgery for the closure of septal defects was being actively carried out, and interest was aroused, in two clinical features which were apparent from close contact with this programme. The first was the nature of the chest deformities associated with septal defects; the second, the striking alleviation of symptoms which followed successful closure of these defects. The reasons for these phenomena were by no means clear and the subsequent work has been concerned with an attempt to understand them.

The presentation is made broadly in the order in which the studies have been carried out. In the first chapter a description of the chest deformities and their haemodynamic associations is made. The relationship is discussed between the presence of hyperkinetic pulmonary hypertension and a chest deformity characterised by a prominent sternum, bilateral recession of the lower ribs, and an increased antero-posterior chest diameter. The question is posed as to whether or not the deformity is due to abnormal pulmonary mechanics. This is dealt with in Chapter II, in which the results of pulmonary function studies in patients with

septal defects are described. Chapter III is concerned with atrial septal defect, the disability which occurs in its presence, and the factors which can or cannot be seen to be associated with it. The results of surgery are mentioned briefly, and a comparison is made between the pre- and post-operative values of several relevant variables, including particularly lung compliance. Hitherto, the disability has been assessed on a historical basis. In Chapter IV studies are described under exercise conditions when symptoms were often present, haemodynamic, metabolic and ventilatory changes being assessed. Finally, in Chapter V similar studies in cyanotic patients with septal defects are presented.

Some of the work in this thesis has been published or submitted for publication; chapter I as 'Chest deformities in congenital heart disease' (Davies, H, Br.J.Dis.Chest, 53, 151, 1959); chapter II, in preliminary form, as 'Lung stiffness in states of abnormal pulmonary blood flow and pressure' (Davies, H, Williams, J.V. and Wood, P. Br.Heart J. 24, 129, 1962); chapter III incorporates some of the data published from Denver on the results of closure of atrial septal defect in 100 cases (Swan H, Kortz, A.B, Davies, D.H, and Blount, S.G. Jr, J.Thorac.Surg. 37, 52, 1959). The material of chapter IV has been submitted to the British Heart Journal as 'Haemodynamic changes on exercise in patients with left-to-right shunts' (Davies, H. and Gazetopoulos, N.) and 'The ventilatory response to exercise in patients with left-to-right shunts'. (Gazetopoulos N, and Davies, H). Chapter V has been published as 'Dyspnoea in cyanotic congenital heart disease' (Davies, H. and Gazetopoulos N. Br.Heart J. 17, 28, 1965).

The work has formed part of a larger study dealing with disability, particularly dyspnoea, in heart disease. For reasons of length, some of the material has had to be presented in a relatively shortened form. Other data bearing on the topic of disability have had to be omitted for the same reason, but are awaiting publication under the titles of 'Ventilation and haemodynamics in heart disease' and 'Ventilation in relation to arterial and venous blood chemistry in heart disease' (Brit. Heart J. with N. Gazetopoulos, D. C. Deuchar and G. C. Oliver); 'The ventilatory and metabolic response to exercise in normal subjects' (Davies, H, Gazetopoulos, N. and Oliver, G. C. Jr, Clin. Sci. in the press); 'The effects of carbon dioxide inhalation in normal subjects and those with cyanotic congenital heart disease' (Oliver, G. C. Jr, Gazetopoulos, N. and Davies, H. submitted to J. Clin. Invest.), and 'Dyspnoea in heart disease' (Gazetopoulos, N. and Davies, H. submitted to Circulation).

All the work described in the thesis has been carried out by its author, either alone or with the assistance of the above-mentioned colleagues, and he wishes to record his appreciation of the help given by the following -

Drs. S. Gilbert Blount, Jr, and Henry Swan of Denver, Colorado; the late Dr. Paul Wood of the Institute of Cardiology, London, who was interested particularly in the problems of dyspnoea in heart disease (it was the author's wish that he would see the conclusion of more than only a part of this work and, hopefully, look kindly on at least some of it); the physicians of the National Heart

Hospital and Guy's Hospital, particularly Drs. Charles Baker and Dennis Deuchar, who have allowed me to study patients under their care; Dr. F. J. Prime of the Institute of Diseases of the Chest, Brompton Hospital, and Dr. M. W. Potts and the Department of Anaesthetics, Guy's Hospital, for allowing me the use of their apparatus, and Mrs. J. R. Samuel for many hours spent in blood-gas analysis; the technicians of the various departments in which the work has been carried out; Mr. Charles Engel and the Department of Photography, Guy's Hospital, and Miss Lola Dalby for assistance with the illustrations; Mrs. K. M. Hasler for help with the planning of the presentation and secretarial work and Mrs. G. M. Brewer also for the latter; finally, and most of all, to Dr. Nikos Gazetopoulos who joined the author in 1963 and proved to be a good friend.

Hywel Davies
September 1965.

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GLOSSARY OF ABBREVIATIONS AND TERMS USED

A.S.D.	Atrial septal defect
V.S.D.	Ventricular septal defect
P.D.A.	Patent ductus arteriosus
P.H.T.	Pulmonary hypertension, defined usually as being present when the systolic pressure exceeds 40 mm. Hg.
P.F. and S.F.	Pulmonary and systemic flow.
P.I. and S.I.	Pulmonary and systemic index (flow/square meter body surface area)
P.V.R.	Pulmonary vascular resistance
Eisenmenger	Refers to patients with pulmonary-systemic communications, a pulmonary : systemic flow ratio of less than 2 : 1 and pulmonary vascular resistance greater than 10 units, with corresponding clinical signs
Flow ratio	Pulmonary : systemic flow ratio
Hyperkinetic pulmonary hypertension	This refers simply to a situation where pulmonary hypertension is accompanied by a flow ratio greater than 2

CHAPTER I

CHEST DEFORMITIES IN PATIENTS WITH SEPTAL DEFECTS

Some children with congenital heart disease have chests of unusual shape, but no attempt has been made to relate the particular type of deformity to underlying pathology. The present study was undertaken with this in mind, being initiated by clinical observations on children with septal defects.

The first patient was a child of seven who had recently undergone surgery for closure of a ventricular septal defect, using total cardio-pulmonary by-pass. He was very breathless and his chest appeared blown-up and barrel-shaped. The sternum jutted forward and was lifted laboriously with each breath; at the same time the lower ribs were sucked in during inspiration. The picture was reminiscent of the severe respiratory embarrassment of an asthmatic attack, or of the exacerbations of illness in adult patients with obstructive emphysema.

It became apparent that this respiratory distress was much more common in children with ventricular septal defects than in those with atrial septal defects at a corresponding post-operative stage, and that this could not be accounted for entirely by the diminished trauma and metabolic upset occasioned by differing surgical techniques. When it was observed that many

children with V.S.D. had, irrespective of surgery, a different chest shape from those with A.S.D, the question arose as to whether or not there was any relation between the chest deformity and the nature of the cardiac lesion and, if there was, whether any significance could be attached to this in view of the manifest differences in behaviour of the two conditions.

The contour of the chest in the sagittal plane is fairly accurately represented by a good lateral chest x-ray, and it was on this basis that the first study was carried out. Before describing the methods and results the clinical features of the chest deformities will be described. In patients with an A.S.D. a chest deformity is present in about one-half of the cases (Taussig 1947, Swan et al. 1959). This deformity consists of a protuberance in the region to the left of the lower sternum where the pulsation of the right ventricle is felt. The upper sternal region is usually normal or flat and tends to be narrow in the antero-posterior diameter, the bulge being low and unilateral. In the V.S.D, on the other hand, the sternum itself often appears to bulge higher in its contour and the antero-posterior diameter of the chest is increased, the lower regions being rather indrawn in the region of Harrison's grooves. Furthermore, the prominence is often bilateral and involves the sternum itself rather than the costo-chondral junctions on one side, as in A.S.D. Sometimes the angle between manubrium and body is sharp; sometimes the convexity forward assumes the form of an arc embracing the whole of the anterior chest from supra-sternal notch to xiphisternum. These differences are recognisable clinically without great difficulty. Figures 1a-k illustrate.

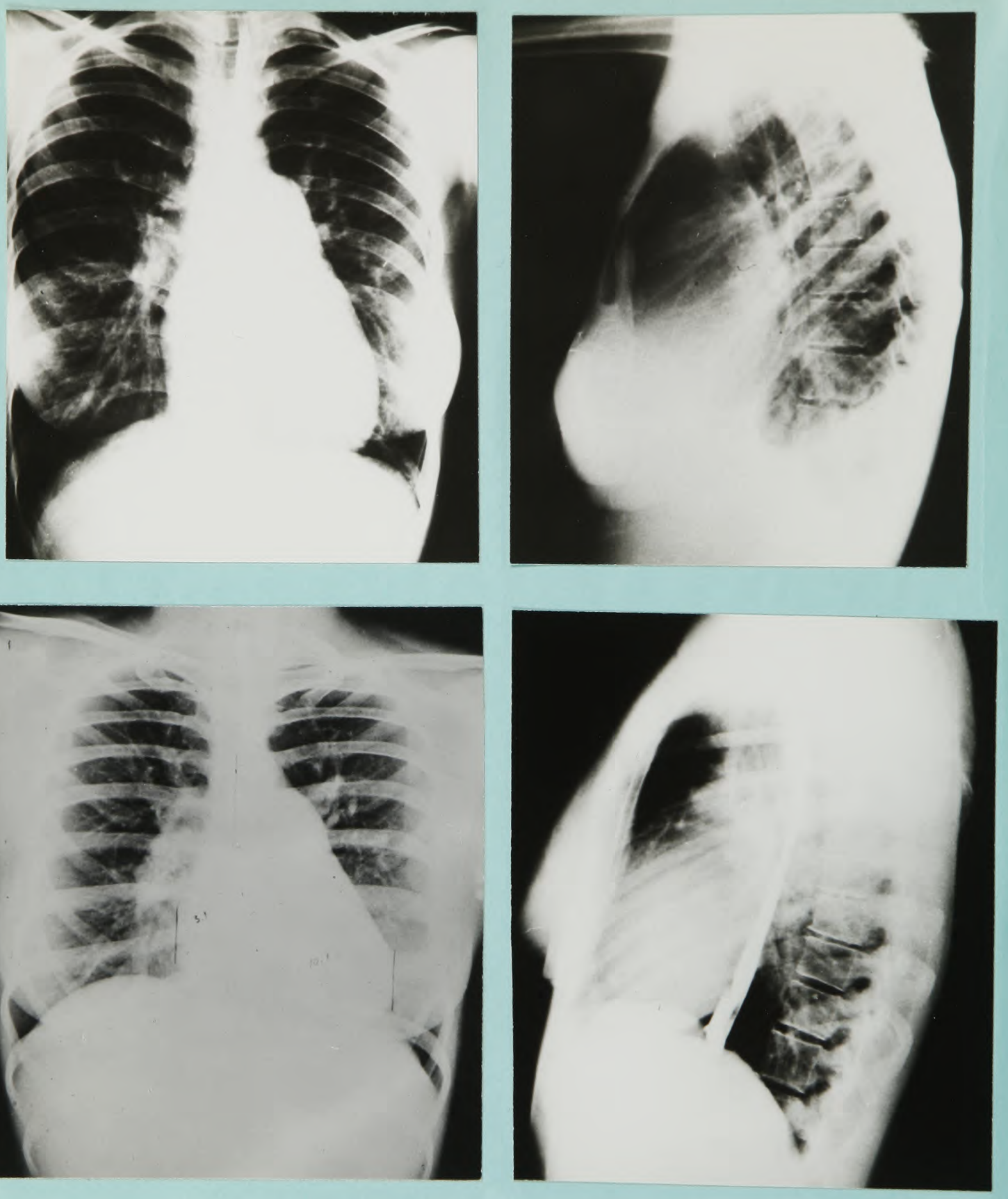


Fig. 1a. Radiological appearances in atrial septal defect.

Above : Mrs. B. G. aged 26. P. A. P. 25/10 PF/SF 2.0
Below : Mrs. R. C. aged 29. P. A. P. 30/15 PF/SF 4.5

In these patients the sternum is depressed and the A-P diameter of the chest is reduced

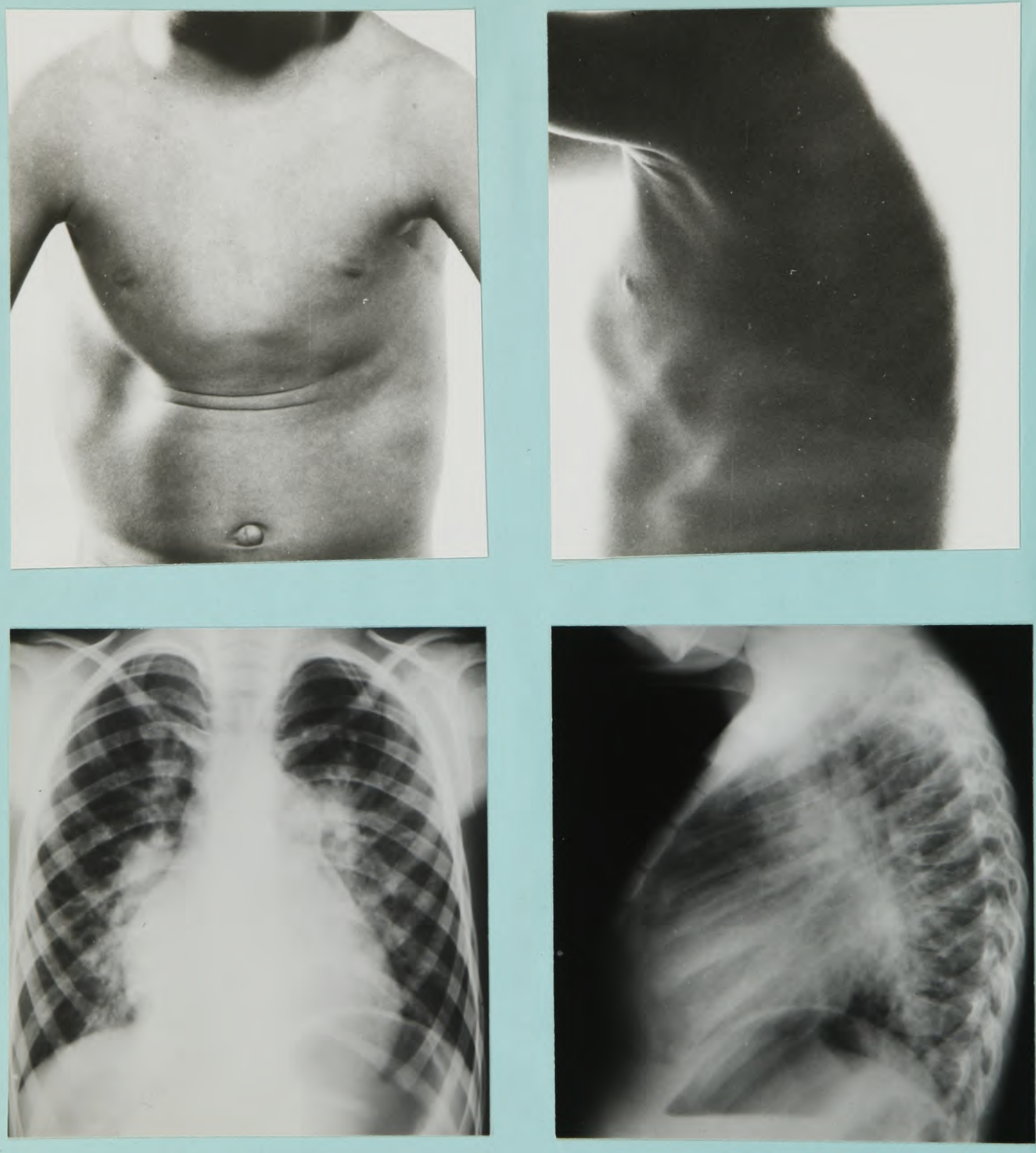


Fig. 1b. A.F. aged 3. V.S.D. with systemic pressure in pulmonary artery. PF/SF approximately 5.0

The increased A-P diameter of the chest, the indrawing of the lower ribs in the region of attachment of the diaphragm, and the normal ossification of the sternum are seen. There was no history of respiratory infection.

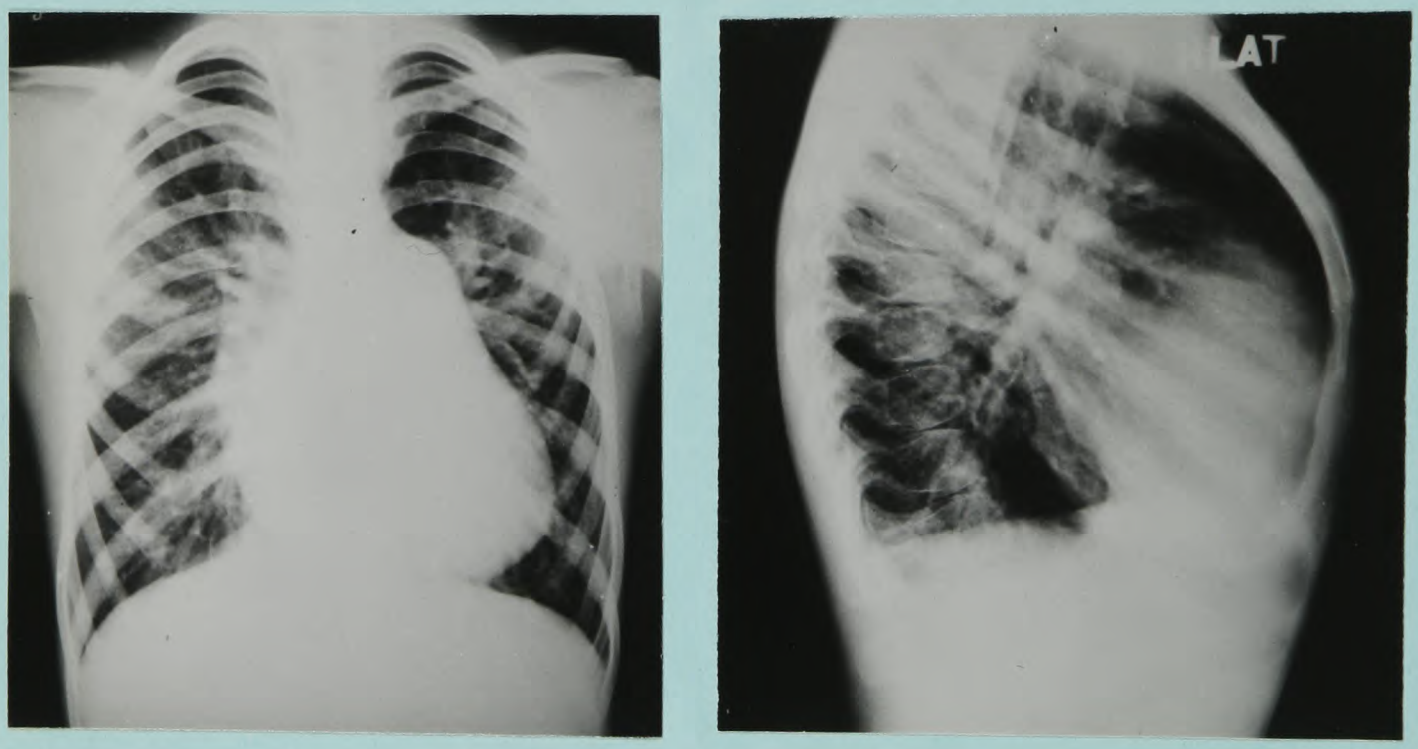


Fig. 1c. P.H. aged 7. V.S.D. P.A.P. 90/45. PF/SF 2.5

Typical V.S.D.-type deformity. The sternum is completely united.







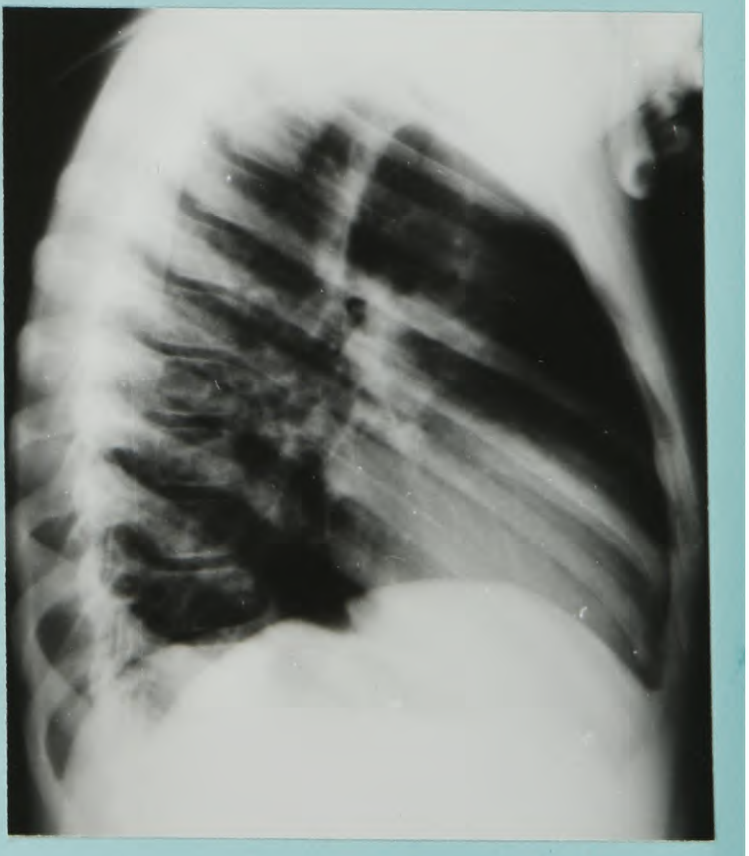


Fig. 1d. F.H. V.S.D.

Above - aged 3 : P.A.P. 33/32. PF/SF 2.5. The degree of chest deformity is unusual in the presence of so low a P.A.P, as indeed is the gross cardiomegaly with right and left ventricular enlargement. The sternal ossicles are normal.

Below - aged 5 : After closure of the V.S.D. The sternal contour appears normal, illustrating the functional nature of the deformity at this age.

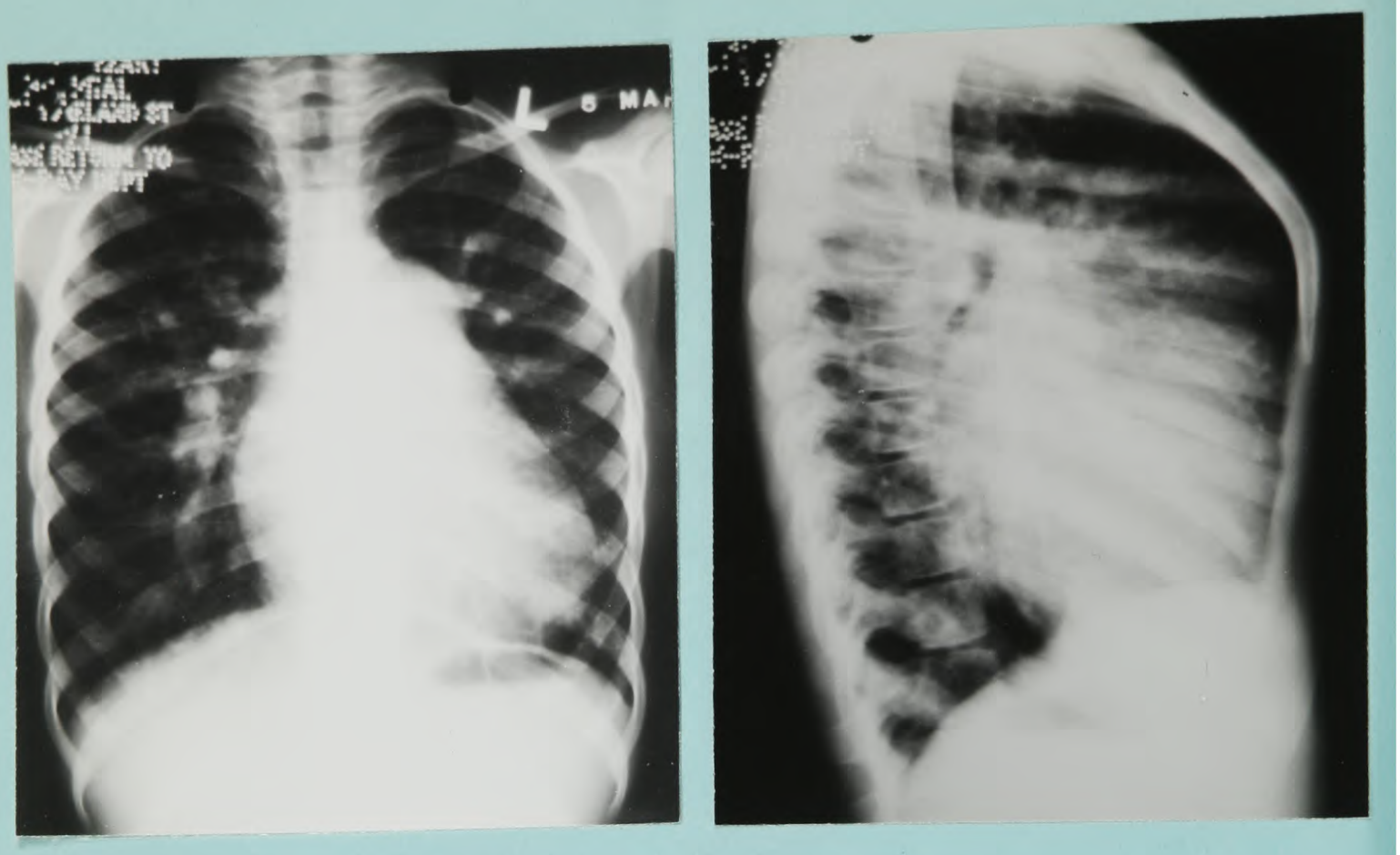


Fig. 1e. C.W. aged 10. V.S.D. P.A.P. 80/50. PF/SF 3.0.
The sternum is united.

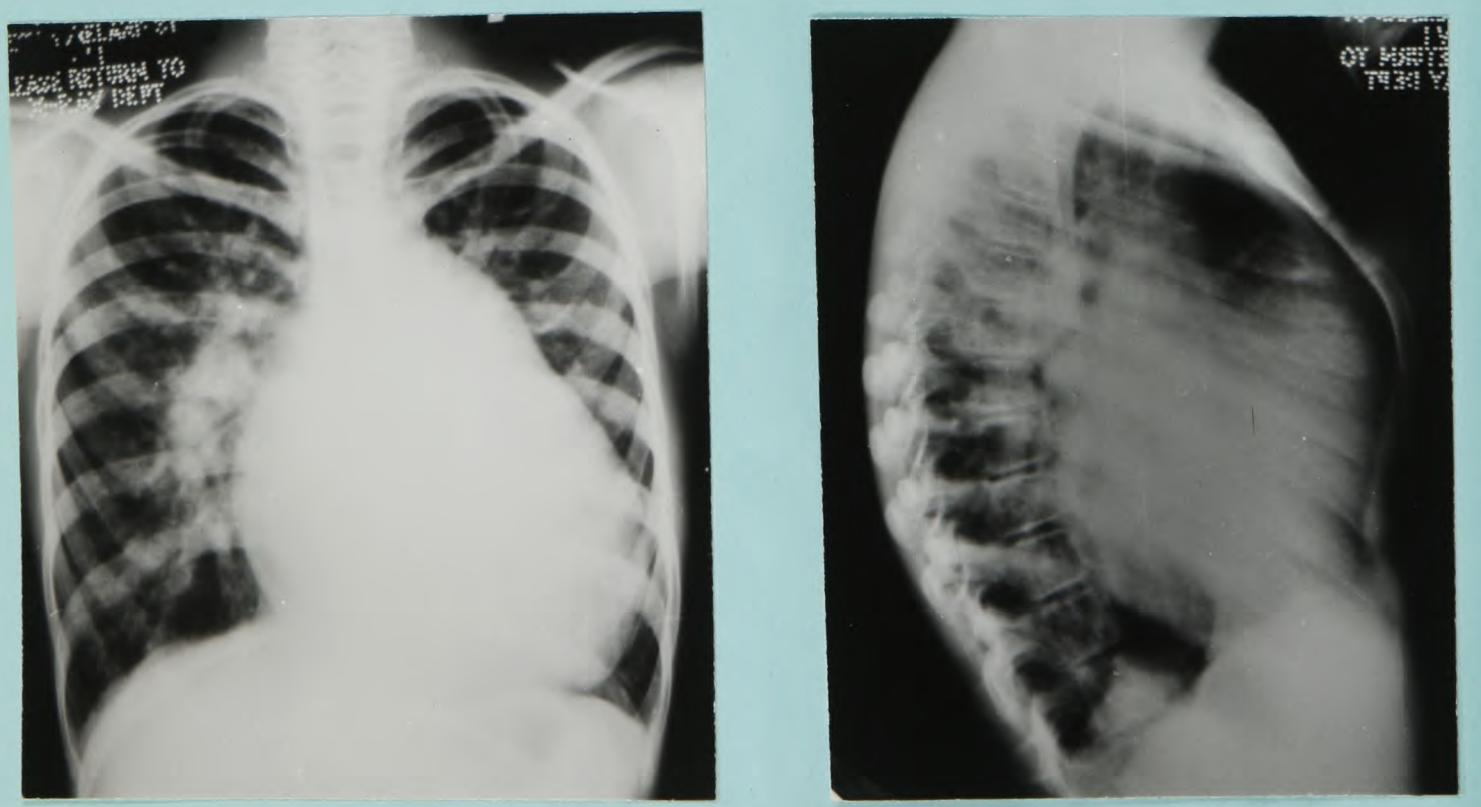


Fig. 1f. M.A. aged 8. V.S.D. P.A.P. 100/50. PF/SF 4.5.



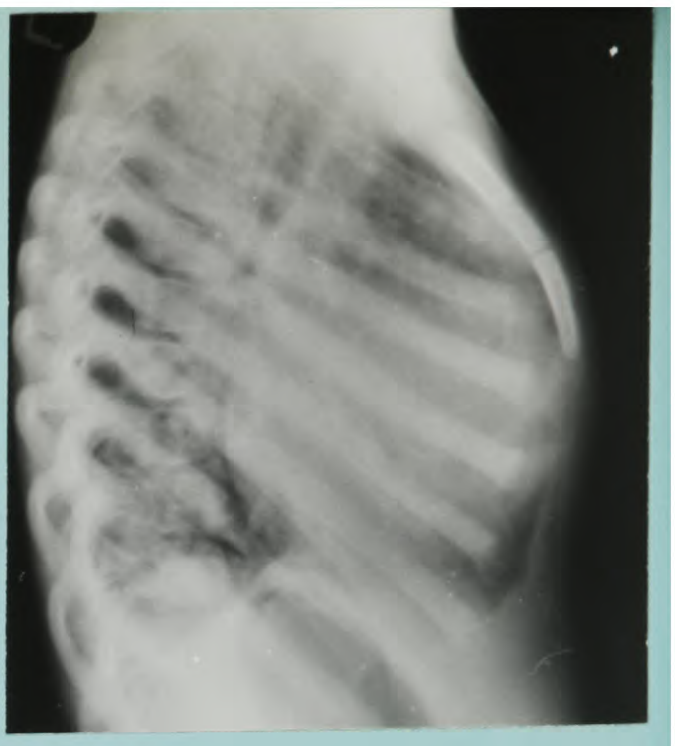
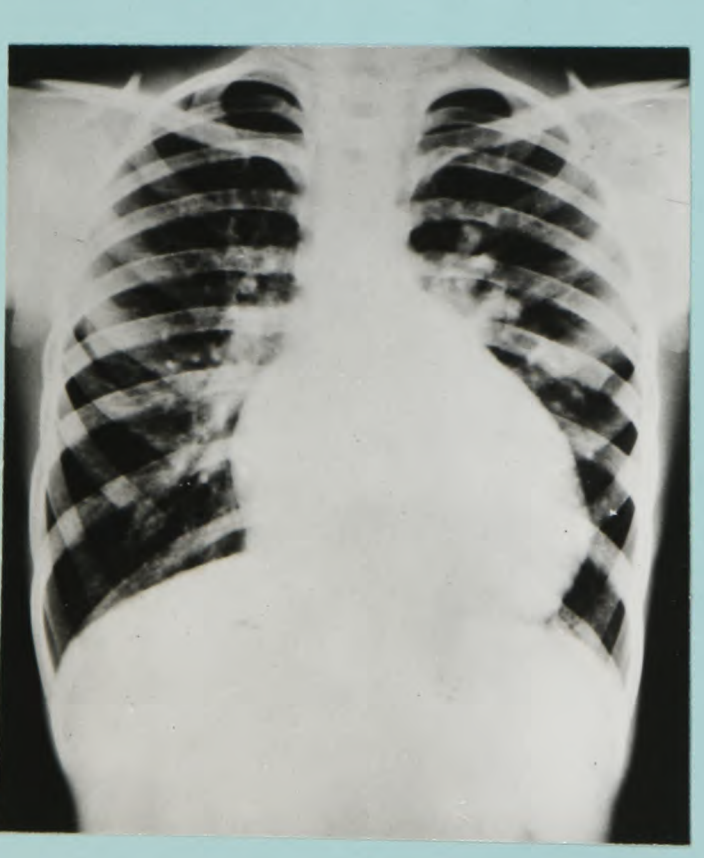


Fig. 1g. S. P. aged 5. V. S. D.

P. A. P. 80/40. PF/SF 2.0.
The sternum is short, but the ossicles are ununited.



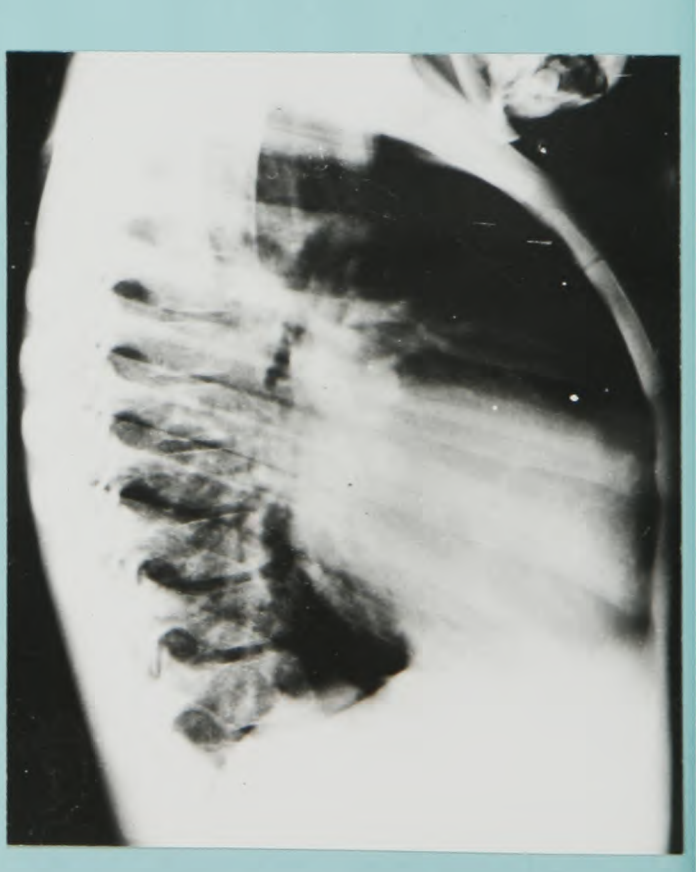


Fig. 1h. B. L. aged 10. V. S. D. P. A. P. 90/60. PF/SF 1.9.

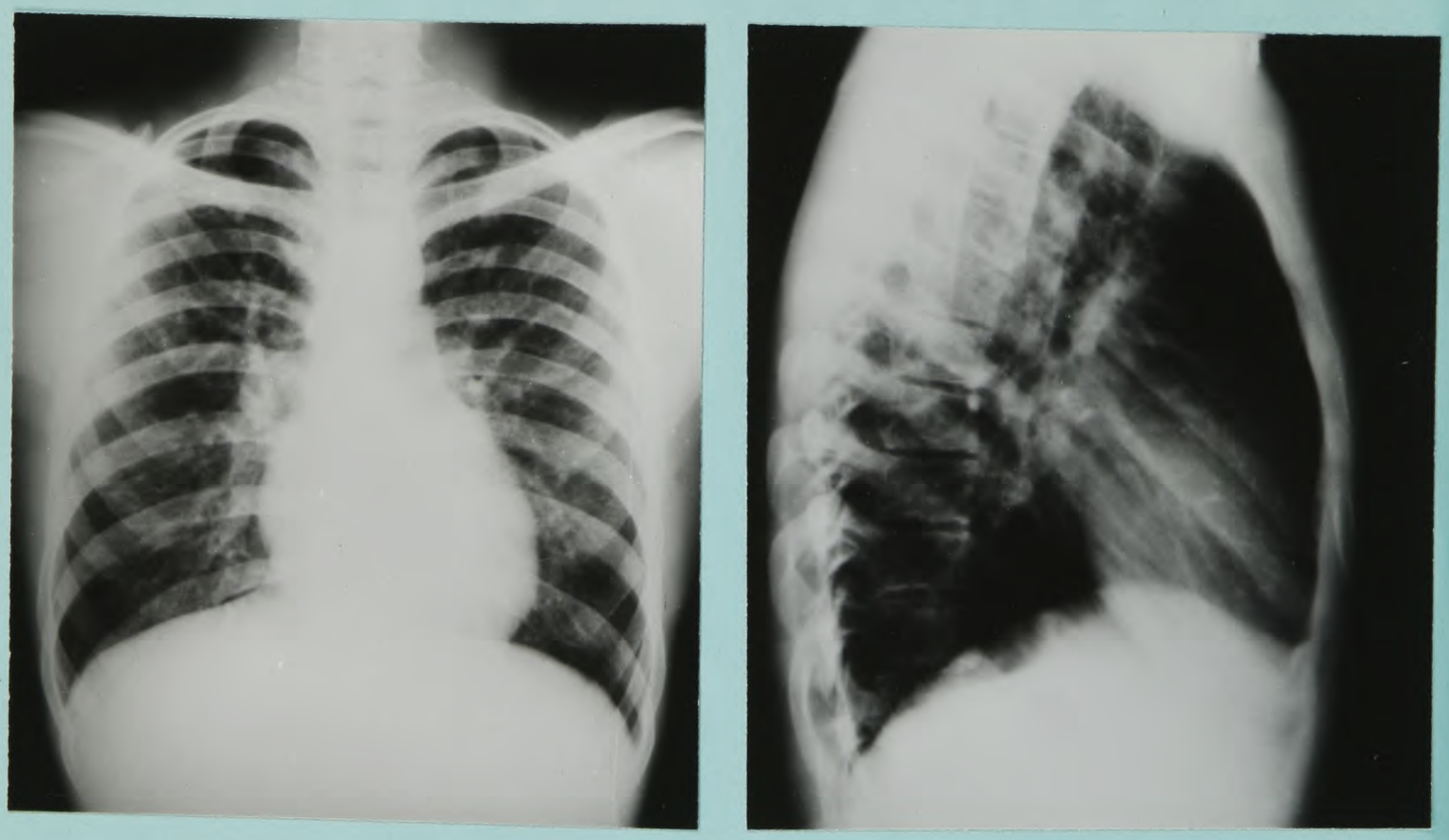
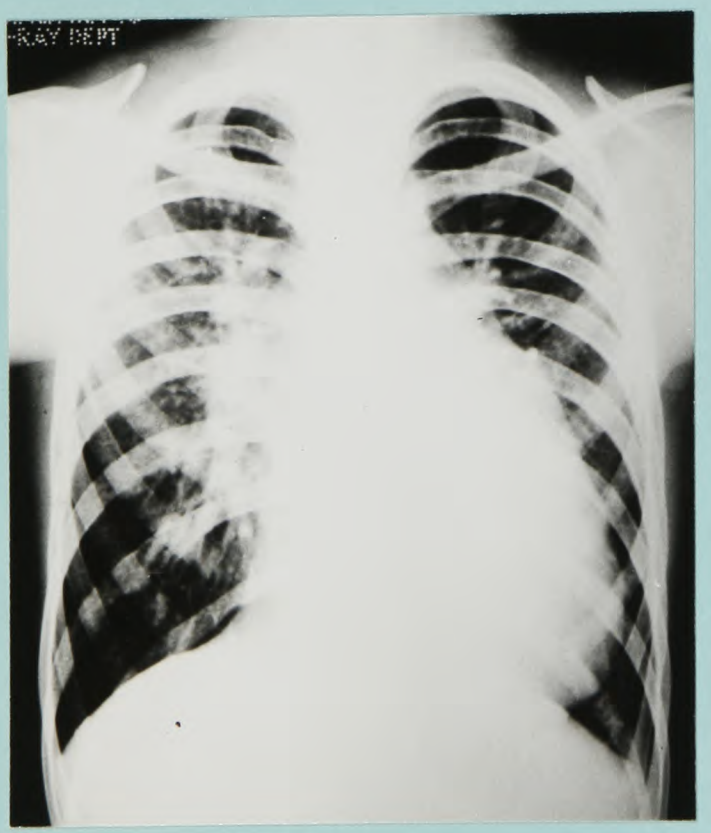


Fig. 1i. J.H. aged 21. Eisenmenger complex.
P.A.P. 90/60. PF/SF 2.0.
The thoracic contour is normal.







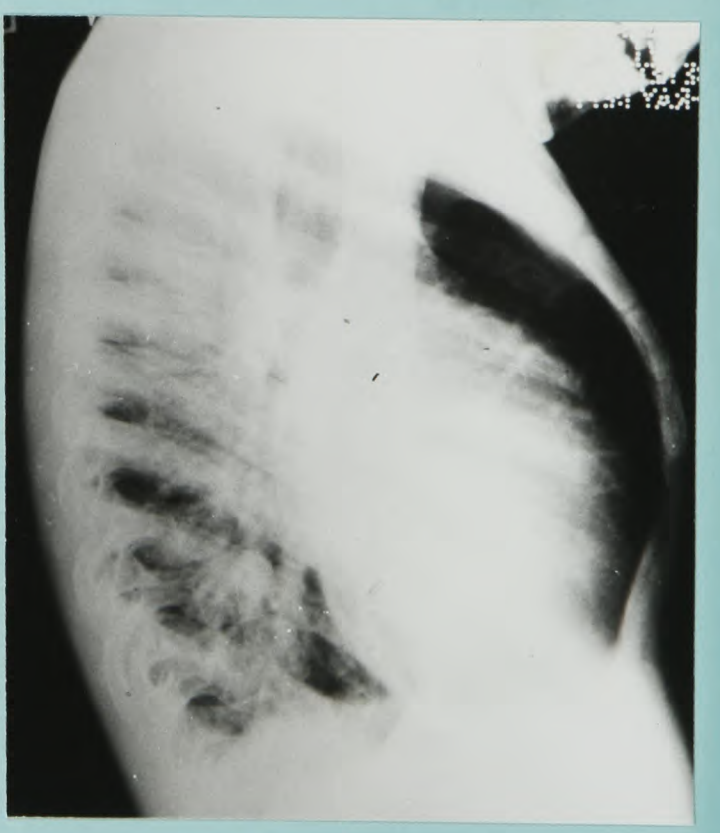
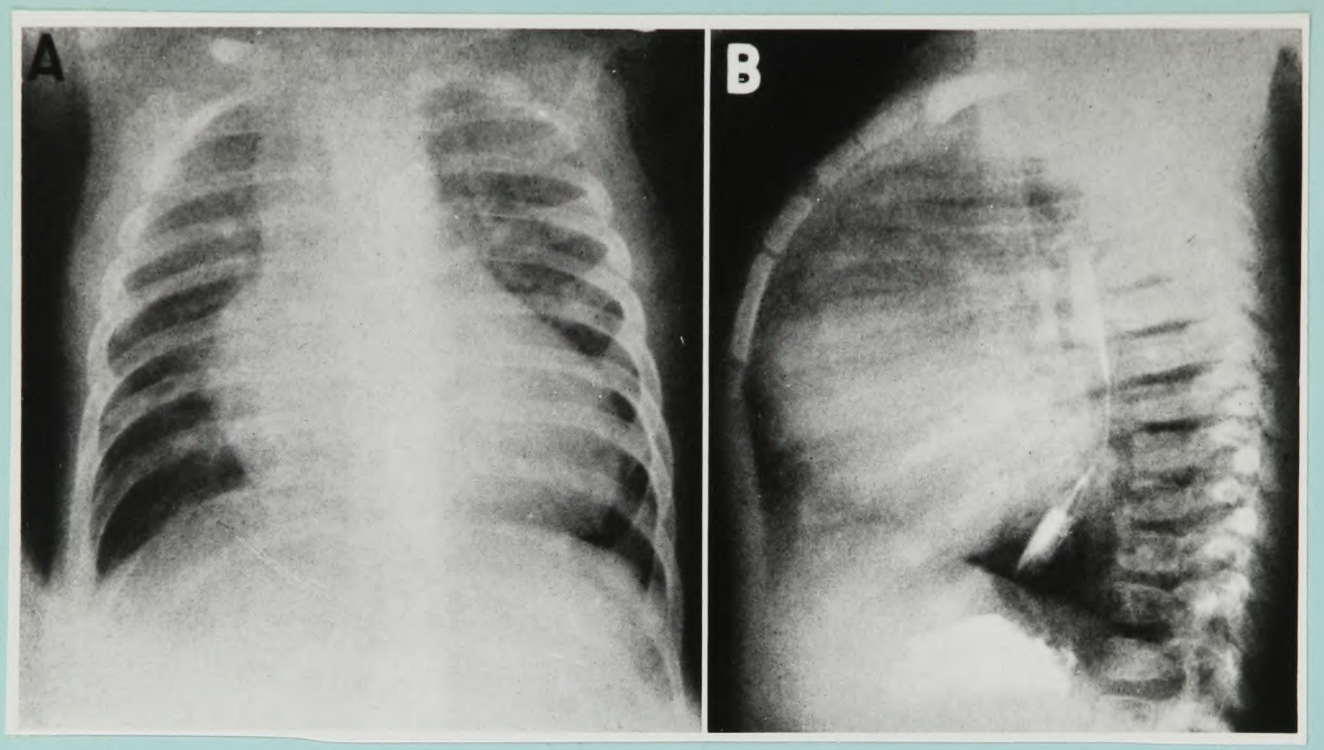


Fig. 1j. W.H. aged 14. Single ventricle with inverted transposition. P.A.P. 50/25. PF/SF 2.5. It is unlikely that the cardiomegaly has been responsible for the chest deformity since the anterior border of the heart is not contiguous with the anterior thoracic wall.



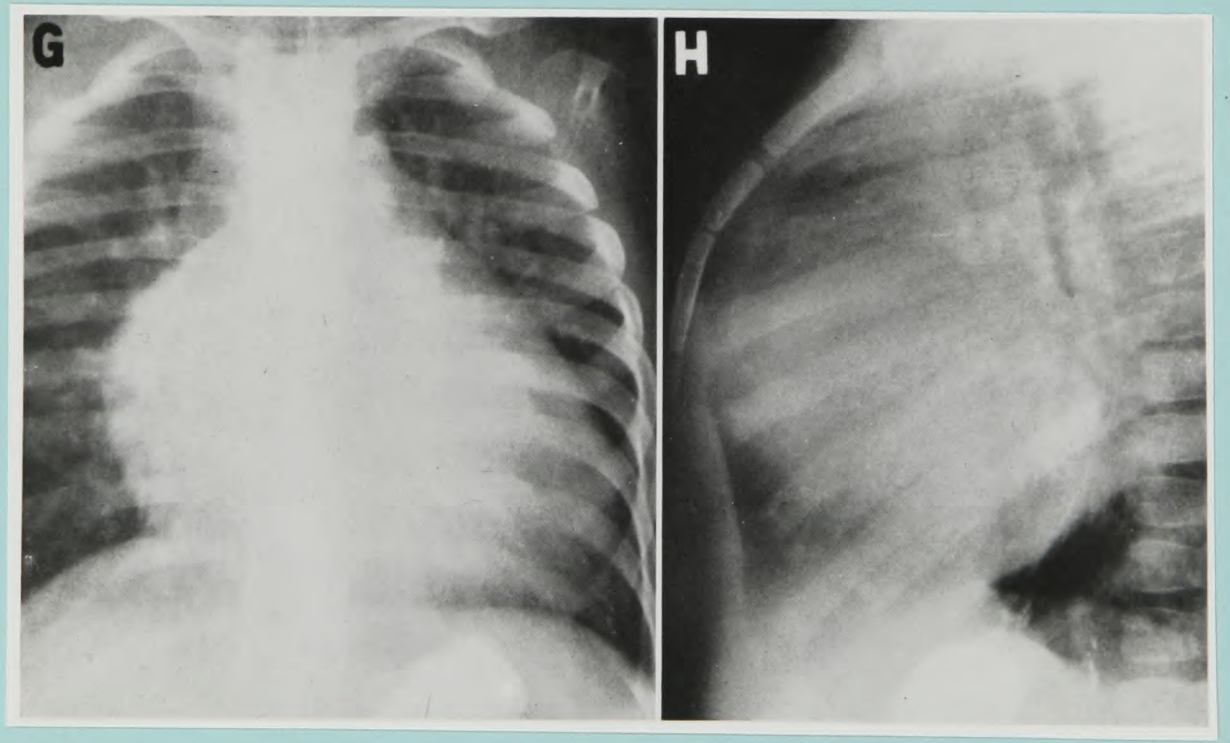


Fig. 1k. R.E. Large V.S.D. with left-to-right shunt and systemic pressure in pulmonary artery.
From Kjellberg et al. 1955, Fig. 281 (Fig. 332 of 1959 edition).
Above: aged 6 months.
Below: aged $2\frac{1}{2}$ years.
The sternal ossicles remain ununited.

Methods The chest X-rays of the last 200 cases of A.S.D. and V.S.D. (excluding the Eisenmenger Complex) to have undergone cardiac catheterisation at the University of Colorado Medical Center were examined. Only those in whom an adequate lateral X-ray was available were retained in the study, since any obliquity distorts the appearance of the sternal contour. When this criterion had been satisfied there remained 80 cases of A.S.D. and 44 of V.S.D. The former ranged in age between one and 45 years, whilst all the latter were between three and 14 years of age. An attempt was made at first to record accurately, in terms of angles and ratios, the mensural characteristics of the X-rays, but this was found to be unrewarding owing to variations in shape, posture and size. Accordingly, the degree of sternal prominence was graded into 'severe', 'moderate' or 'absent' without knowledge at the time of the diagnosis or haemodynamic data. Those cases in whom the deformity was thought to be only mild were included in the 'absent' group. It is emphasized that the deformity sought has been that of the 'V.S.D. type' described above.

Results Severe sternal deformity (V.S.D. type, Fig. 1b, etc.) was present in 11 of the 44 cases of V.S.D. and in none with A.S.D. Moderate deformity was seen in a further 11 cases of V.S.D, and again in none with A.S.D. Thus the deformity was seen in 22 of the cases of V.S.D. and in none of A.S.D. The results are summarised in Table I.

TABLE I

INCIDENCE OF 'V.S.D.-TYPE' DEFORMITY

Deformity	V.S.D.	A.S.D.
Severe	11	0
Moderate	11	0
None	22	80
Total cases	44	80

Table II (Appendix) gives details of the cases of V.S.D. and relates the findings to the haemodynamic data obtained at cardiac catheterisation. All 22 patients with moderate or severe chest deformity had hyperkinetic pulmonary hypertension except one (case 4). The average values for pulmonary arterial flow and pressure and total pulmonary resistance were similar in the two groups with moderate and severe deformity respectively.

Excluding the Eisenmenger Complex, therefore, it is evident that this type of chest deformity occurs in about one-half of the patients with V.S.D, and in these the mean pulmonary arterial pressure and total pulmonary vascular resistance are approximately twice as high as in the group in which the deformity is mild or absent.

Eisenmenger's Complex

Six cases fulfilled the necessary criteria of an adequate lateral x-ray and haemodynamic data, and in these the deformity was present in moderate degree in only one. The other five had normal chests (Table II). (Fig. Ii).

Discussion There is a difference between the chest configuration of the patient with an A.S.D. and the one with a V.S.D. In the case of the former lesion, the deformity is explicable on the basis of direct pressure by the enlarged right ventricle on the malleable structures of the thoracic cage in childhood. The bulge occurs in the region just over the right ventricle. (One patient with an A.S.D. was seen in whom the heart lay to the right of the sternum; in this case the bulge was right-sided). Why the deformity occurs in some cases of A.S.D. and not in others is not clear, but it may be related to the age at which the significant right ventricular enlargement occurs. It is highly likely that the left-to-right shunt is not present at birth, but develops durin g the first year of life in cases of A.S.D., depending on the filling resistance of the right ventricle and perhaps the size of the defect.

Examination of patients with V.S.D. and consideration of their x-rays leads to the conclusion that in a number of cases the sternal protuberance in question is not contiguous with the heart or great vessels and is, therefore, unlikely to be a consequence of direct pressure (see Fig. Ij). One possible

explanation is that the mechanical forces at work in the thorax of such patients are different from those of normal children. Certainly the V.S.D. differs from the A.S.D. in that when a left-to-right shunt develops, it is present much earlier, usually in the first weeks or months, and cardiac enlargement is therefore present early in life. The effect of this may be to cause a relative protuberance of the left side of the chest, and sometimes patients with bilateral chest deformity are seen in whom the left chest is more prominent anteriorly than the right. This is by no means always so however, and there is likely to be an explanation other than cardiomegaly per se for the symmetrically bilateral deformity often seen.

The cause of the phenomen must, therefore, be sought in the extra-cardiac forces of the thorax and these, of course, are related to respiration. Clinical observation of the breathing pattern of infants with left-to-right shunts (see Fig. 1u) and pulmonary hypertension suggests at once the picture of respiratory embarrassment: tachypnoea, indrawing of the lower ribs, and lifting of the sternum on inspiration. By orthodox criteria cardiac failure is not always present, in that all pressures in the heart are not high and, in particular, the pulmonary venous pressure is not usually elevated to levels where pulmonary oedema or gross interference with the mechanical properties of the lungs due to pulmonary venous hypertension would be expected to occur. It seems logical to ask, nevertheless, whether or not the development of the deformity in question is related to the mechanical

properties of the lungs and the work of breathing. If this were the case, it would explain why the bulging is bilateral, why the antero-posterior diameter of the chest is increased, and why there is often indrawing of the lower ribs. The problem therefore turns on the mechanical properties of the lungs in cases of V.S.D. This information was not available in 1959, partly no doubt because it is notoriously difficult to perform pulmonary function studies on children.

Several factors could operate in these cases to alter the mechanical properties of the lungs. The first is that their expansion might be impeded merely by the presence of a large heart; the second, that there may be bronchial blockage and consequent atelectasis; the third, that 'pulmonary congestion', in the sense that there is an abnormally high volume of blood in the lungs, could make them turgid; the fourth, that the pulmonary vasculature might have erectile properties which are modified by the abnormal haemodynamics (see Appendix p.142). Whichever factor or combination of factors is responsible for disturbing the pulmonary mechanics is probably not ultimately important in determining the final effect on the thoracic contour.

That changes in the properties of the lungs could produce the deformity of the V.S.D. seems not unlikely. The 'pigeon-breast',

with raised sternum, increased antero-posterior chest diameter, and indrawing of the lower chest wall occurs classically in rickets, being here the response of abnormal bone to presumably normal respiratory forces; this sternal protuberance was recorded as early as 1645 by Whistler. Naish and Wallis (1948), in a study of Harrison's grooves, found that they were much commoner in children suffering from asthma than in normals, and that their depth depended on how early the disease had started. They also found the grooves to be present in 23 out of 36 cases of congenital heart disease. The grooves were also noted frequently in children with a pigeon-breast deformity. A few years earlier, Naish (1945) had recorded marked inspiratory indrawing of the lower intercostal spaces in eight cases of congenital heart disease, seen in infancy, in whom there was no evidence of rickets or of upper respiratory tract infection.

Sheldon (1938) noted the forward bulging of the sternum and costal cartilages in young infants with congenital heart disease, and ascribed it to cardiac hypertrophy. He made the point that there may be collapse of the bases of the lungs due to enlargement of the heart, and noted that in these infants the character of the breathing is often peculiar. It is impossible to deny that this explanation, based on the mechanical effects of an enlarged heart, may be correct. It has the merit of suggesting abnormality of the respiratory apparatus, but is probably an over-simplification. Downing and Goldberg (1956) reported the frequency of praecordial bulge in V. S. D. to be up to 50%. Sandøe (1963) found it to be present in pronounced degree in 12 of his 87 patients with V. S. D.

He does not identify the patients individually and the detailed haemodynamics are therefore not available. Inspection of his Table I makes it clear, however, that there are only 14 cases with considerable pulmonary hypertension and a flow ratio greater than 2.0 as against 33 in the Eisenmenger group.

Kjellberg et al. (1955), in their description of the clinical findings in ventricular septal defect, remark particularly that a praecordial bulge was absent in their group 1a (Maladie de Roger) and in group 1b with a definite left-to-right shunt but a normal pressure in the right ventricle. In group 2, with an increased though not systemic pressure in the right ventricle, a praecordial bulge was present in five patients out of 15. In group 3a a "marked or distinct praecordial bulge" is recorded, presumably in all the patients: these are patients with systemic pressure in the right ventricle, but a shunt which is left-to-right only. Group 3b, where there is also a right-to-left shunt, and which would appear from the description to be typical of the Eisenmenger Complex, a praecordial bulge is also recorded in all. Examples of the lateral x-rays showing the typical configuration are shown in Figures 271, 272, 281 and 282 of Kjellberg et al.'s book. These findings are, group 3b excepted, in keeping with those of this study.

If it were correct that the lungs were stiffer than normal in V. S. D, it would be expected that the sternal bulging would occur in any case where the essential haemodynamic requirements are met, viz. increased pulmonary vascular resistance and increased pulmonary blood flow. These factors are present in some cases



Fig. 11. J.C. aged 3. P.D.A. P.A.P. 80/50. PF/SF 3.0.

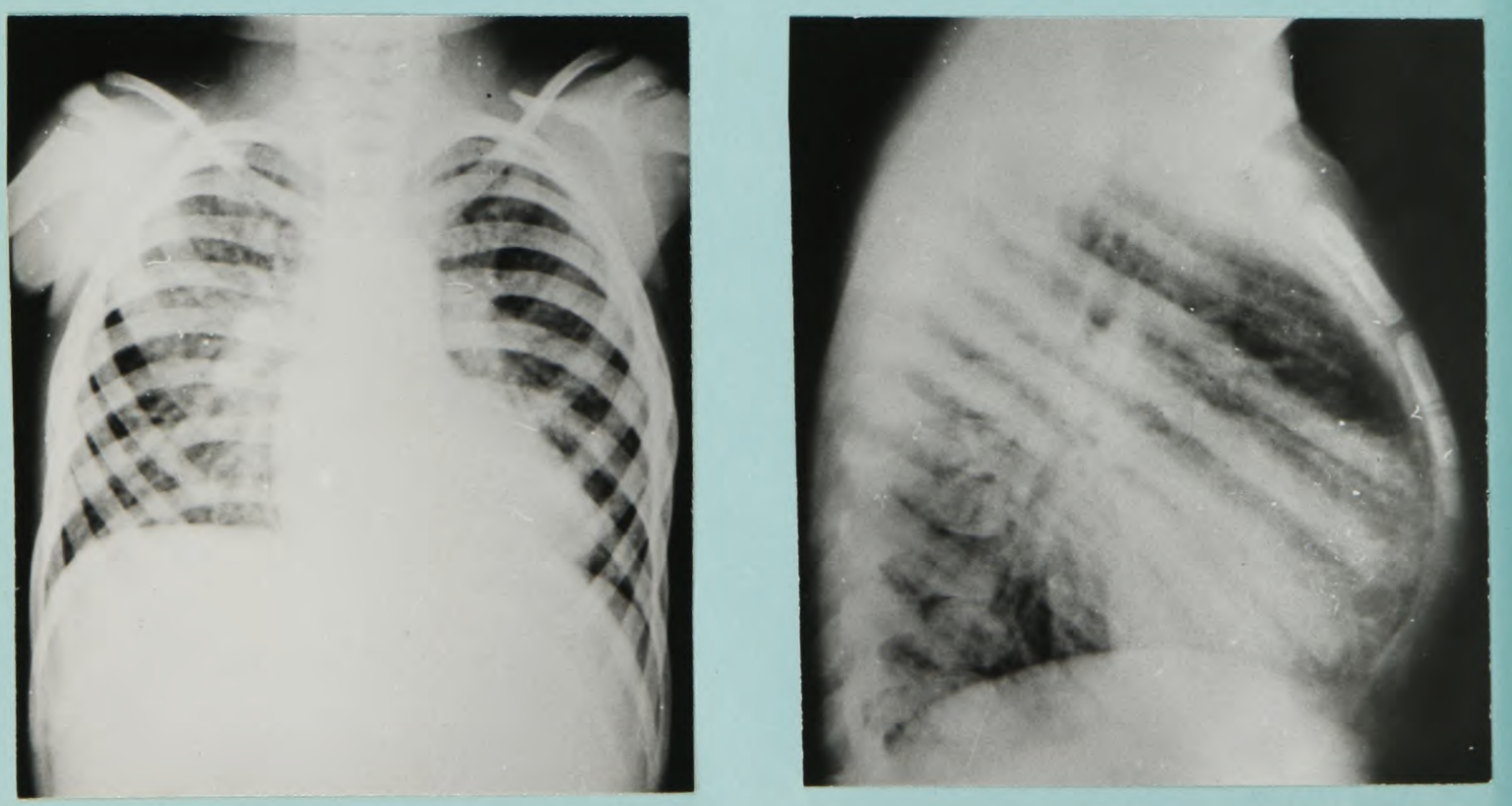


Fig. 1m. S.H. aged 2. Complete transposition of the great vessels. P.A.P. not measured, but pulmonary plethora is considerable and hyperkinetic pulmonary hypertension very likely.





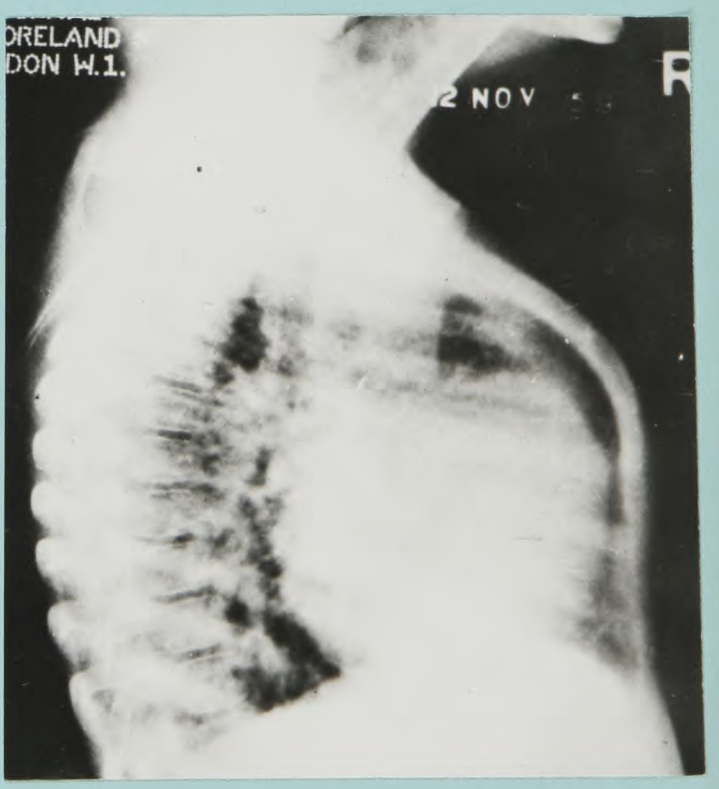


Fig. 1n. A.W. aged 4. Complete transposition of the great vessels. Comment as in 1m. There is abnormal sternal ossification.

of patent ductus arteriosus, and indeed the deformity is seen in such patients (e.g. Fig. 11). In one, the elevation of the sternum and the insucking of the lower ribs were very marked, as was hyperventilation. This child, aged 3, was operated upon and at the time the surgeon's unsolicited remarks were that "the lungs were stiff". She died soon afterwards. The situation in atrioventricularis communis is similar to that in V. S. D. and the deformity is also seen with this lesion, as it is when a V. S. D. is present together with other lesions, such as patent ductus arteriosus and coarctation of the aorta. Hyperkinetic pulmonary hypertension is also a feature of those patients with transposition of the great vessels who have pulmonary plethora. The chest deformity is seen in such cases, e.g. Figs. 1m and 1n.

Lester (1953), under the title 'Pigeon Breast (Pectus Carinatum) and other protrusion deformities of the chest of developmental origin' made an attempt to analyse this problem. He makes the following points: first, that pectus carinatum is different from the pigeon breast of rickets in that the former is congenital and the latter acquired; second, that it is usually noted at about one year of age and may become worse or better or stay the same as the years go by; third, that patients are divided into two groups, those (a) who have a mid line deformity involving the sternum and attached cartilages - in this group the sternum protrudes either with the lowest part the most prominent, or in an arcuate manner with the mid portion of the sternum the most prominent and the lower end pointing backward, and (b) whose sternum seems to be in its normal position, the protrusion

corresponding to the costochondral junction of several consecutive ribs, thus making a ridge lateral to the sternum.

These two groups of Lester's would appear to correspond broadly with the V. S. D. and A. S. D. groups respectively. He comments that many observers have believed that the diaphragm has something to do with the protrusion deformity. Brown (1951) thought that overstimulation of the peripheral fibres of the diaphragm was a factor. Brodkin (1949) studied a 14-months-old mongoloid infant with an interventricular septal defect and a pigeon breast who died of a respiratory infection. The central tendon of the diaphragm was much enlarged at the expense of the anterior muscle fibres, and it was to this that he attributed the deformity. Lester (1953) could not confirm this anterior deficiency and considered other factors. Overgrowth of the ribs below the second, or under-development of the upper ribs, will "force the sternum forward by buckling the ribs along the weak costochondral junction. If the diaphragm increases its size to keep pace with the overgrowth of ribs, the sternum will protrude in an oblique line from above down. If the diaphragm does not keep pace, especially in the tendinous portion, the xiphoid and lower end of the sternum will be restrained and the protrusion of the sternum will take an arcuate form, curved from above down".

Currarino and Silverman (1958) described a developmental anomaly of the sternum characterised by premature obliteration of its sutures, and by a tendency toward forward angulation, associated with an increase in the sagittal diameter of the thorax of the type seen in 'arcuate pigeon breast'. Their first case was a child of

four in whom a pigeon breast deformity had been present since early infancy together with multiple congenital anomalies, though none apparently affected the heart. The deformity was obviously not gross, but lateral x-rays of the chest showed that at one year the sternum was straight, but its sutures irregularly shaped and abnormally narrow. At four years of age the sternum was angulated forward and consisted of a solid bony plaque without any residue of sutures. The second case, a child of six months, was poorly nourished and retarded. There was a mid-line pigeon breast deformity with a sternum that was devoid of suture lines. Apart from an aberrant right subclavian artery crossing behind the oesophagus, no cardiac abnormality is mentioned. The third case was followed from the age of eight months to death at thirteen years. This child had 'cardiomegaly and gross pulmonary over-circulation', found at autopsy to be due to a large V. S. D. and a P. D. A. There was clinically and radiographically a deformity of the anterior wall of the thorax, characterised by a pronounced mid-line bulge. This thoracic deformity was present from at least the eighth month of life and apparently increased in severity thereafter. The x-ray shows that the contour of the chest was of the 'V. S. D. type' now described, and that the sternum was entirely devoid of sutures.

In an addendum to their article, Currarino and Silverman show seven additional x-ray plates of sterna. The fourth case was a four-months-old baby with congenital laryngeal stridor and almost complete obliteration of the sternal sutures. The fifth and sixth were twins aged eight months with skeletal deformities and very mild pigeon breast; the latter had a P. D. A. The sternal

sutures were almost obliterated. The seventh shows a marked deformity in a seventeen-year-old girl with a P. D. A. and pulmonary hypertension. The chest deformity had been present since infancy. The eighth was a thirteen-year-old boy with a V. S. D. and pulmonary hypertension, but said to be in the cyanotic group. The ninth was an eleven-year-old male with marked pigeon breast which had probably increased slightly since infancy. No other congenital anomalies were present. In all these cases the sternal sutures were obliterated.

The authors comment that there was a high incidence of obliteration of manubriosternal synchondrosis in the parents of these children who were examined roentgenographically. They found the association of the sternal protrusion and the synostosis to be so close that it suggested a cause-and-effect relationship between the two factors (i. e. the synostosis causing the forward angulation). They thought that the sternal anomalies might be an expression of an abnormality of development that affects other organ systems in the body as well.

Monnet et al. (1956) described a baby with a sternal anomaly - "ossification prématurée du sternum" - who died at the age of four-and-a-half months. Autopsy showed what would now probably be called a double-outflow-tract right ventricle and partial anomalous pulmonary venous drainage. Again there was the forward bulging, almost certainly in association with hyperkinetic pulmonary hypertension, and the synostosis - "...les trois noyaux habituels à cet âge sont réunis en un seul, formant ainsi une bande opaque légèrement en retrait de la concavité antérieure du thorax".

Andrén and Hall (1961) found early fusion or defective segmentation of the sternum in six patients with congenital heart disease. Subsequent search of the roentgen files of 1100 patients admitted because of suspected chest disease failed to reveal any cases of diminished segmentation but, in addition to the above cases, they state that they have seen a number of patients with less striking defective segmentation of the sternum, often in association with congenital heart disease. They also saw diminished segmentation in another seven cases without detectable cardiovascular disease. Their published x-rays show severe protrusion deformity, already present at the age of nine months, and severe at the age of five, in a fifteen-year-old girl with A. S. D. and V. S. D. and pulmonary hypertension. They comment on the fact that maldevelopment of the sternum appears to be one of the commonest malformations associated with congenital heart disease, and suggest as possible reasons for its'having been overlooked' (a) that it has been variously called funnel chest or 'voussure', or that it is a bulging of the praecordium due to hypertrophy and dilatation of the heart during childhood; (b) it has been regarded as a sequel of rickets; (c) it has not been observed roentgenologically because cardiac examinations do not always include lateral views; and (d) the sternum is seldom the seat of disease and is therefore not often examined. They conclude that the condition is probably due to some exogenous intrauterine injury, but that sternal anomalies are "more common in the presence of septal defects than with aortic coarctation or pure pulmonary stenosis".

The theme thus recurs of the association of sternal anomalies of the protrusive type with underlying congenital cardiovascular

disease, the two factors mainly considered as being responsible for the deformity being the pressure of the enlarged heart and the premature synostosis of the sternal sutures. The former has already been discussed. The latter is worthy of further consideration.

The cases of Monnet et al. (1956), Currarino and Silverman (1958) and Andrén and Hall (1961) are entirely acceptable as showing premature synostosis. To establish that the synostosis is the cause of the protrusive sternal deformity demands, however, a fairly consistent relationship between these. In other words, if it can be shown that the deformity occurs with normal segmentation in a significant proportion of patients, the case for their causal association becomes much weaker. That this is so is seen from Figs. 1b, d, g, m, q and t, and from Figs. 271, 281 and 282 in the book of Kjellberg et al. (1955).

In the nine weeks' embryo the sternum is uniformly cartilaginous and resembles in shape the future bone, but it is still entirely unsegmented and solidly united with the ribs. Definite segmentation with sternebrae is a late occurrence both in ontogeny and phylogeny (Hanson, 1919; Gladstone and Wakely; 1932; Arey, 1954). Bony union of the four segments of the mesosternum occurs usually from below upward, starting in early childhood, and is said to be complete between the sixteenth and twenty-fifth year of life. The manubrio-sternal synchondrosis usually remains open throughout life, though in some cases it ossifies spontaneously (Ashley, 1954).







Fig. 1o. N. M. aged 7 . Valvar P. S.

There is slight chest deformity, unusual in this group. It is occasionally seen in Fallot's Tetralogy, suggesting that the patient may be one of the unusual ones who in early life had a left-to-right shunt with hyperkinetic pulmonary hypertension, and later developed right ventricular infundibular stenosis.

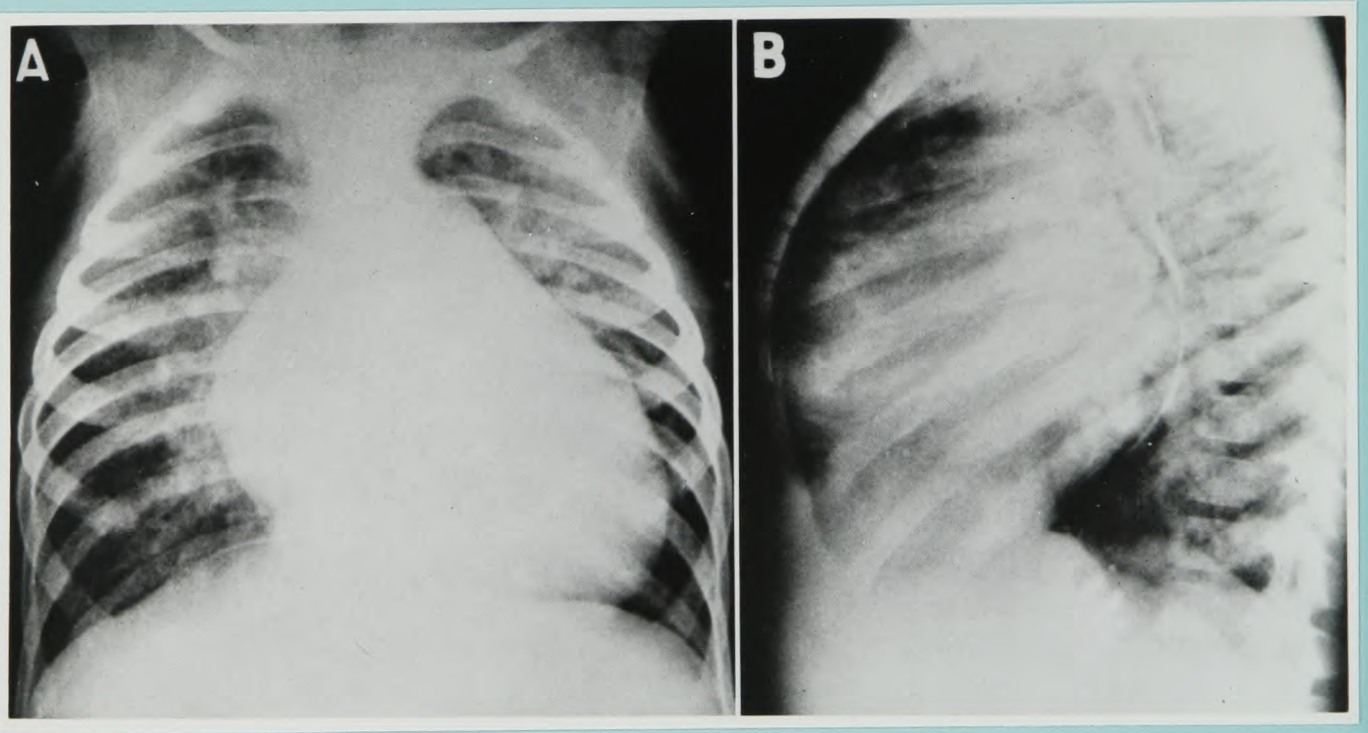
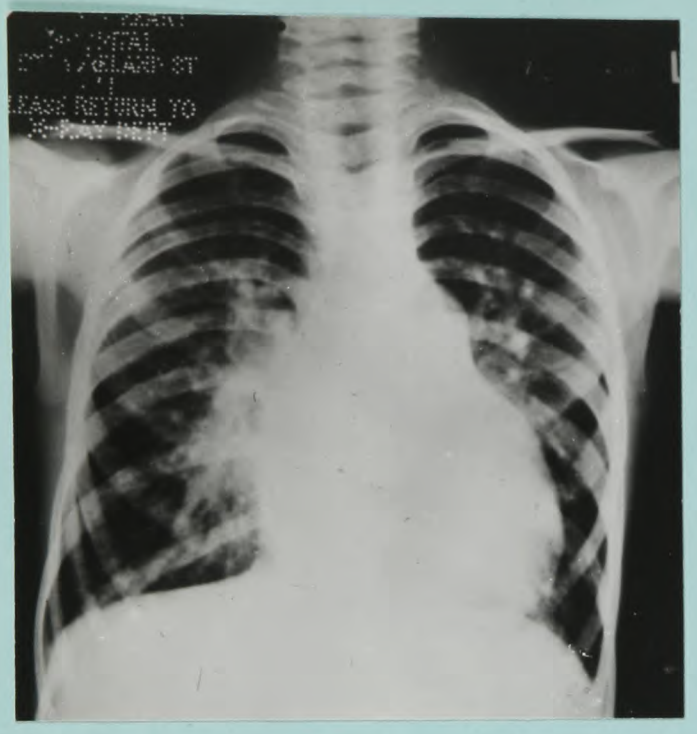


Fig. 1p. P. B. aged 3. V. S. D. and infundibular pulmonary stenosis with large left-to-right shunt. The sternal ossicles appear to be in process of uniting.
As in Fig. 1j, the heart is not in contact with the sternum.
From Kjellberg et al. 1955, Fig. 282 (Fig. 333 of 1959 edition).





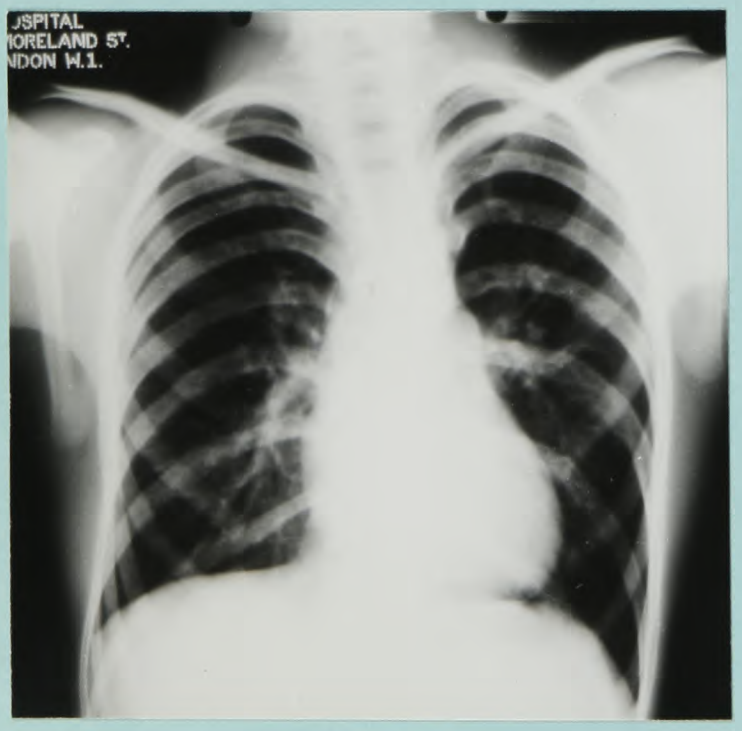




Fig. 1q. P.W. V.S.D.

Above : Aged 7. The typical chest deformity is present. Normal ossification of the sternum is just appreciable. P.A.P. 85/50. PF/SF 2.1.

Below : Aged 9. After surgical closure of the defect. The sternal deformity is less pronounced.

There was also a congenital deformity of the spine with fusion of T7 and 8, leading to increasing kyphosis.

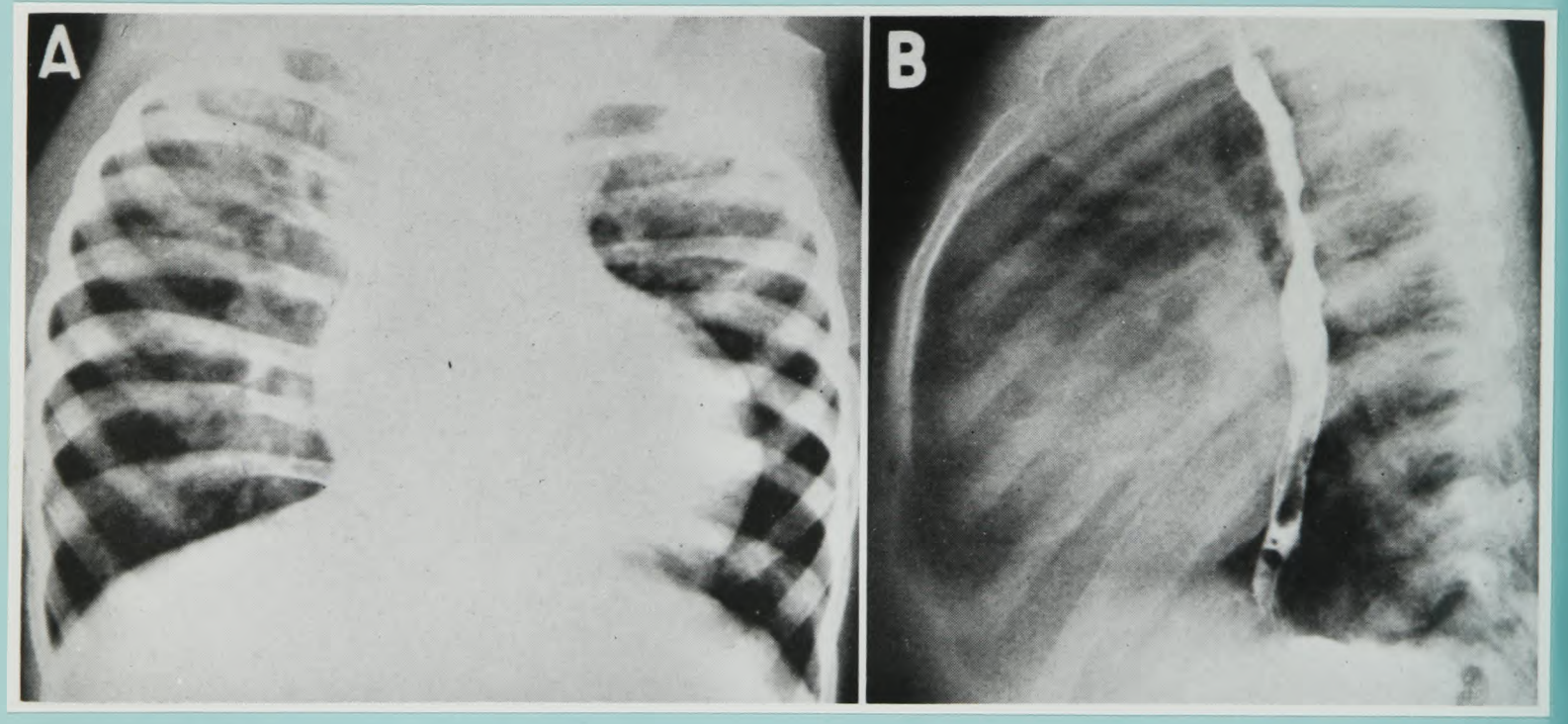


Fig. 1r. M.A. aged 2. V.S.D. with dominating left-to-right shunt and equilibrated pressure in ventricles. The sternal ossicles are united.
From Kjellberg et al. 1955, Fig. 276 (Fig. 327 of 1959 edition).

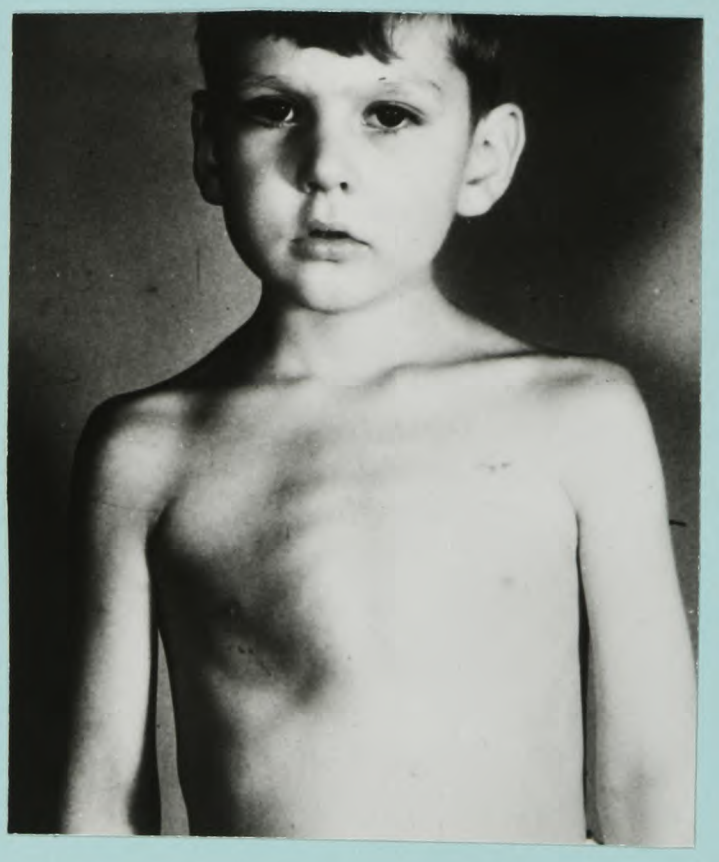


Fig. 1s. G. T. aged 5. Cor. triatriatrum. Mean wedge pressure 23 mm, P. A. P. 95/62.

The bulging sternum and indrawing of the lower ribs can be seen. There was no history of chest infection.





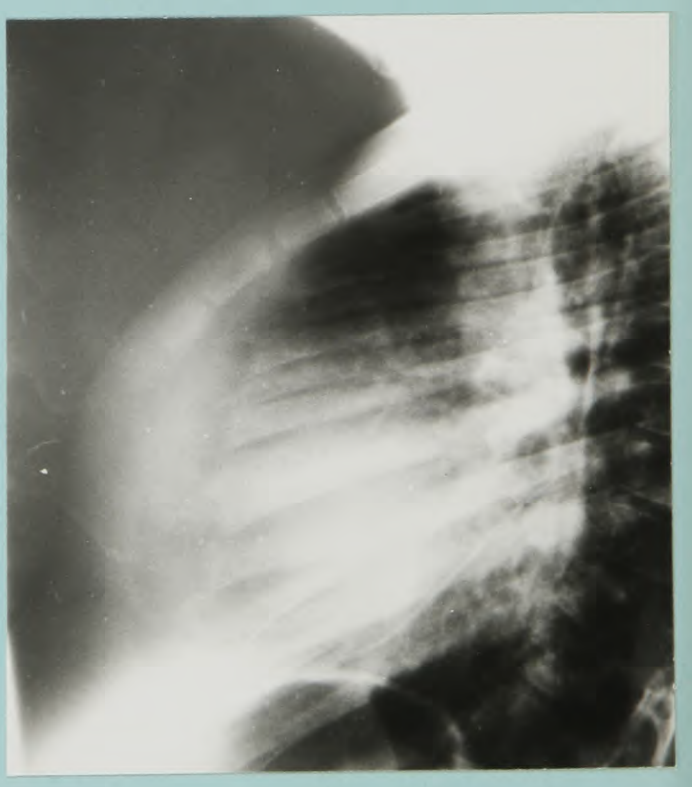


Fig. 1t. S. T. aged 10 months. Congenital mitral incompetence.
P. A. P. 65/30.

The sternal ossicles appear normal despite the gross chest deformity. The abnormal translucency of the left lung was not explained. The chest deformity in this case was more pronounced on the left than on the right, due to the pressure of the large heart.

According to Paterson (1904) bone production in the sternum may be excited by stress or strain affecting particular points in the cartilaginous mass, thus causing vascularisation and ossification. Whilst in some cases no underlying abnormality of pulmonary haemodynamics or lung mechanics is evident (see Fig. 1o), usually such features are present. Fig. 1p illustrates a case where ossification of the sternum appears to be in progress. Provided that the ossicles have remained unfused, it is probable that removal of the causative factor will allow the shape of the chest to return towards normal: this appears to be the case in Fig. 1q (see also Fig. 1d). When fusion is complete, however, as in Figs. 1c, e, f, n and r, it is improbable that this would occur.

The strong association of the chest deformity with hyperkinetic pulmonary hypertension, whatever its cause, makes it likely that the association exists between these rather than with the lesion per se that causes the haemodynamic state. The finding of the deformity in association with other lesions which are known to disturb the mechanics of the lung would, however, strengthen the argument. Figs. 1s and t illustrate two such cases, the former being a boy of nine with cor triatriatum and pulmonary venous and arterial hypertension, the latter aged ten months with congenital mitral incompetence.

It is not denied that chest deformities sometimes occur without disturbed pulmonary haemodynamics and that abnormal development of the sternum may be present without apparent cause. Non-segmentation

of the sternum has been found in a recessive mutation of mice called 'screwtail', obtained from brother and sister inbreeding of the CBH-Bagg albino strain (Bryson, 1945). An unsegmented sternum has also been noted by Warkany and Nelson (1941) in rats reared on deficient diet. Babies with hyperkinetic pulmonary hypertension are under-developed (Kjellberg et al, 1955) and show an increased incidence of respiratory infection. In fact, in reviewing the recorded incidence of lower respiratory infection (bronchitis and pneumonia) in a series of 300 patients with septal defects, it was found that it was 65% in the group with V. S. D. and hyperkinetic pulmonary hypertension, and between 30% and 40% in A. S. D., V. S. D. without pulmonary hypertension, and the Eisenmenger state (personal observations with McCredie, 1960). McCance (1962) has shown clearly in rats the permanently deleterious effect of repeated infections on the growth of the animal.

Whilst it is possible that synostosis may occur in the sternum as an expression of an abnormality of development that affects multiple organ systems, as thought by Currarino and Silverman (1958), it is more likely that when the synostosis is seen with the protrusion deformity, it is the result of the processes which produce the deformity. Increased mechanical stresses and poor overall development, with or without respiratory infection, may contribute to the creation both of the synostosis and the deformity, though the latter has been seen in small babies where there was no question of respiratory infection (own observations and Wood (1961) personal communication). The prototype of the



Fig. 1u. The prototype of the chest deformity can be seen in the pattern of breathing of infants such as this one, C.G. aged 19 weeks, with V.S.D., pulmonary hypertension at systemic level, and a large left-to-right shunt. This child was in heart failure, with tachypnoea and respiratory distress, but this is not an essential prerequisite for the development of the deformity (see Fig. 1b)

deformity is apparent in the breathing patterns of babies with large left-to-right shunts (Fig. 1u) and it becomes obvious that further elucidation will depend on the study of the mechanics of breathing in such small children.

CHAPTER II

STUDIES OF PULMONARY COMPLIANCE IN PATIENTS WITH CARDIAC SEPTAL DEFECTS

INFANTS AND YOUNG CHILDREN

Pulmonary function studies have been performed in the newborn by Cross (1949), Cook (1957), Tooley (1960) and others. At this age oesophageal intubation is well-tolerated provided that the infant is not hungry. This is not so in older infants, and sedation then becomes necessary. Problems relating to chest deformity and lung stiffness are particularly apposite to the age range three months to three years, and despite the difficulties of measurement it was resolved that an attempt should be made in such children.

Methods A stainless steel plethysmograph≠ was used. It had a capacity of 50 litres and was 32 inches in length. At one end it was 9 inches deep and at the other 6 inches; its width was 11 inches. The lid was of the quick-release type and was made of lucite in a stainless steel frame, with an oval orifice for the baby's face, which could be sealed by a pneumatic

≠ Specially constructed by Messrs. Michel and Pfeiffer, San Francisco.

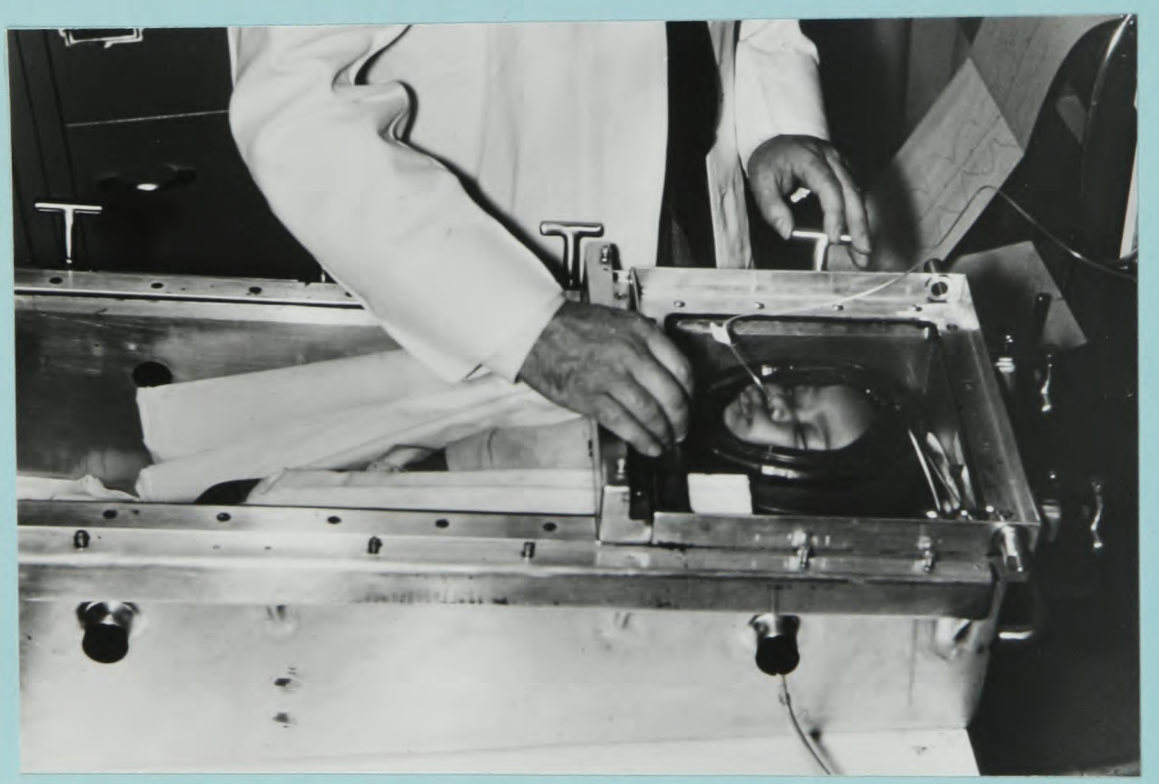


Fig. 2a. The measurement of lung compliance in infants by plethysmography

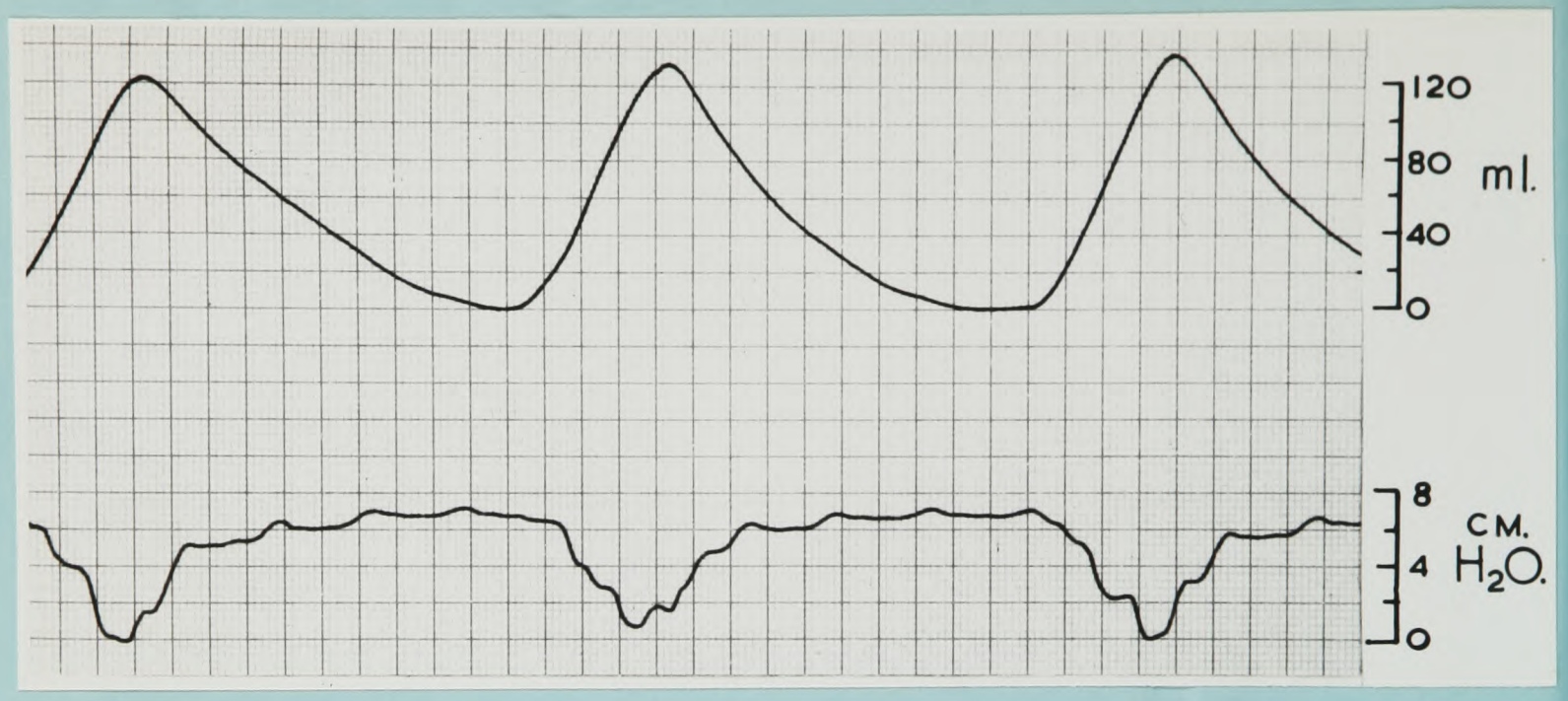


Fig. 2b. Case V10 (V. J) aged 16 months. Maladie de Roger.
Compliance 25.7 ml./cm. H_2O. C/F.R.C. 0.087.

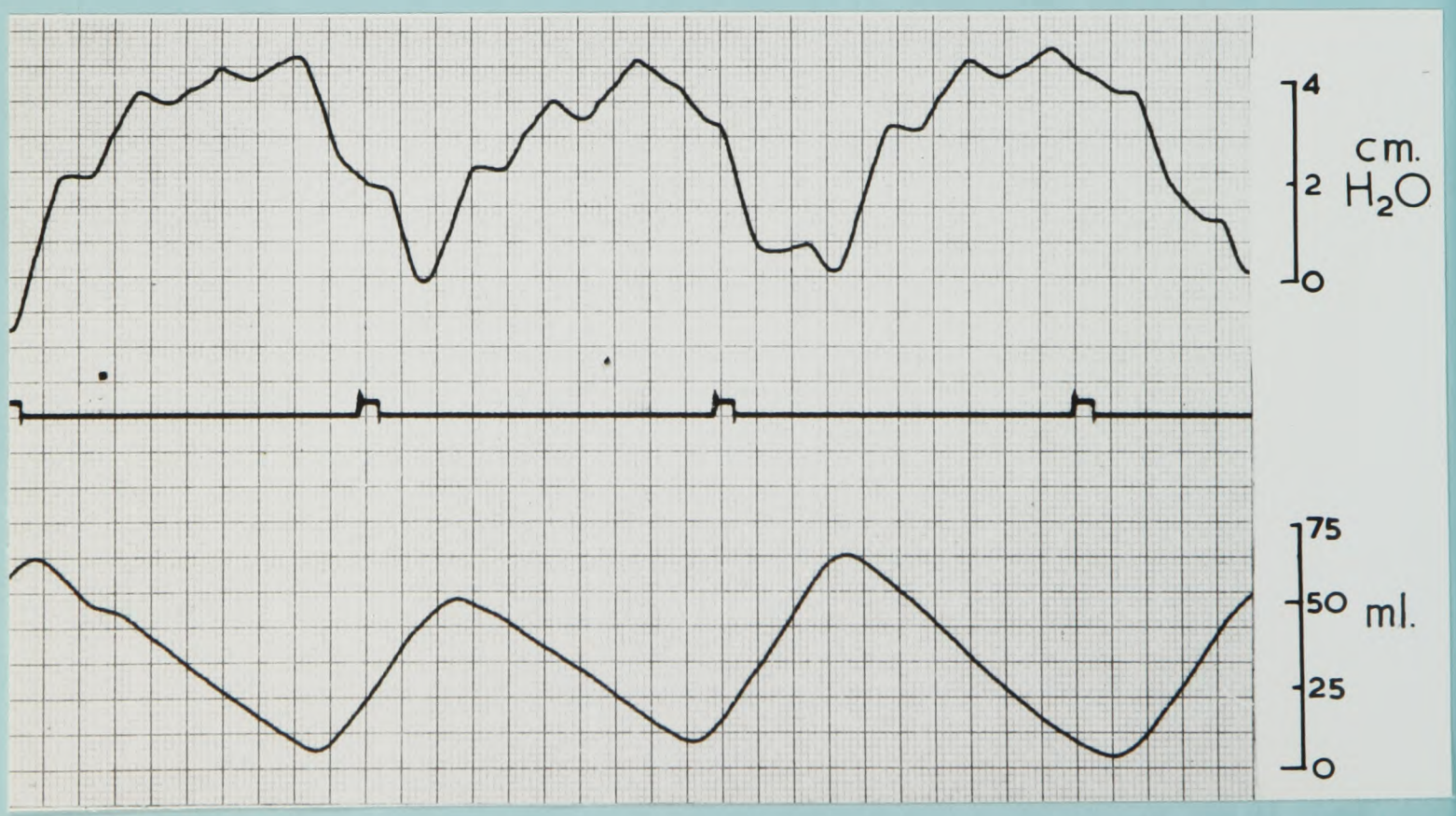


Fig. 2c. Case V5. (G. B) aged 8 months. Maladie de Roger.
Compliance 18.7 ml./cm. H_2O. C/F.R.C. 0.092.

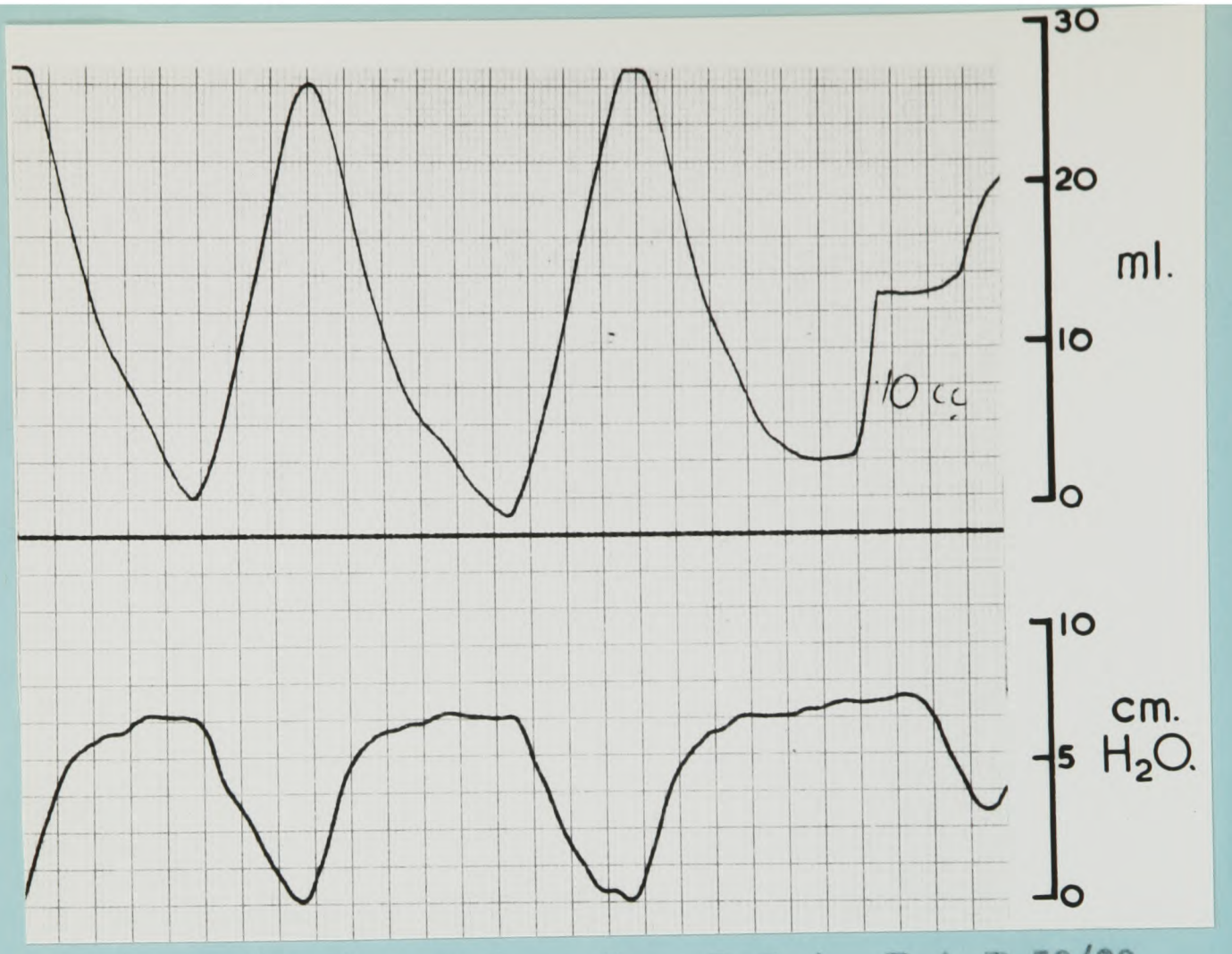


Fig. 2d. Case V21 (B.C) aged 4 months. P.D.A. P.A.P. 50/20. PF/SF 2.4. Compliance 3.9 ml./cm. H_2O. C/F.R.C. 0.031

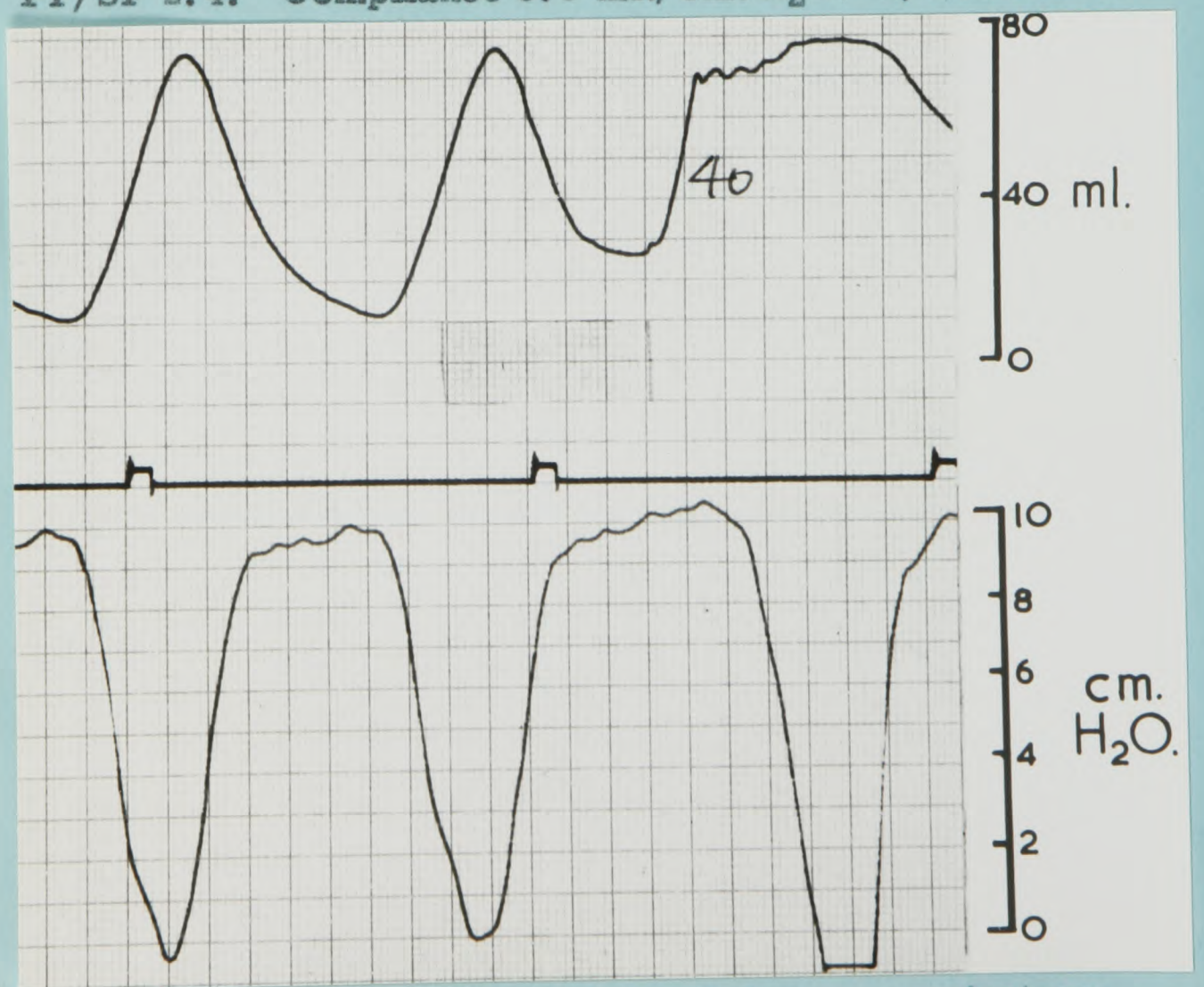


Fig. 2e. Case V22 (V.A) aged 19 months. V.S.D. + respiratory infection. Compliance 5.8 ml./cm. H_2O. C/F.R.C. 0.016.

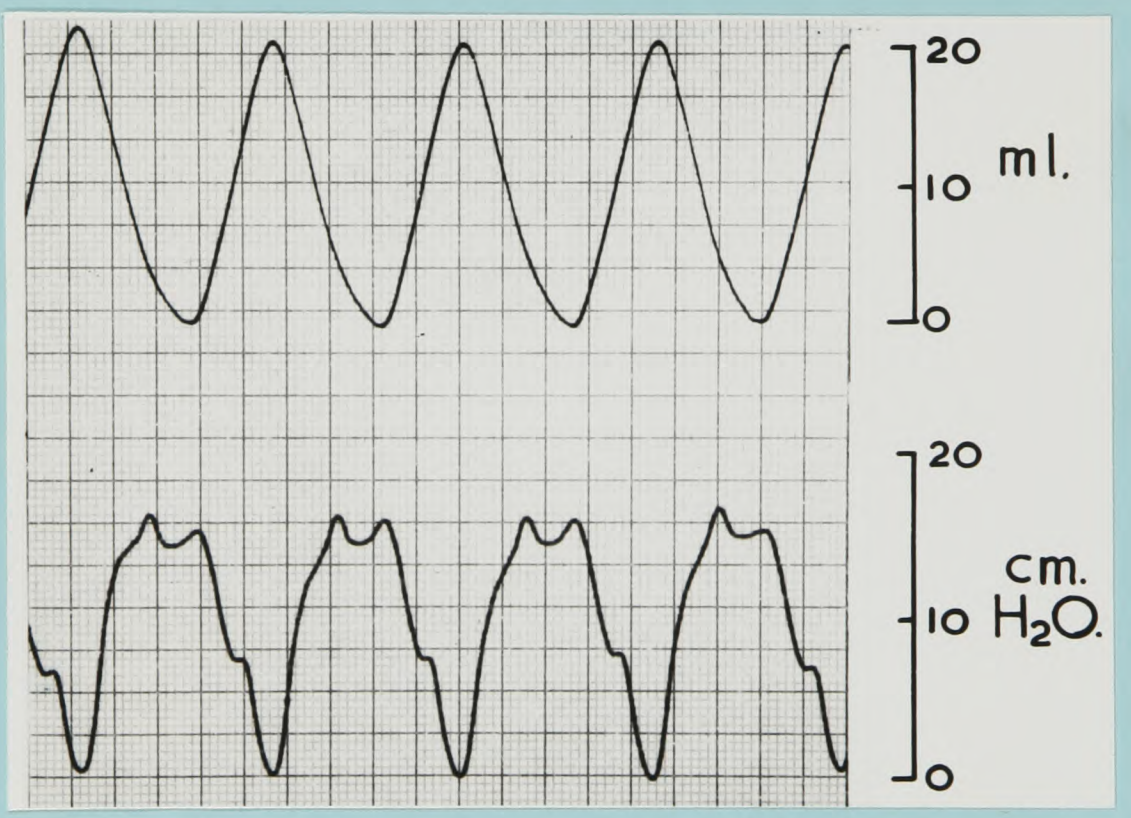
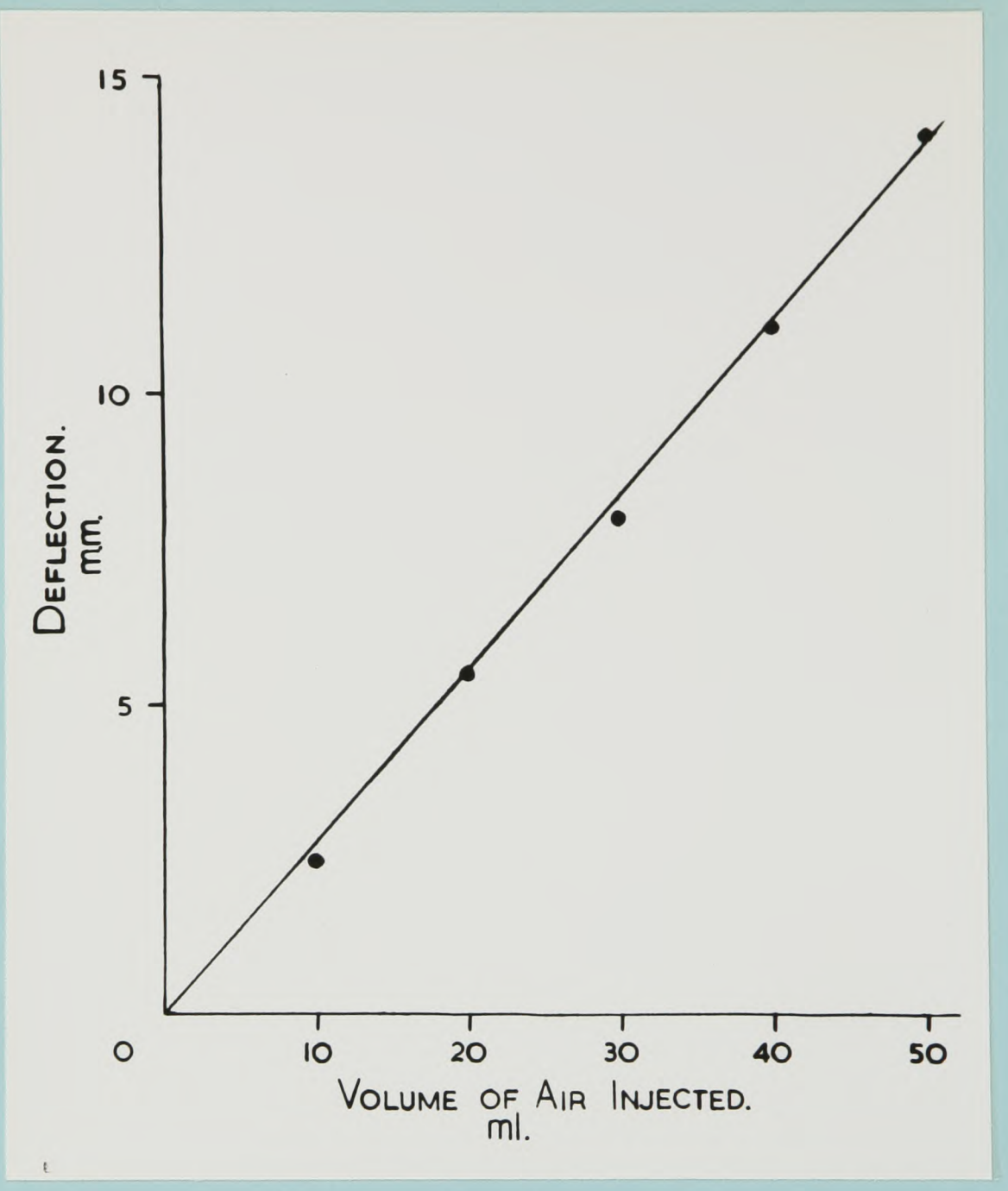


Fig. 2f. Case V18 (D. P) aged 4 months. V. S. D. + respiratory infection. P. A. P. 70/20. Compliance 1.4 ml./cm. H_2O. C/F. R. C. 0.011.

cuff (Fig. 2a). Changes in pressure within the plethysmograph, due to the child's respiration, were recorded by means of a Statham gauge (PE 5) and intra-oesophageal pressure by means of a balloon, previously passed through the child's nostril into the oesophagus and connected to another Statham gauge by means of polyethylthene tubing of 0.034" or 0.048" internal diameter. Both gauges were connected to a direct-writing Gilson recorder (Polygraph MP 5 4-channel, equipped with three Chopper strain gauge amplifiers).

In the earlier studies sedation was by means of oral chloral hydrate. Later, an injected mixture was used of promethazine 6.25 mg./ml, chlorpromazine 6.25 mg./ml, and meperidine 25.00 mg./ml, giving 1 ml. per 20 lb. body weight as recommended for cardiac catheterisation by Keith, Rowe and Vlad (1958). The oesophageal balloons, 10 cm. in length, were made in the laboratory from latex, and after lubrication were easily passed through the nostril into the oesophagus. The child was then put in the plethysmograph, the shoulders being supported by folded towels and the head tilted back to the appropriate angle. The lid was clamped down and the rubber cuff was put in position around the child's face and inflated until the cavity of the box was completely sealed from the outside atmosphere. Measurements were then made. The pressure swing was calculated between the points of no flow. Typical tracings are reproduced in Figs. 2b-f.

In a number of cases the effect of tilting the plethysmograph was investigated, the baby being supported laterally by suitably placed rolled towels.



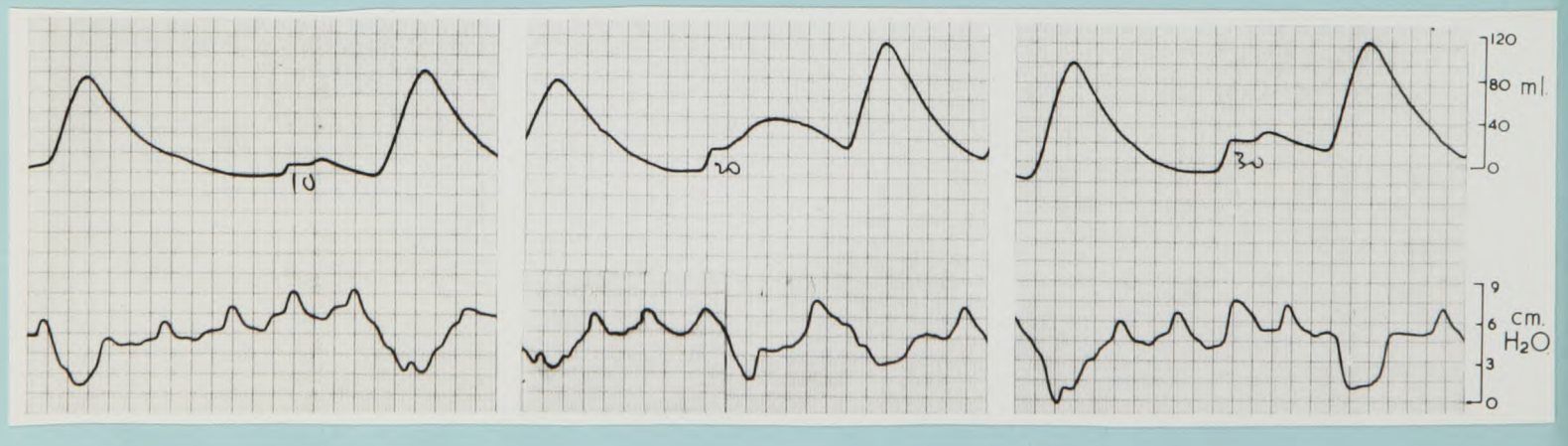


Fig. 2g. Calibration was performed separately for each study.

Whilst it is possible by means of suitable modification of the apparatus to measure the functional residual capacity, this was not attempted during this study. Its value was calculated from the baby's measurements using the regression equations of Helliesen et al. (1958). The lung compliance was then deduced from the volume changes of the thorax, as expressed by the pressure changes in the plethysmograph and the intra-oesophageal pressure swing; it was then related to the F.R.C. to make comparable the results in children of different sizes. This, or some similar method, is clearly necessary since an infant increases its height by 75% and more than trebles its body weight and lung weight within the first two years of life.

Calibration of volume and pressure

Fig. 2g illustrates the linearity obtained in the calibration of volume changes within the plethysmograph. Since each child occupied a different volume of the box, the pressure swing within it per unit volume change varied directly with the size of the child. Since the latter was not measured, it was necessary to calibrate separately for each patient. This was done by pinching the child's nostrils at the end of a normal expiration and, in the apnoeic interval before the first inspiratory effort, a known amount of air was injected into the plethysmograph through one of its side ports, using a 50 ml. syringe and a large bore needle piercing a rubber bung. The linearity in response, in accordance with Boyle's law, is seen to be achieved. The intra-oesophageal pressure changes were calibrated by means of a water manometer.

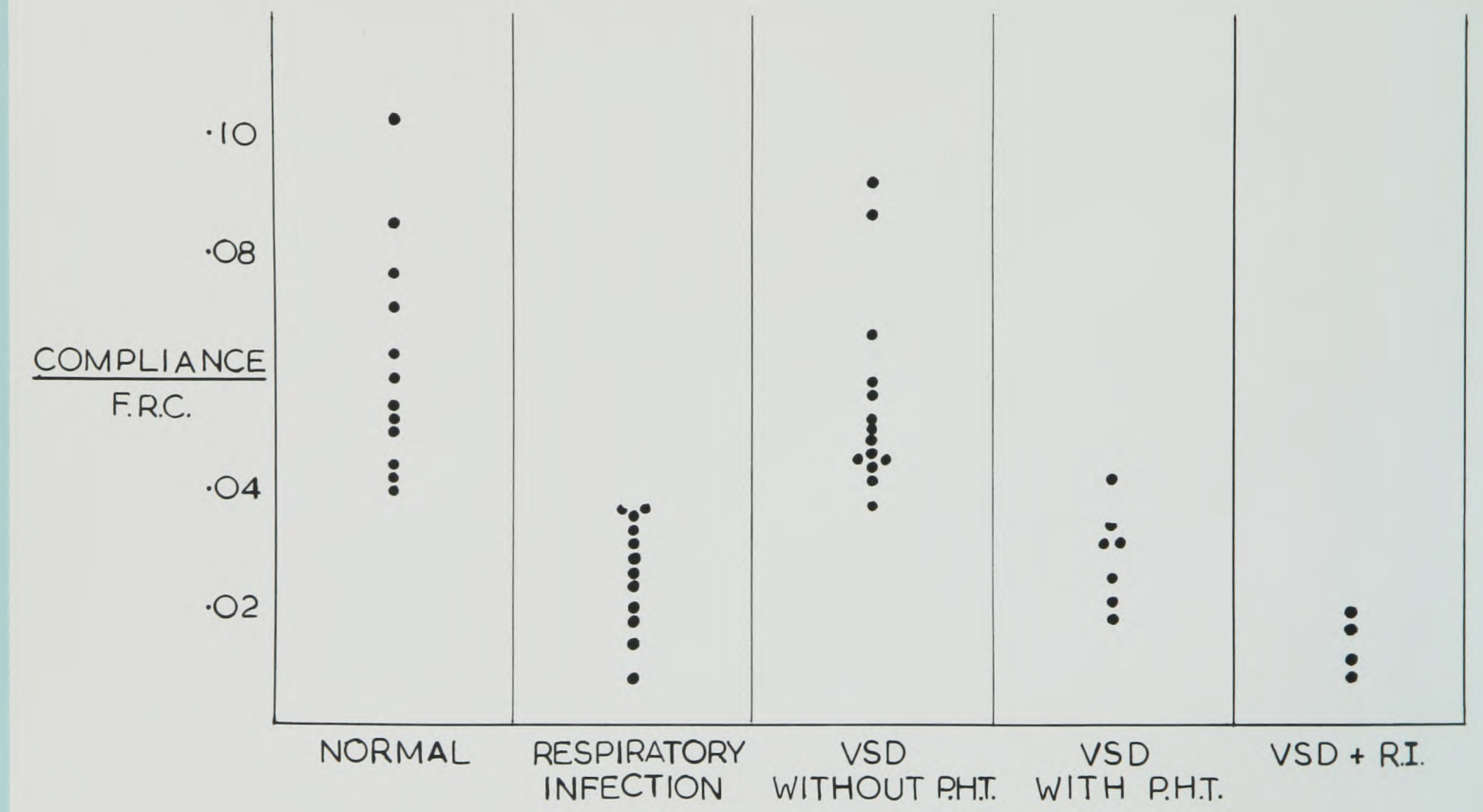


Fig. 2h. The specific compliance in the different groups studied.

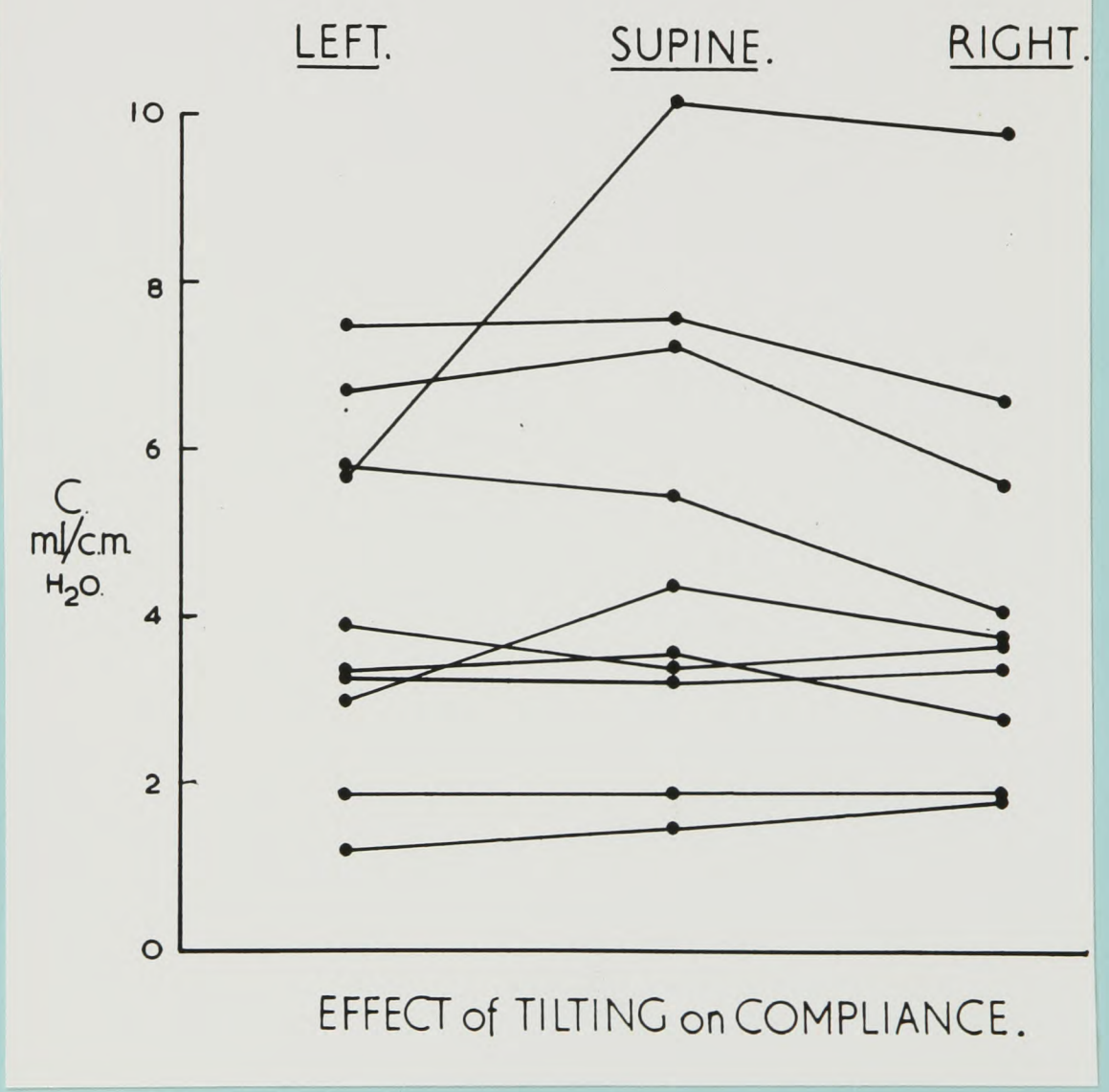


Fig. 2i. The effect of tilting the plethysmograph on the compliance (see Table IV).

Patients studied

Twelve children were normal, ranging in age between three months and two-and-a-half years. Ten children, otherwise normal, had respiratory infections. Twenty-three children had ventricular spetal defect; in most of them cardiac catheterisation data were available. One patient had a patent ductus arteriosus and one an atrial septal defect. Where the child had not been catheterised, the clinical evidence was such as to make the diagnosis acceptable. The children with V. S. D. are divided into three groups: thirteen had V. S. D. without pulmonary hypertension - the patient with the A. S. D. is included in this group; six had V. S. D. with hyperkinetic pulmonary hypertension, the child with P. D. A. being included here; four had V. S. D. together with evidence of pulmonary infection at the time of study.

Results These are presented in Table III and Fig. 2h. The 'specific compliance', or ratio of C/F. R. C, was 0. 062 in the normal group, 0. 027 in infants with respiratory infections, 0. 055 in those with V. S. D. uncomplicated by infection or pulmonary hypertension, 0. 029 when V. S. D. was accompanied by pulmonary hypertension, and 0. 014 when V. S. D. and infection were both present.

Our patients with V. S. D. and hyperkinetic pulmonary hypertension had a C/F. R. C. ratio significantly different from that of the normal group ($p < 0.001$) and the group with V. S. D. but no P. H. T, ($p < 0.001$). When V. S. D. and pulmonary infection existed together, the values found appeared to be particularly low.

ADULTS AND OLDER CHILDREN

Satisfactory studies of lung compliance have been made in 77 older patients with cardiac septal defects; these were among 97 in whom pulmonary function studies were attempted. All except one were from the National Heart, Brompton and Guy's Hospitals, and their distribution was as follows:

Group I:	A.S.D. with low P.V.R.	19
Group II:	A.S.D. with elevated P.V.R.	11
Group III:	V.S.D. with low P.V.R.	18
Group IV:	V.S.D. with elevated P.V.R.	18
Group V:	Eisenmenger	11

The first four groups consisted of those patients who had a dominant left-to-right shunt, usually with a pulmonary : systemic flow ratio greater than 2 : 1 and with corresponding clinical signs. The fifth group consisted of patients with severe elevation of pulmonary vascular resistance and clinical and haemodynamic evidence of the Eisenmenger syndrome as defined by Wood (1958).

Methods Measurement of lung compliance was achieved by passing a thin latex balloon 10 cm. long into the retro-cardiac region of the oesophagus via the nostril. The balloon was connected through a polythene tube 1.5 mm. internal diameter to an inductance manometer, the other side of this being connected

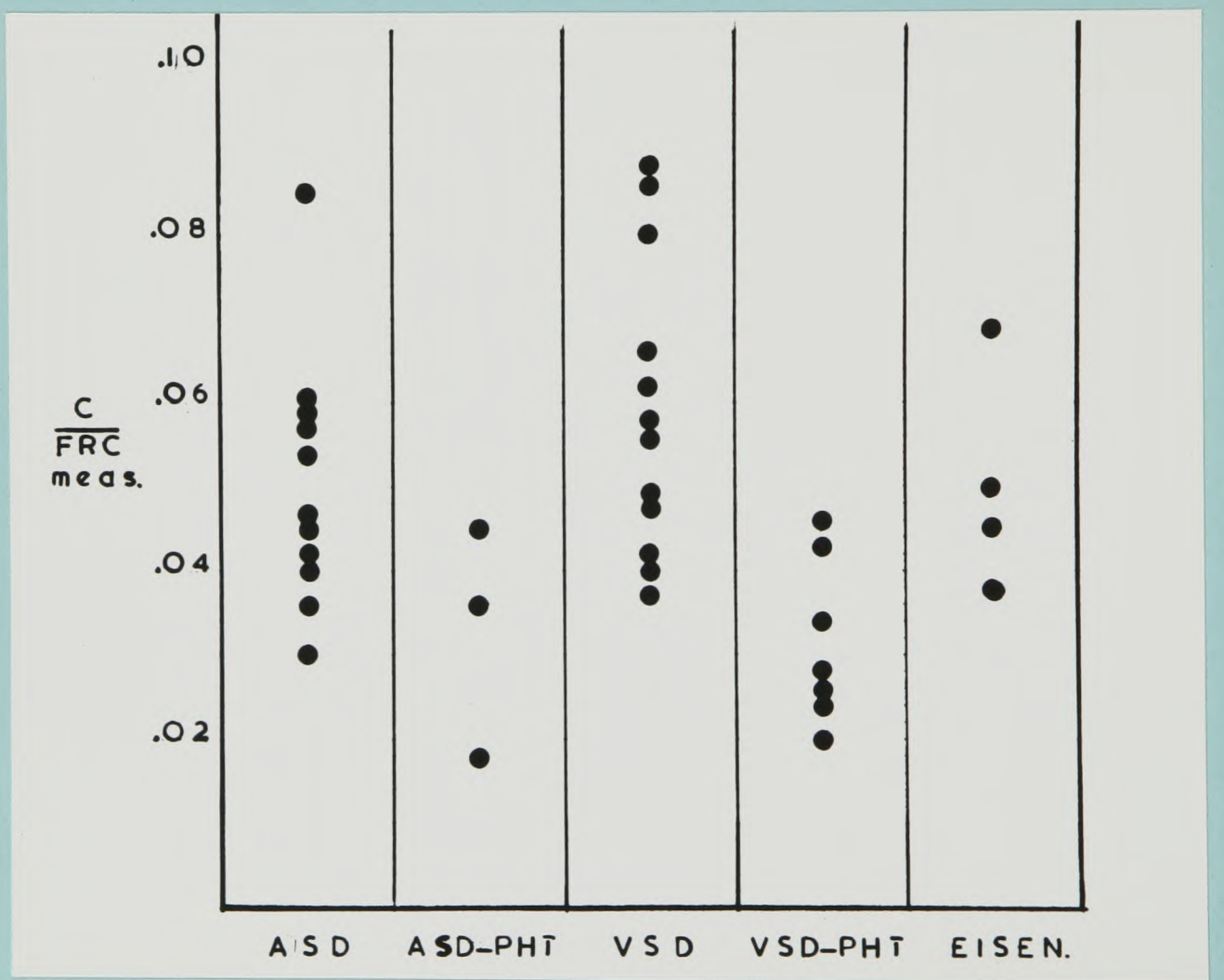


Fig. 2j. Specific compliance, based on measured F.R.C, in the different groups studied.

to the mouth-piece: hence the differential pressure between oesophagus and mouth (transpulmonary pressure) was recorded after amplification, either with a cathode-ray oscilloscope and camera (Brompton cases) or an infra-red recorder (Guy's cases). The tidal volume during quiet breathing was recorded by means of a spirometer with linear-wound potentiometer (Brompton) or with a Fleisch pneumotachograph whose output was electrically integrated and amplified (Guy's). The pressure-swing was measured between the points of no-flow. All compliance measurements were made in the sitting position, except where the influence of other postures was being studied.

Ventilatory function was assessed with the use of a dry-bell spirometer (Godart); F.R.C. by the closed-circuit helium dilution method of McMichael (1939). When the F.R.C. was not measured (Guy's cases), its value was calculated from the patient's height and weight from the regression equations of Needham et al. (1954) in adults, and Hellieson et al. (1958) below the age of 17. Vital capacity was predicted from the tables of Myers (1925).

Results The values for lung compliance are shown in Table V, which also gives the relevant haemodynamic data. Individual findings in each patient are shown in the Appendix (Table VI) Fig. 2j illustrates the ratio of compliance to measured F.R.C. in the different groups.

For the purposes of comparison between individuals of differing size and lung volume, the compliance has again been related to the functional residual capacity. It was possible to measure this in only 37 of the 77 cases, and both measured and predicted values have therefore been shown in Tables V and VI.

Our values for the ratio C/F.R.C. (specific compliance) in normal subjects is 0.06, which is of the same order as that given by Cook et al. (1957 and 1958) and close to that of our Group III which consists mainly of young subjects with small left-to-right shunts and normal pulmonary arterial pressure.

The mean specific compliance, based on measured F.R.C., in patients with A.S.D. and no pulmonary hypertension (Group I) was $0.050 \pm$ S.D. 0.015, which does not differ significantly from that of Group III ($p > 0.1$). In Group II it was 0.033 ± 0.014; there were only three cases in this group in whom F.R.C. was measured, and the mean specific compliance differed significantly from that of Group III ($0.01 < p < 0.05$). In Group IV, V.S.D. with hyperkinetic pulmonary hypertension, the value was 0.031 ± 0.010, which is significantly different from that of Group III.

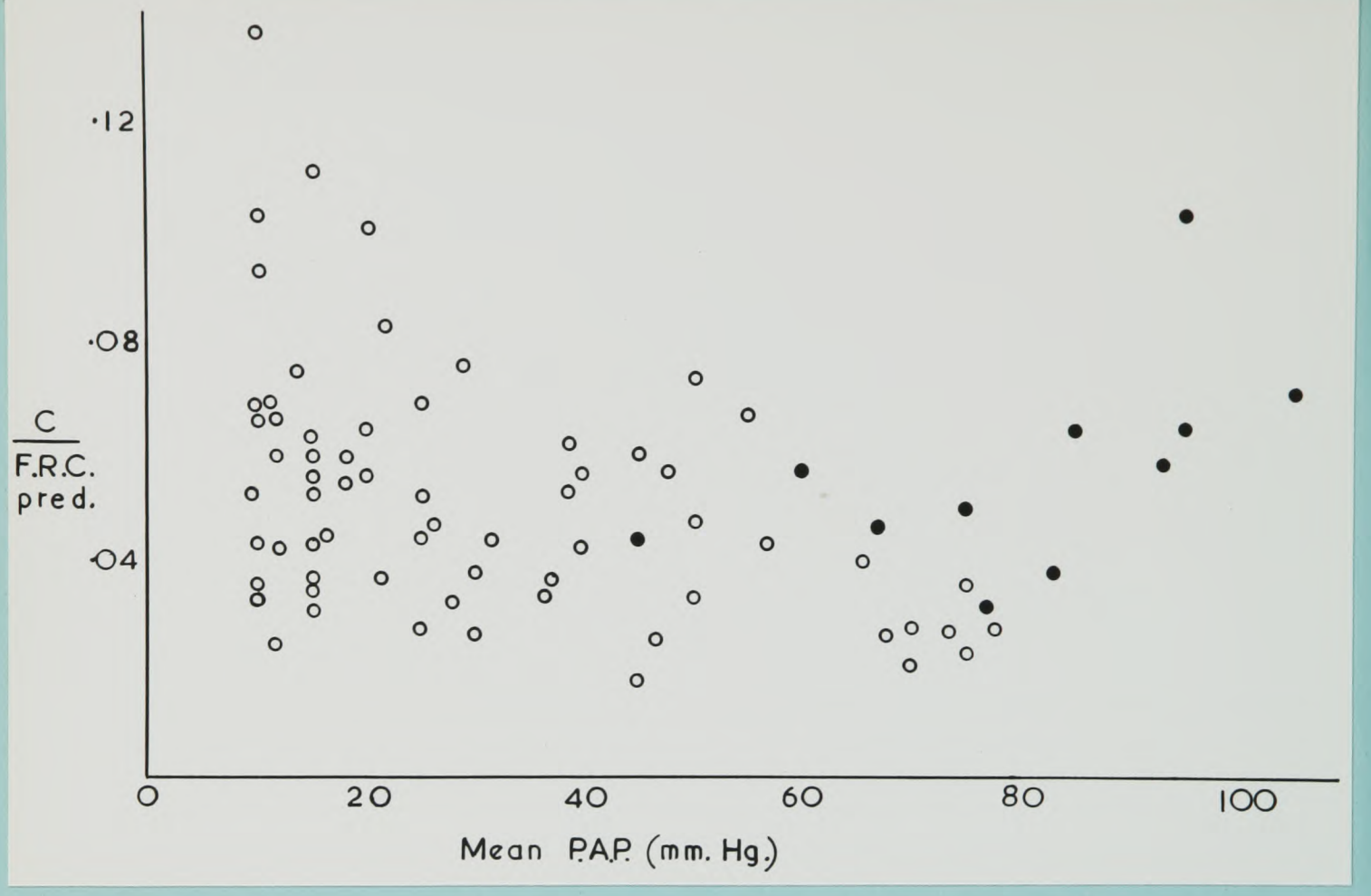
In Group V, patients with the Eisenmenger syndrome, the specific compliance was 0.050 ± 0.014, not significantly different from Group III ($p \geq 0.1$).

LUNG COMPLIANCE IN ADULTS AND OLDER CHILDREN

TABLE V

Group	No.	Age	P.A.P. mm.Hg. S / D	P.I. L/min./sq.m.	S.I.	Compliance L/cm. H_2O.	F.R.C. Meas.	F.R.C. Pred.	C/F.R.C. Meas.	C/F.R.C. Pred.
		22	22 / 8	11.5	3.4	0.126	2.7(11)	2.2	0.050(11)	0.055
I	19	11	8 4	5.1	0.8	0.071	1.0	0.3	0.015	0.018
		9-42	18-36 5-15	5.4-23.3	2.4-5.6	0.051-0.350	1.3-5.9	1.1-3.3	0.030-0.085	0.025-0.10
		49	59 / 25	8.6	2.4	0.140	3.7(3)	2.8	0.033(3)	0.048
II	11	11	15 9	5.9	0.5	0.059	1.4	0.6	0.014	0.036
		24-59	40-85 15-40	3.4-22.2	1.5-4.5	0.040-0.213	2.2-5.1	2.1-4.2	0.018-0.045	0.019-0.077
		19	29 / 11	7.8	3.7	0.155	2.3(12)	2.3	0.059(12)	0.067
III	18	13	14 5	3.0	1.1	0.074	0.8	0.8	0.018	0.026
		6-56	15-45 5-20	3.0-13.6	2.1-5.5	0.050-0.340	0.9-4.0	1.0-4.3	0.037-0.088	0.029-0.139
		21	80 / 39	10.8	3.6	0.080	1.6(7)	2.3	0.031(7)	0.037
IV	18	15	25 18	6.8	1.2	0.042	0.9	0.9	0.010	0.012
		6-62	50-130 5.75	3.8-30.0	2.1-6.2	0.023-0.190	0.9-3.6	0.9-3.4	0.020-0.043	0.021-0.68
		27	114 / 58	3.8	3.0	0.151	3.1(4)	2.7	0.050(4)	0.048
V	11	10	24 17	1.8	0.8	0.058	0.7	1.7	0.014	0.019
		9-55	75-150 40-80	1.6-6.6	2.1-4.5	0.051-0.214	2.2-3.9	0.8-4.3	0.038-0.069	0.032-0.071

Means, standard deviations and range are given for each variable.



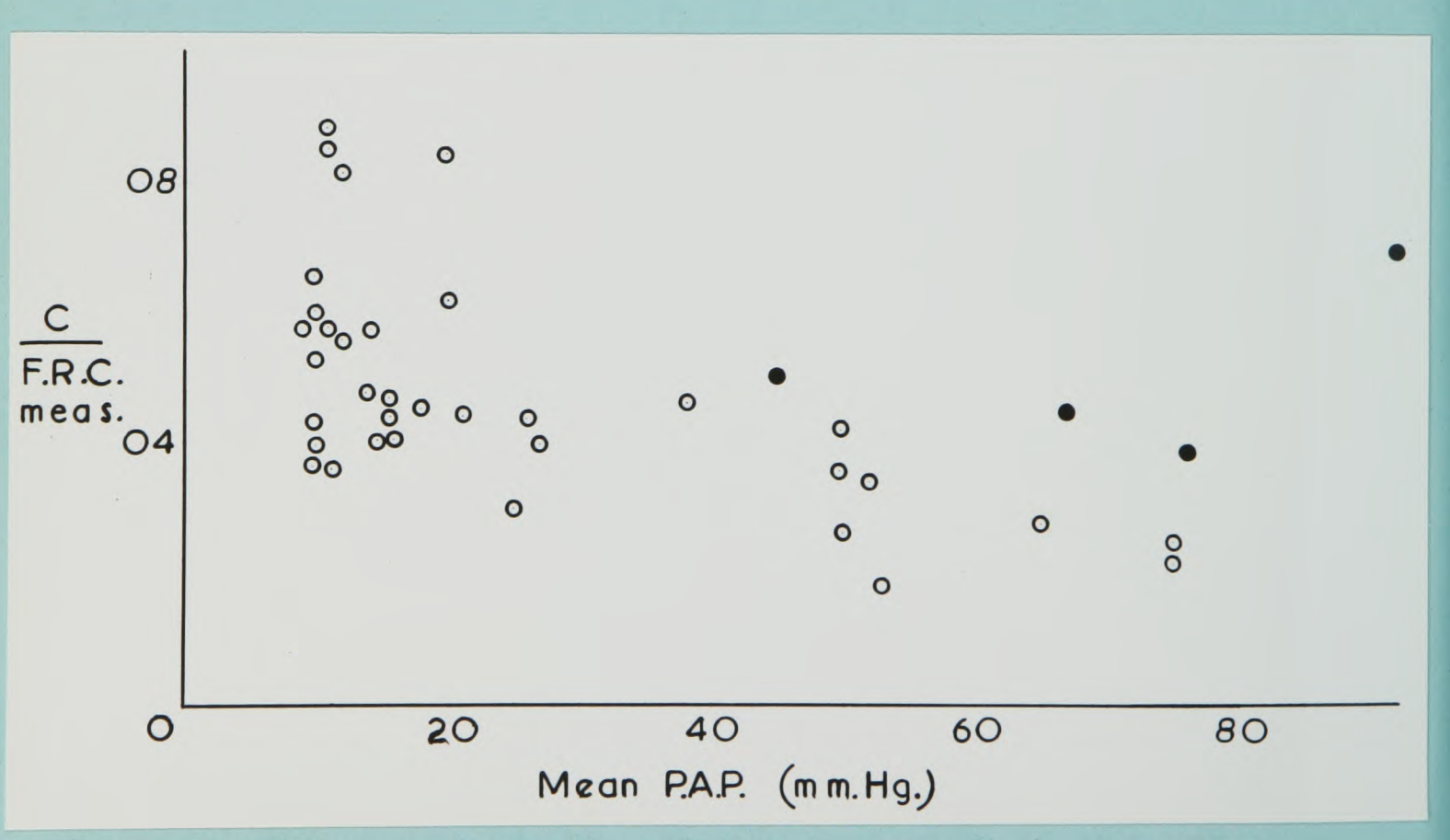
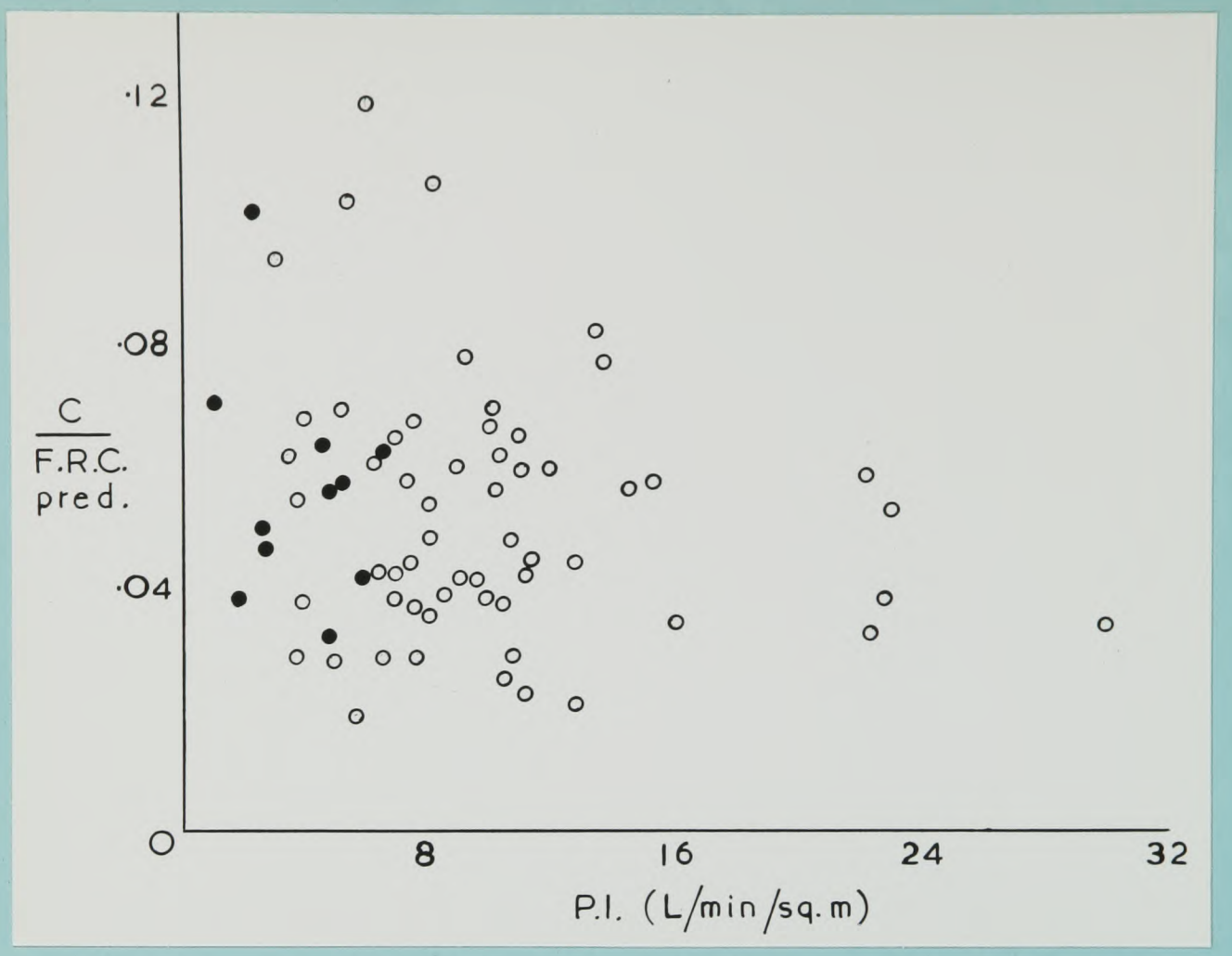


Fig. 2k. Specific compliance in relation to mean P. A. pressure. Patients with the Eisenmenger syndrome are designated by solid symbols.



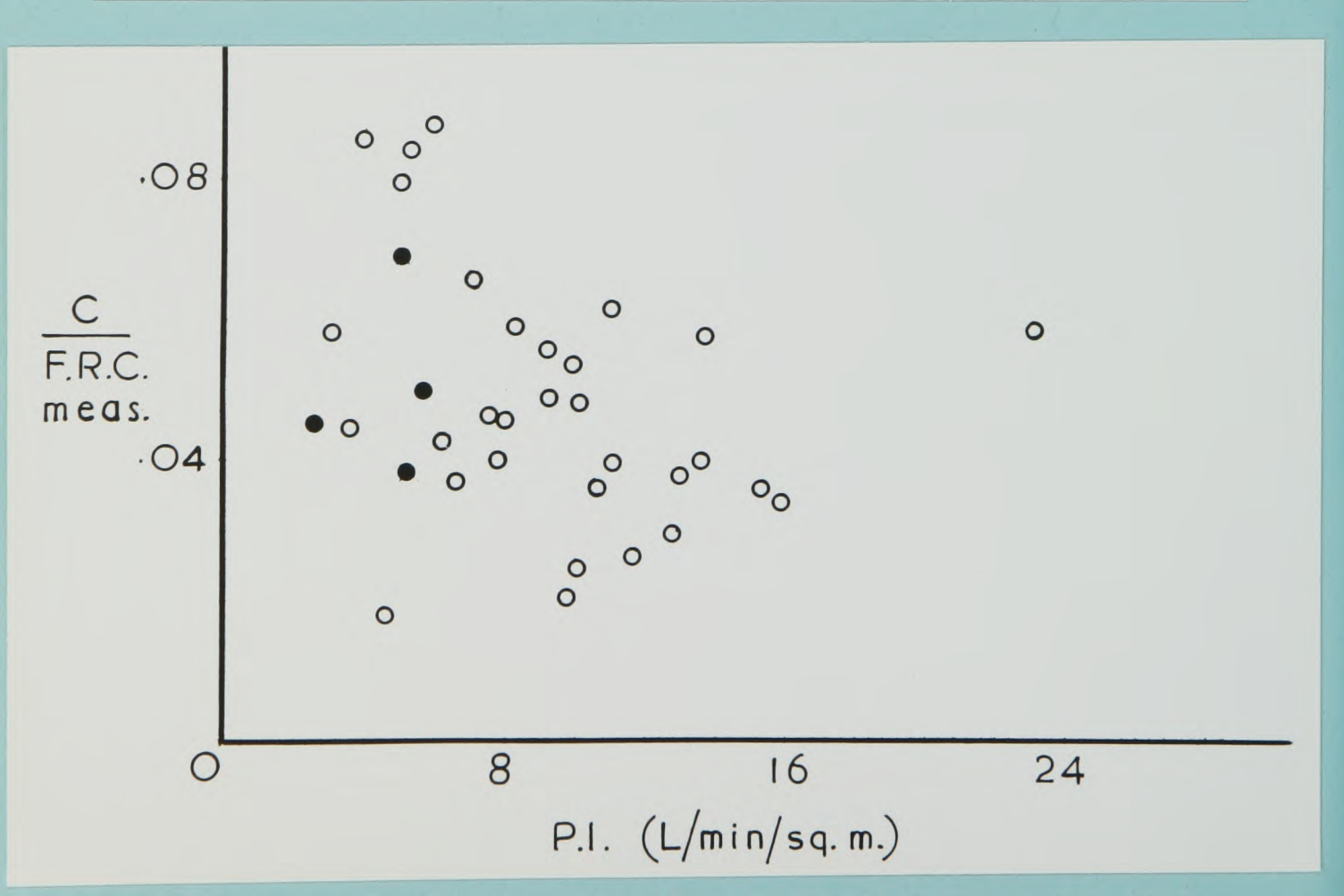
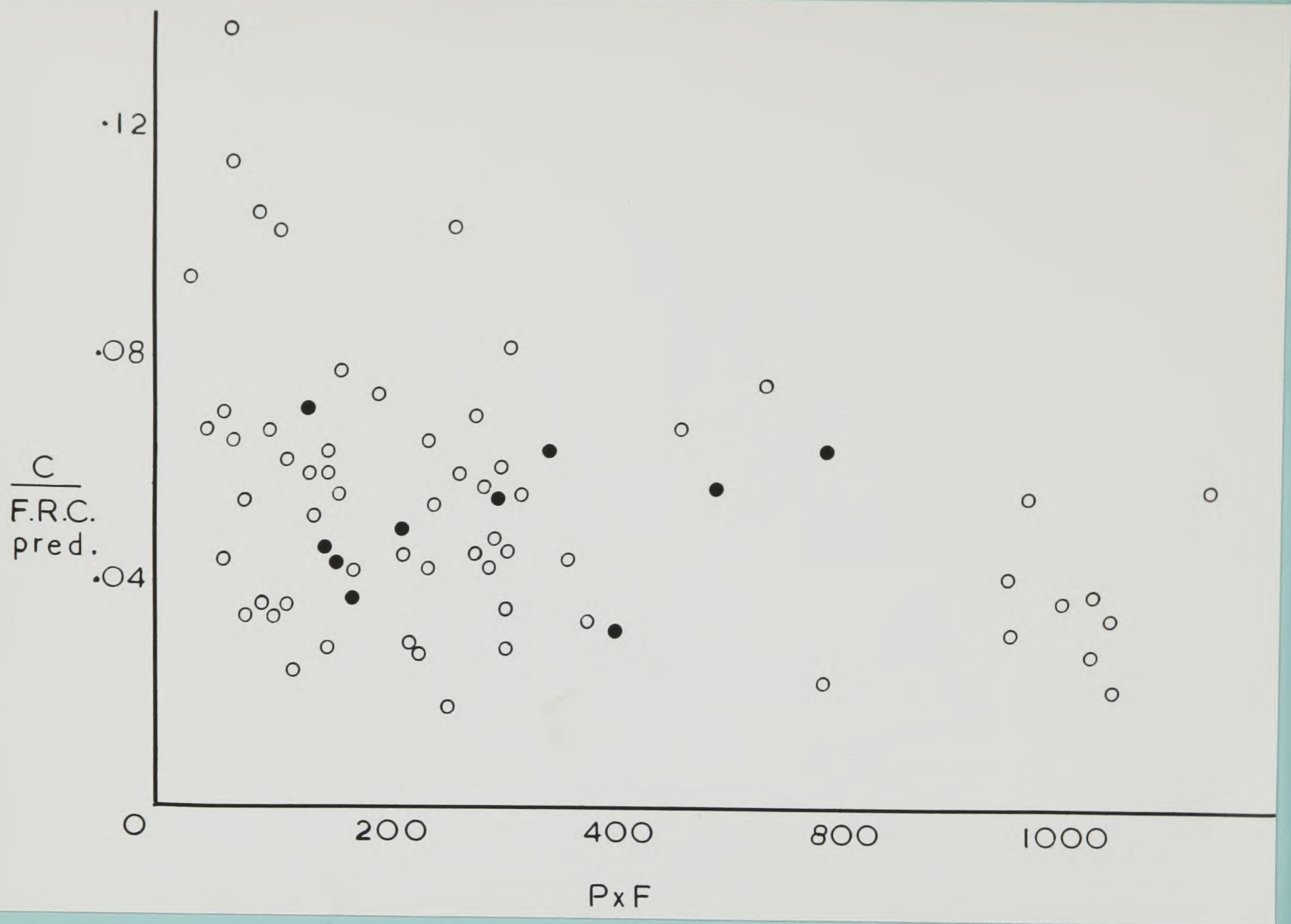


Fig. 21. Specific compliance and pulmonary index.



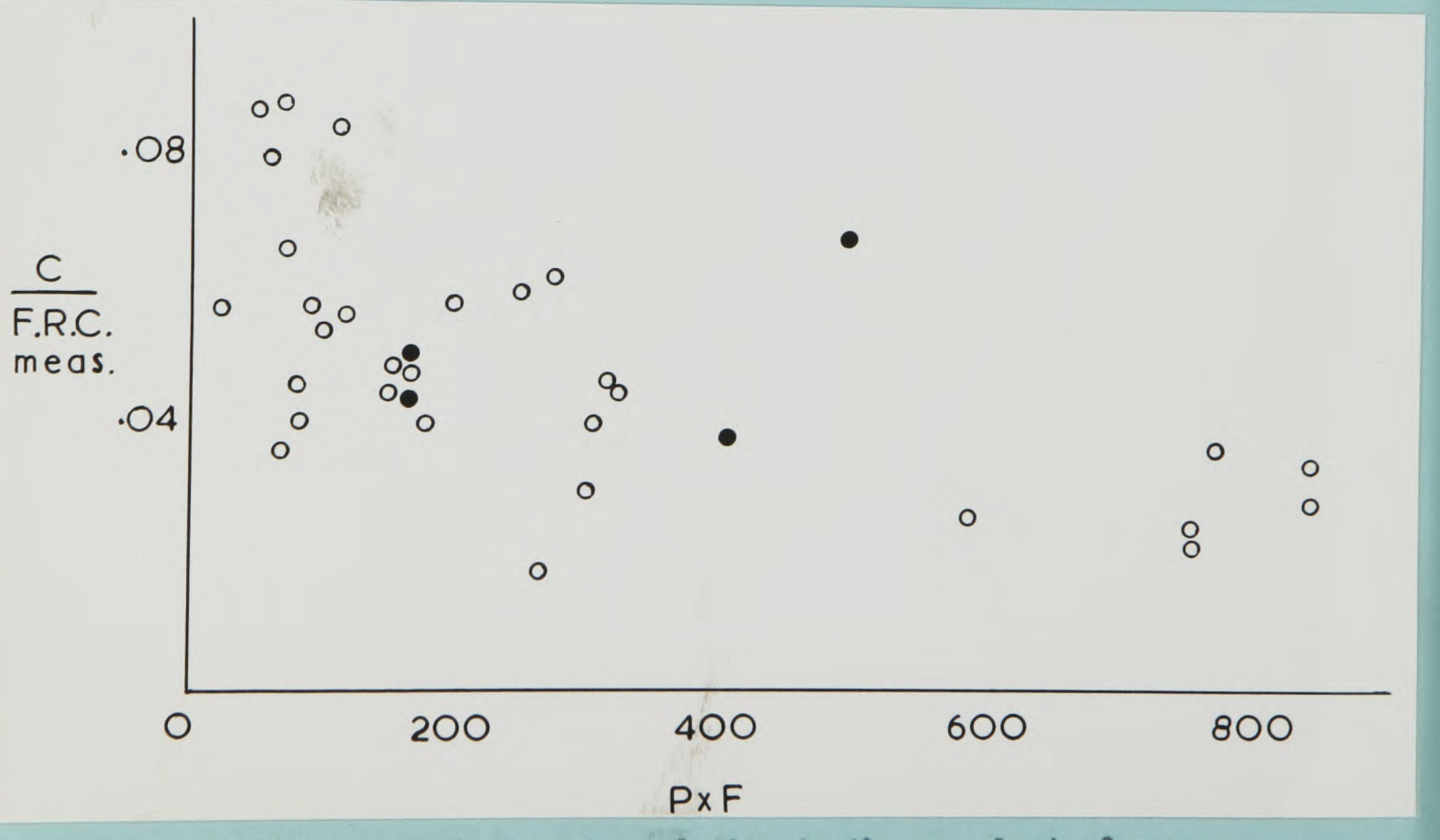


Fig. 2m. Specific compliance in relation to the product of mean pulmonary arterial pressure and pulmonary index.

Fig. 2k shows the relationship between the specific compliance and the mean pulmonary arterial pressure, using predicted and measured F.R.C. This is not significant when predicted F.R.C. is used ($r = -.113$, $p\ 0.1$) but significant for measured F.R.C. ($r = -.378$ $.05 > p > .01$). It is likely that if there were more cases of the Eisenmenger syndrome in whom F.R.C. was measured, the significance would diminish.

When the pulmonary index is considered, no significant relationship exists between specific compliance and pulmonary flow (Fig. 2l).

Since the clinical impression was formed that the combination of high pressure and high flow in the pulmonary arterial circuit might act in a manner such as to influence the pulmonary mechanics, the product of these parameters has also been related to the specific compliance, and the results are shown in Fig. 2m. Using the predicted F.R.C., the relationship is significant ($r = .318$, $.01 > p > .001$). When the measured F.R.C. is used, however, the relationship becomes highly significant ($r = -0.566$, $p < .001$). The patients with the Eisenmenger syndrome then fall into line with the others and their relatively normal compliance becomes explicable since their low pulmonary blood flow yields a P x F product which is also low in comparison with Groups II and IV.

It may be concluded, therefore, that while pulmonary flow and pulmonary arterial pressure are not in themselves powerful

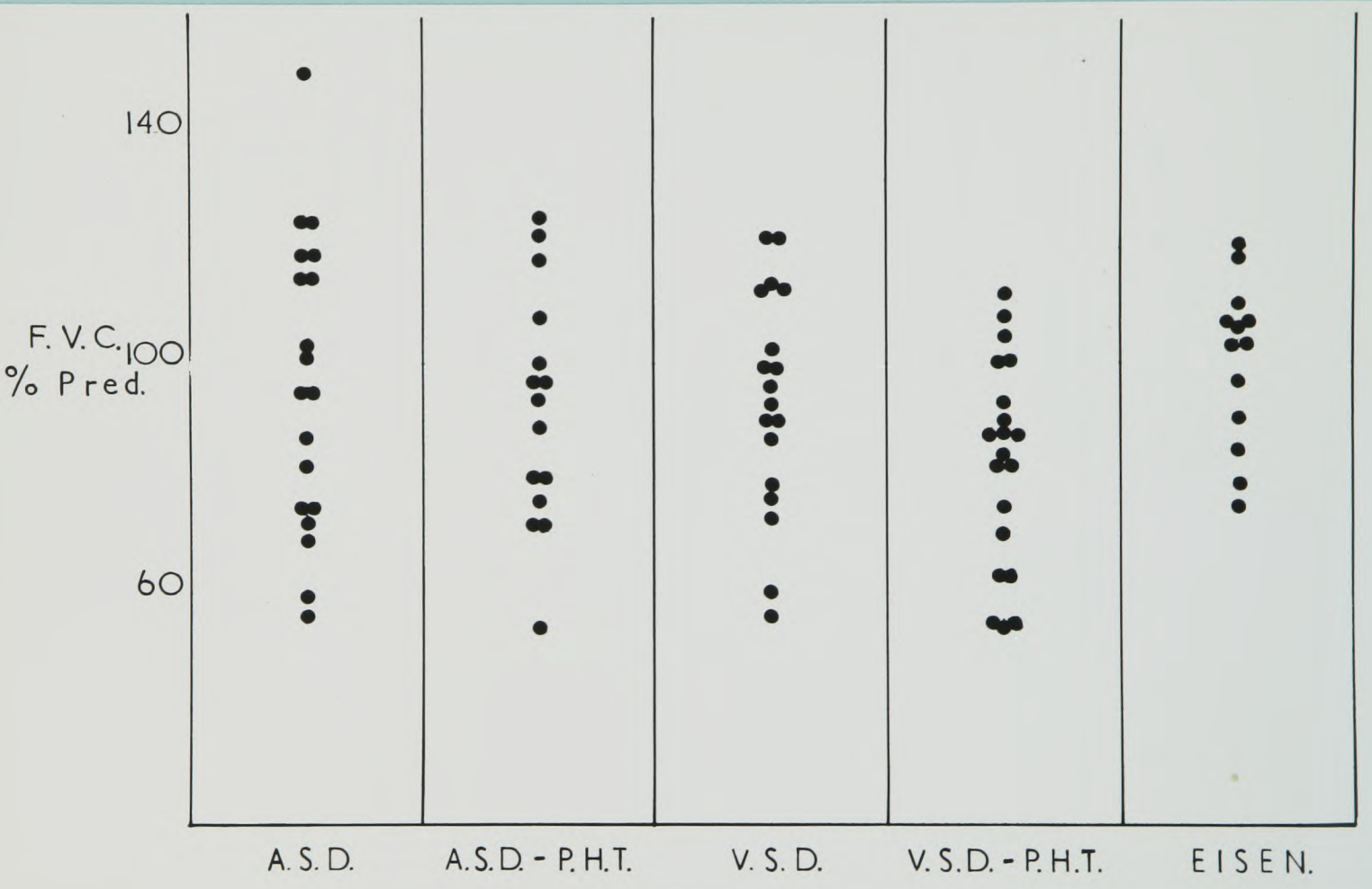


Fig. 2n. **Forced vital capacity, expressed as percentage of anticipated normal, in the different groups studied.**

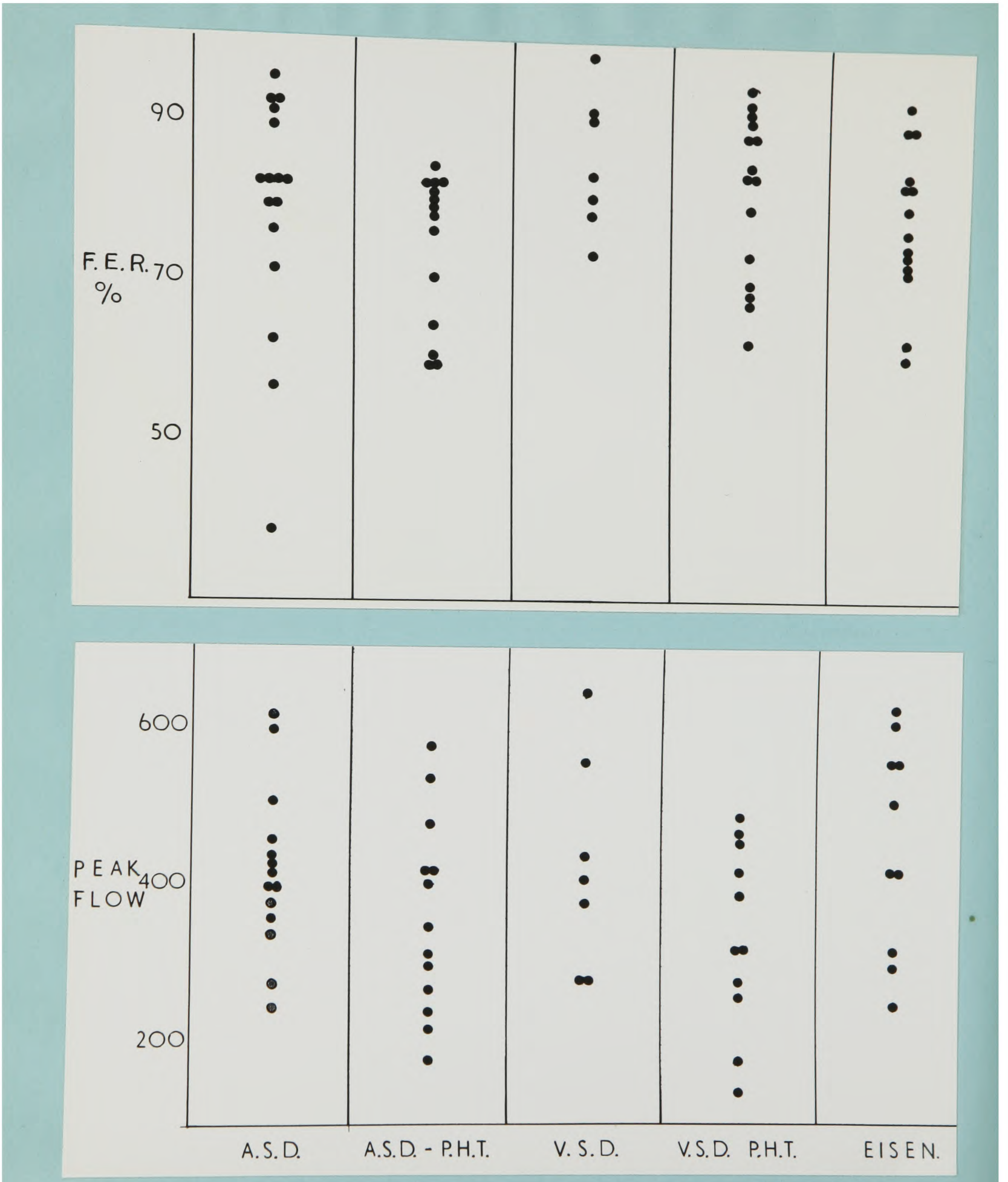


Fig. 2o. **Forced expiratory resistance and peak flow (L/min.) in the different groups studied.**

determinants of decreased lung compliance, the association of these in the same patient does appear to be associated with disturbance of the compliance. This is in accord with the finding that the compliance rises in A. S. D. following closure of the defect; here the problem of F. R. C. does not arise, since each patient serves as his own control. (see Table XI and Fig. 3j). This data points clearly to a functional and reversible association between hyperkinetic pulmonary hypertension and reduction in lung compliance.

Other aspects of pulmonary function

Since the measurement of compliance was the primary object of these studies, data on other parameters of pulmonary function have been less complete. Vital capacity was assessed in 75 patients, forced expiratory resistance in 52, peak flow in 41. The results are shown in Tables VII and VIII (Appendix) and illustrated in Figs. 2n and 2o. Whilst a number of cases show impairment of vital capacity, the mean values are not greatly removed from normal, the largest deviation being Group IV. The Eisenmenger syndrome is not associated with any abnormality of vital capacity. Airway resistance and peak flow remain normal in all groups.

DISCUSSION

One of the earliest references to any systematic enquiry into the mechanical properies of the lungs appears to be the communi - cation of Carlson in 1820 to the Royal Society. In this he describes how he inflated the lungs of various animals, noting what pressure was necessary to expand them to the dimensions of the thorax with the chest wall open. Somewhat immodestly it seems in the reading, he claimed priority in the appreciation of the importance of lung elasticity: "In investigating the manner in which the elasticity of the lungs is rendered subservient to the great functions of respiration and the circulation, I shall be found, I trust, to have opened to the views of the physiologist a new and boundless field which, I will venture to predict, will reward every skilful and assiduous cultivator with a rich harvest of discovery."

Despite this fertilising infusion, the field lay fallow until Rosenthal in 1880 first suggested the equivalence of the intra-oesophageal pressure with the intra-pleural. Morphological alterations in the lungs due to heart disease having been demonstrated by the pathologists of the nineteenth century, von Basch (1891-96) suggested that lung rigidity was increased in heart disease owing to pulmonary congestion and tested his theory in models.

Systematic investigations of respiratory mechanics began with Rohrer (1925), and van Neergaard and Wirz in 1927 introduced clinically applicable methods of study in this field. Such studies were continued by a number of investigators, including Christie and Meakins (1934), Bayliss and Robertson (1939), Vuilleumier (1939),

Otis and co-workers (1950), Mead and Whittenburger (1953), Noelpp et al. (1954) amongst others.

It is of interest that in his original paper on 'congenital defects of the ventricular septum', Eisenmenger wrote in 1898 that "in ventricular septal defect ... the pulmonary circulation was overfilled, the systemic circulation underfilled; increased stiffness of the lungs hindered ventilation and hampered gaseous exchange ..." It is perhaps surprising that so little data exists about the function of the lungs in congenital heart disease.

Lung compliance is a function of lung volume, and the comparison of results in infants and adults can only be made with reference to this. The values for the various fractions expressed as a percentage of the total lung volume are not remarkably different in humans from infancy to maturity, not between species (Richards, 1956; Cook et al. 1957 and 1958; Pierce and Ebert, 1958, Agostini et al. 1959). It is also apparent that compliance, expressed as a function of F.R.C, is also comparable at different ages. Cook et al. (1957 and 1958) found the mean ratio of compliance to F.R.C. to be 0.065 in infants and 0.063 in adults, and that the respiratory difficulty of the neonatal distress syndrome is accompanied by a considerable decrease in compliance to the region of 1 ml./cm, a moderate increase in viscous work and a marked increase in the work of breathing. These observations were considered to explain the marked sternal retraction observed clinically.

Values for pulmonary compliance in older normal children have also been given by Krieger (1963), working in the age range

three weeks to two years. Calculating the F.R.C. from the height, she found C/F.R.C. to be 0.038. In normal adults McIlroy (1954) found the value to be 0.049, Frank et al. (1956) 0.049, Marshall (1957) 0.050 and Lim and Luft (1959) 0.05.

The figures in normal babies obtained during the present study are identical with those of Cook et al. It is not possible, however, to draw emphatic conclusions from these data in sick children, since there are several variables which are unaccounted for. First, the F.R.C. was calculated rather than measured, and there are no grounds for assuming that its value was normal. Second, the effect of sedation was not necessarily uniform and, as shown by Nims et al. (1955), anaesthesia lowers the compliance of the human thorax. It was clear that in some cases the rate of breathing was slower than normal for this age-group - viz. 28 - 40 breaths per minute. Third, the effect of the supine posture (Miller et al. 1956, Mead and Gaensler 1959, Ferris et al. 1959, Knowles et al. 1959) may vary according to the degree of cardiomegaly present. With Cook (1960) we found no constant artefact due to posture (Fig. 2i), but Klaus (1960) found that the compliance was lower in the supine position than in the right and left lateral positions in four of eight infants studied.

Fourth, the use of the oesophagus for assessment of intra-pleural pressure changes in such cases is open to error (Stead et al. 1952, Frank et al. 1956, Bondurant et al. 1960). Fifth, the presence of occult infection cannot be excluded in the sick children with large

hearts and hyperkinetic pulmonary hypertension. They are notoriously liable to respiratory ailments, and Edwards and Burchell (1960) amongst others have demonstrated how the enlarged left atrium can press on the left lower lobe bronchus and lead to atelectasis. The presence of stenosis of a major airway will make itself apparent in the mechanical properties of the lungs and, as pointed out by Otis (1956), this effect is rate - dependent. The fact that respiratory infections of a relatively benign nature influence the measurements of compliance so much substantiates the point made by Comroe et al. (1962) that dynamic compliance is an indefinite function of resistance as well as of true compliance.

For all these reasons the observations in infants must be interpreted with caution, and the most that can be stated is that they are in keeping with the concept that hyperkinetic pulmonary hypertension is assosicated with impairment of pulmonary compliance. No comparable data are available in the literature, and there are likewise few in respect of adults with left-to-right shunts. Ayres et al. (1960) found that in A.S.D. with a two to four-fold increase in pulmonary flow, the compliance was significantly lowered in eight of twelve patients, and that the total inspiratory lung work in these patients was twice normal.

Woolf (1953) found, in a study of 45 patients with A.S.D., V.S.D. or both, that a number of them had low pulmonary compliance. Case details are not given, however, and the patients are not designated nor separated in the analysis according to their haemodynamic status. Little difficulty in ventilation was observed in these cases. Woolf found that a minute volume of ventilation greater than 18 L/min. occurring together with a work of breathing greater than 2 Kg.m./min. distinguished patients with moderate and severe dyspnoea from the remainder: no relationship was found between the minute volume of ventilation and the compliance on exercise. There was no statistically significant relationship between mean pulmonary arterial pressure and compliance during exercise, though of 11 patients with compliance less than 0.1 L/min. eight had a mean pulmonary arterial pressure greater than 30 mm. Hg.

McIlroy and Apthorp (1958) studied lung function in patients with pulmonary hypertension and found in general a variable reduction in lung compliance. Their cases included five with V.S.D. but all were in the Eisenmenger category: in only one of these (Case 12) was the lung compliance reduced.

Wessel et al. (1964) have studied twelve patients with severe pulmonary hypertension. Four of these had A.S.D. or V.S.D, but no cardiac defects were demonstrated in the other eight, one of whom was shown at autopsy to have 'primary pulmonary hypertension' and another by lung biopsy to have schistosomiasis. The mean pulmonary artery pressures at rest varied between 40 and 90 mm. Hg. All vital capacities were normal except in the patient with schistosomiasis. The residual volume was moderately increased in all patients except one, and maximum breathing capacity was normal in eight and only slightly reduced in four. With the exception of one patient, all had an abnormally large physiological dead space and a high dead space to tidal volume ratio which increased further with exercise. The steady-state diffusing capacity, by the end-tidal sampling method, was normal or slightly decreased at rest; with one exception the values calculated from the physiological dead space were higher. Diffusion increased normally with increasing oxygen consumption during exercise in seven patients, though in one other it did not increase even with strenuous exertion. The arterial oxygen saturation was reduced at rest in all but one patient, though all the six cases with solitary pulmonary hypertension had a saturation greater than 90%; in only one of these did it fall on effort, from 91 to 72%.

It is thus clear that in hypertensive pulmonary vascular disease the vital capacity remains normal despite loss of compliance in some patients, suggesting that excess lung rigidity in itself does not cause a restrictive ventilatory defect unless there is a concomitant reduction in alveolar volume. The finding of a high physiological

dead space by Wessel et al. is consistent with the presence of non-perfused or under-perfused alveoli. Further, the rise of the dead space to tidal volume ratio on effort renders estimates of the dead space, as carried out by Woolf (1963), erroneous; hence values for diffusion based on these estimates are likely to be false. The failure of the diffusion capacity to increase on effort despite exercise sufficient to give a ventilation of 65 L/min, as in one patient of Wessell et al. (1964), might result from a decrease of the volume of the pulmonary capillary bed. This has been demonstrated in two patients with primary pulmonary hypertension by McNeill et al. (1958), but was not confirmed by McCredie et al. (1961) and Bucci et al. (1961).

Experimental studies in humans

These studies have been concerned mainly with the effects of 'congestion', though the exact meaning of this term has not always been clear. Pryor and Page (1954) found that rapid intravenous infusions led to a fall in compliance in normal subjects. Lewis et al. (1956) demonstrated that G-suit inflation caused an increase in intravascular pressures throughout the pulmonary circulation, comparable with the increase in systemic venous pressure; Bondurant et al. (1957) showed that G-suit inflation led to a fall in lung compliance, as did immersion of the subject in water. Reductions as large as that from 0.217 to 0.093 Lit./cm. were noted, though it was evident that the healthy young adult tolerated such changes without experiencing dyspnoea at rest. The immersion of an arm in ice-cold water also led to a lowering in compliance from 0.170 to 0.098 Lit./cm. and a rise of central venous pressure. The authors felt that pulmonary

vascular engorgement was responsible for the mechanical effect, and that it was caused by the transfer of blood from the systemic to the pulmonary circuit. Obenour et al. (1963) have confirmed these findings with the pressure suit.

Experimental studies in animals

Animal experiments relating flow and pressure in the pulmonary vessels to lung functions other than the property of diffusion appear to be uncommon. Again, the difficulty arises as to the exact meaning and haemodynamic significance of 'congestion'.

Drinker, Peabody and Blumgart (1922) produced pulmonary congestion by compression of the pulmonary veins in the anaesthetised cat and noted interference with the entry of air into the lungs; this was reversible so long as pulmonary oedema was not produced. Mack, Grossman and Katz (1947) investigated the effects of 'pulmonary vascular engorgement' on the distensibility of the lung, both by inflating canine lungs in a sealed reservoir and by experiments in the open-chested dog. They found that in the former preparation the injection of only 60 ccs. of blood into the pulmonary artery, whilst the pulmonary veins were clamped, markedly decreased the distensibility of the lungs, the changes being reversible on the withdrawal of the injectate. In their second preparation, clamping of the pulmonary veins led to an immediate fall in compliance, followed by a rise towards the original level which was thought to be due to subsequent failure of the right ventricle. Furthermore, a clamp placed on the pulmonary artery often resulted in decreased distensibility of the lung; this was not invariable, but the authors felt that on the few occasions when the reverse effects were seen

it was due to the great dilatation of the right heart which pressed on the lungs.

Heyer, Holman and Shires (1948) infused saline into dogs and noted the decrease in lung distensibility thus caused, together with the greatly increased swing in intrapleural pressure. The accompanying tachypnoea they found to be abolished by vagotomy, though the pressure changes remained the same. Borst et al. (1957) recorded pressure-volume curves in open-chest dogs, varying the pulmonary blood-flow and the left atrial pressure. When the latter was kept constant, changes in flow as large as from zero to 450 ml./Kg. body weight were not associated with changes in lung stiffness during stepwise inflation, nor were flow increases from 40 to 190 ml./Kg. during continuous volume cycling simulating normal respiration. Contrariwise, when left atrial pressure was elevated to 30 cm. H_2O or more, there was a small but definite change in the direction of increased lung stiffness. At left atrial pressures of 50 cm. H_2O the decrease in pulmonary compliance was 20-30 per cent, with return to control levels simultaneously with reduction of left atrial pressure. When pulmonary oedema was intentionally produced, pulmonary compliance decreased progressively from more than 0.035 to less than 0.005 L/cm. H_2O and remained low despite reduction of left atrial pressure to control levels. There was no change in pulmonary air flow resistance during these experiments. The pulmonary arterial pressures varied from 12 to 60 cm. H_2O with alterations in blood flow.

Borst et al. comment on the data of Drinker, Peabody and Blumgart that it is not possible to conclude whether the decreased compliance

found on occlusion of the pulmonary veins of cats related to altered elastic behaviour of the lungs or to changes in air flow resistance. They find a limitation in the measurements of Mack, Grossman and Katz in excised dog lungs and in lungs of living dogs in that measurements were made over extremely limited ranges of lung volume increase (25 ml. in excised lungs, 60 ml. in vivo) and were initiated from the passively collapsed state. They mention also that in Heyer, Holman and Shires' experiments the lungs at post mortem were found to be haemorrhagic and heavy, and the possible effects of pulmonary oedema could not be dissociated from their results. None of the above three experiments included measurements of vascular pressures or rates of blood flow through the lungs. In discussing the results of Bondurant, Hickam and Isley in humans, following G-suit inflation or submersion in water, Borst et al. question the reliability of oesophageal pressure as a measure of intrapleural pressure in circumstances of central vascular congestion (though the immersion of an arm in ice-cold water would be unlikely to invalidate this). They conclude that the relatively large changes in compliance observed in patients with chronic congestive failure or in pulmonary hypertension must be due to factors other than pulmonary congestion per se, such as effusion, chronic changes in vessel walls or increased heart size. They state, nevertheless, that the definite changes in compliance associated with increased pulmonary venous pressure suggest that the effect is due either to distension of the veins or capillaries, or to increased filtration through the capillary walls - if the latter were the case, however, it would require an extremely rapid fluid exchange inasmuch as the

compliance returned to control level within 10 seconds after the left atrial pressure had been lowered from 50 to 5 cm. H_2O.

Frank et al. (1959) measured the static volume-pressure curves for excised cat lungs, and found that the changes were slight and of uncertain significance when the pulmonary vascular system was expanded under pressure varying from 0 to 16 cm. H_2O. This was true in the presence of interfacial forces as well as in their virtual absence. The experiments extended the range of vascular pressure used by Borst et al. (1957) in open-chest dogs and by Cook et al. (1959) in intact dogs. The results of the study confirmed the impression that vascular congestion by itself has only a limited effect on the elastic behaviour of the lungs. Frank et al. (1959) also found that the equilibrium volume of the lungs at any fixed airway pressure varied with the state of pulmonary vascular distension, and that the magnitude of change in equilibrium volume was different, depending on whether the vessels were filling or emptying. At zero airway pressure, the volume in the lungs increased during vascular congestion; on the other hand, at airway pressures of 3 and 6 cm. H_2O the volume became smaller at peak vascular pressures. These changes could not be accounted for on the basis of unit-for-unit displacement by the fluid within vessels, and it was suggested that they might reflect true tissue hysteresis. The presence of vascular hysteresis in these experiments confirmed previous observations by Sarnoff and Berglund (1952) in isolated dogs' lungs and Sarnoff et al. (1953) in open-chest dogs, though these were made at higher vascular pressures of 15-30 mm. Hg. That such hysteresis was not due to vascular leaks or fluid trapping was shown by the fact that almost all the fluid was recovered during emptying of the vessels. The significance of this hysteresis was not known, but

it was considered mainly to be caused by vessels within the structure of the lungs rather than by larger external arteries. One possibility mentioned was that it might arise in elastic materials because of a time-independent change or 'set', leading to differences in tension during loading and unloading. Another possibility was that the phenomenon of critical closure of blood vessels (Burton, 1951) played a part, the volume of the vascular system during withdrawal of fluid being necessarily greater than during its injection. Lastly, the possibility that interfacial forces play a role in the volume-pressure relationships of blood vessels (Nichol et al, 1951) is mentioned by Frank et al.

There seems to be some evidence, therefore, that the state of the pulmonary vasculature affects the mechanical properties of the lungs, though the mechanism is not clear. As already mentioned, von Basch as long ago as the last decade of the nineteenth centure was of the opinion that while the alveolar space and lung size increased with congestion of the lungs, the rigidity ('lungenstarrheit') of the pulmonary tissues also increased. Traube, quoted by Eppinger et al. (1924), contended, on the other hand, that enlargement of the pulmonary vessels caused their protrusion into the alveolar space, with consequent diminution in the volume of this and interference with the respiration. Romanoff in 1911 supported the views of von Basch, finding that air entered the excised lung when the pulmonary vessels were filled with fluid. Weiss and Robb (1933) demonstrated how the congested lung becomes fixed in the inspiratory position.

Whilst in vivo estimations of pulmonary blood volume in heart disease have failed to show any correlation between increasing pulmonary

blood volume, increasing pulmonary vascular pressures and dyspnoea (Borden, Ebert, Wilson and Wells, 1949; Lagerlof, Werkö, Buckt and Holmgren, 1949; Kopelman and Lee, 1951), the methodology in these studies leaves some doubt as to the significance of the results. Rossier (1960) states, moreover, that his data indicate that no strict relationship exists between the severity of pulmonary congestion and the degree to which respiratory mechanics are deranged. This lack of correlation is especially striking in patients with mitral stenosis in whom he finds that, despite severe pulmonary congestion, normal respiratory mechanical conditions are maintained. This experience of Rossier's seems to be unique. The studies made by the present writer in patients with mitral stenosis indicate that the lung stiffness is usually increased. Donald (1959) found that the compliance was lowered when the pulmonary venous pressure was above 15 mm. Hg. In another study comment has been made on the important role of pulmonary venous hypertension in determining hyperventilation in heart disease (Gazetopoulos, Davies, Oliver and Deuchar, 1964) and Mauck and Shapiro (1961) have discussed the effect of increased pulmonary venous pressure in the disability of patients with left heart lesions, finding that a value of 30 mm. Hg. constituted a critical level. With this we agree, though there may be a variable effect between 20 mm. Hg. and 30 mm. Hg.

It is unlikely that increased pulmonary venous pressure is responsible for the usually lowered compliance of hyperkinetic pulmonary hypertension, since on measurement its value rarely exceeds 15 mm. However, the physical factors may conceivably not be too dissimilar. When pulmonary venous hypertension of

significant degree is present, the exact mechanism by which it may act to produce a diminution of compliance is not known, and several possibilities exist. The histology of the lungs is disturbed in chronic mitral valve disease (Parker and Weiss, 1936; Hayward, 1955; Harris and Heath, 1961; Arnott, 1963), and thickening of the capillary walls, interstitial oedema and fibrosis may be seen. It remains possible, however, that the state of the small vessels in the lung is of importance in determining the mechanical properties. The appendix gives a mathematical scheme by which alterations in the size, the wall thickness and the tension in the wall of a tube might conceivably alter its resistance to torsion and distortion. In that the greatest movement occurs peripherally in the lung, in relation to the alveolar sacs, so will it be these vessels rather than the larger ones near the fixed hilum that will partake most of the distorting effects of the movement accompanying respiration.

When pulmonary venous hypertension exists, the venules and capillaries are dilated and under tension. In hyperkinetic pulmonary hypertension with V. S. D, the small muscular arteries are dilated, hypertrophied and under tension and the capillaries are dilated to accommodate the increased flow. Wagenfoort (1960) showed that in the periphery of the lung in hyperkinetic V. S. D, a much greater area of any cross-section is occupied by vascular muscle, which is of necessity bulkier and more rigid than the frail alveolar tissue.

If this were the case, and it is mentioned only as tentative hypothesis, it would explain why severe pulmonary arterial hypertension, e.g. in primary pulmonary hypertension or in the

Eisenmenger syndrome, can exist without disturbance of lung mechanics, since the smaller vessels are protected by the obstructive lesions from the high pressure source. Furthermore, they are not dilated, the media of the walls is often atrophic rather than hypertrophied, and in association with the vascular obstruction in the Eisenmenger syndrome the typical thin-walled 'dilatation lesions' are seen (Wagenfoort, Heath and Edwards, 1964).

The results of the human and animal experiments mentioned above then become more easily understandable. Compression of the pulmonary veins clearly tends to produce pulmonary venous hypertension if the right heart continues to beat. That the injection of blood into the pulmonary artery of the isolated lung with clamped pulmonary veins (Mack et al. 1947) should produce such a clear and reversible effect is presumably associated with the fact that the blood is distributed between the pulmonary arterial, capillary and venous compartments. The failure of some experimenters to produce acute changes in the compliance of animals' lungs by altering pressure-flow relationships in the pulmonary artery bears no direct relevance to the situation in human beings with hyperkinetic pulmonary hypertension, since the factor of increased vascular muscle mass is absent in the former circumstances.

Such considerations may play a part in explaining the observations linking disturbances of pulmonary vascular dynamics and pulmonary function, though the ultimate effect on the symptoms of the patient is another matter which involves the nervous pathways from the lungs and the drive towards hyperventilation. In 1929 Churchill and Cope, by producing experimental congestion of the lungs in animals,

demonstrated the role of nervous influence in causing a rapid and shallow type of respiration. Harris and co-workers (1938) showed that the most important stimulus to rapid, shallow breathing seen in pulmonary congestion arose from vagal reflexes, while Christie and Meakins (1934) suggested that the increased rigidity of the pulmonary tissues led to a hyperactivity of the Hering-Breuer reflex. The abolition of congestive tachypnoea by vagotomy, shown by Heyer et al. (1948), has already been mentioned and a similar effect has been seen during sedation in an infant with V.S.D. and hyperkinetic pulmonary hypertension. The consistent reports by cardiac surgeons (Ross, 1964) of immediate diminution of the stiffness and turgidity of the lung of an infant with hyperkinetic pulmonary hypertension when the pulmonary artery is banded, confirmed by an apparent diminution of inflation pressure which needs to be exerted by the anaesthetist, lends support to the view that the mechanical properties of the infant lung are disturbed when there is hyperkinetic pulmonary hypertension. One factor frequently present in conditions where the stiffness of the lung is increased is, therefore, the presence of changes in the capillaries and adjacent small arteries and veins, the compliance of each alveolar unit thus being altered. It may well be that von Basch was in principle correct when he ascribed increased lung stiffness to the erectile properties of the small vessels of the human lung.

CHAPTER III

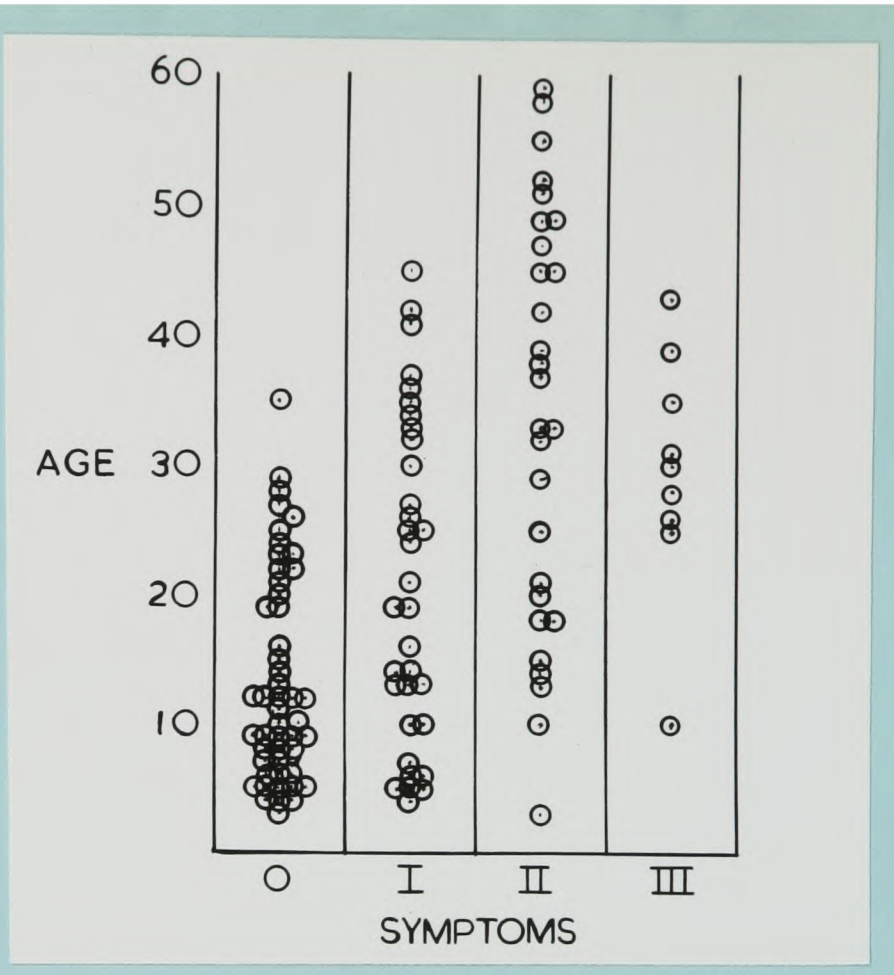
DISABILITY IN ATRIAL SEPTAL DEFECT AND THE EFFECT OF SURGERY

Cases studied These consisted of the first hundred patients operated on for closure of their defects at the University of Colorado Medical Center, Denver, U.S.A. The follow-up exceeded five years in one case, four years in seven cases, three years in 14 cases, two years in 16 cases, one year in 30 cases and six months in 19 cases. Cardiac catheterisation data was available in 93 cases before surgery and in 44 cases after surgery.

Table IX in the Appendix, gives the personal and haemodynamic data of these 100 cases, and also the degree of disability from which each patient suffered. Information pertaining to the pre- and post-operative periods is included.

The principle symptoms of atrial septal defects are those of dyspnoea and fatigue. These were graded as follows:

Grade 0:	No symptoms.
Grade I:	Symptoms noticed only on exertion greater than that in which they would normally indulge; thus, breathlessness to a greater extent than their fellows on playing games, running upstairs, etc.
Grade II:	Ditto - during ordinary activity, e.g. shopping, house-cleaning, etc.
Grade III:	Ditto - during less than usual activity, e.g. walking slowly on the flat.



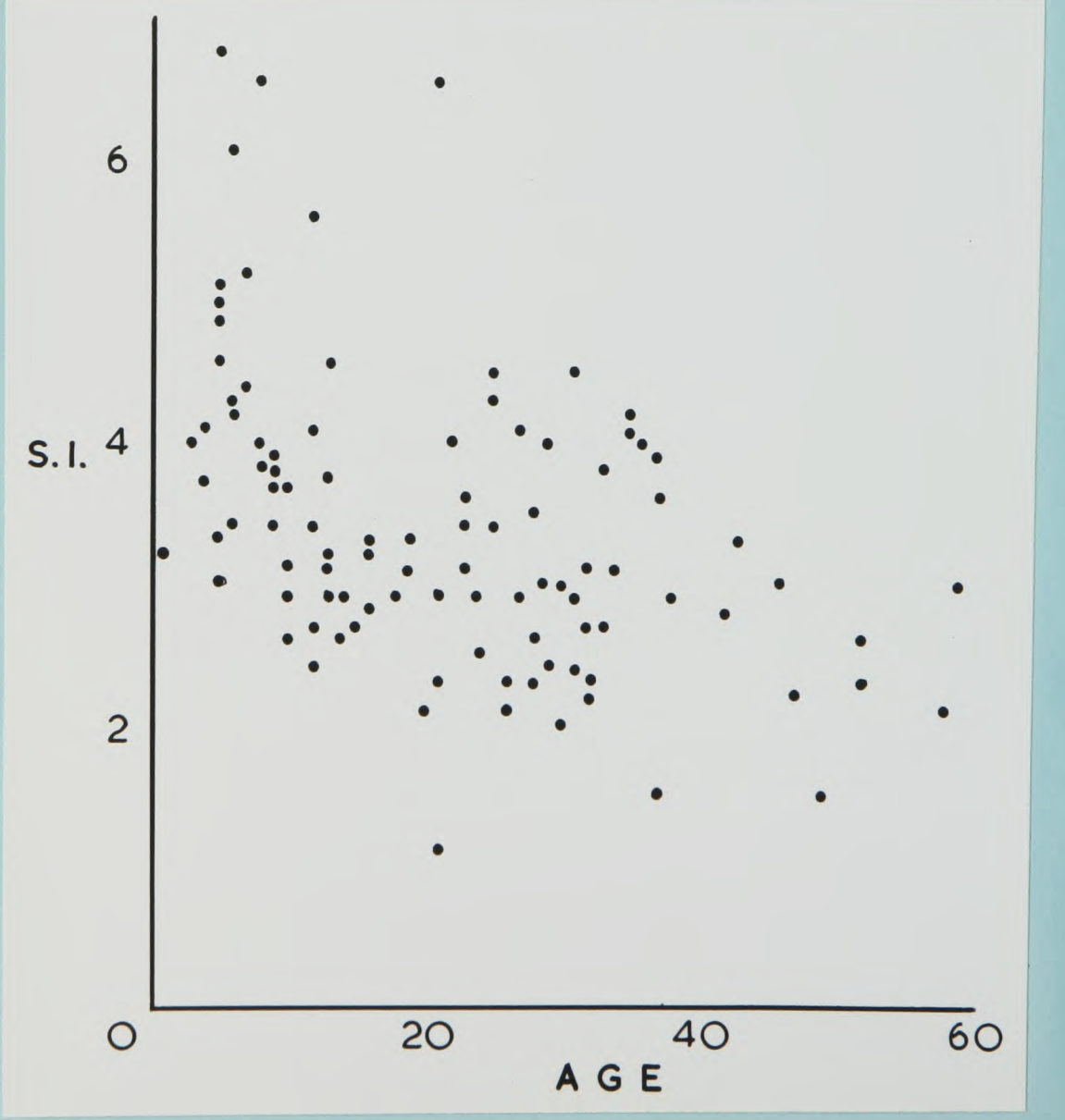


Fig. 3a. Relationship of age to symptoms (above), and age to systemic index (below) in A. S. D.

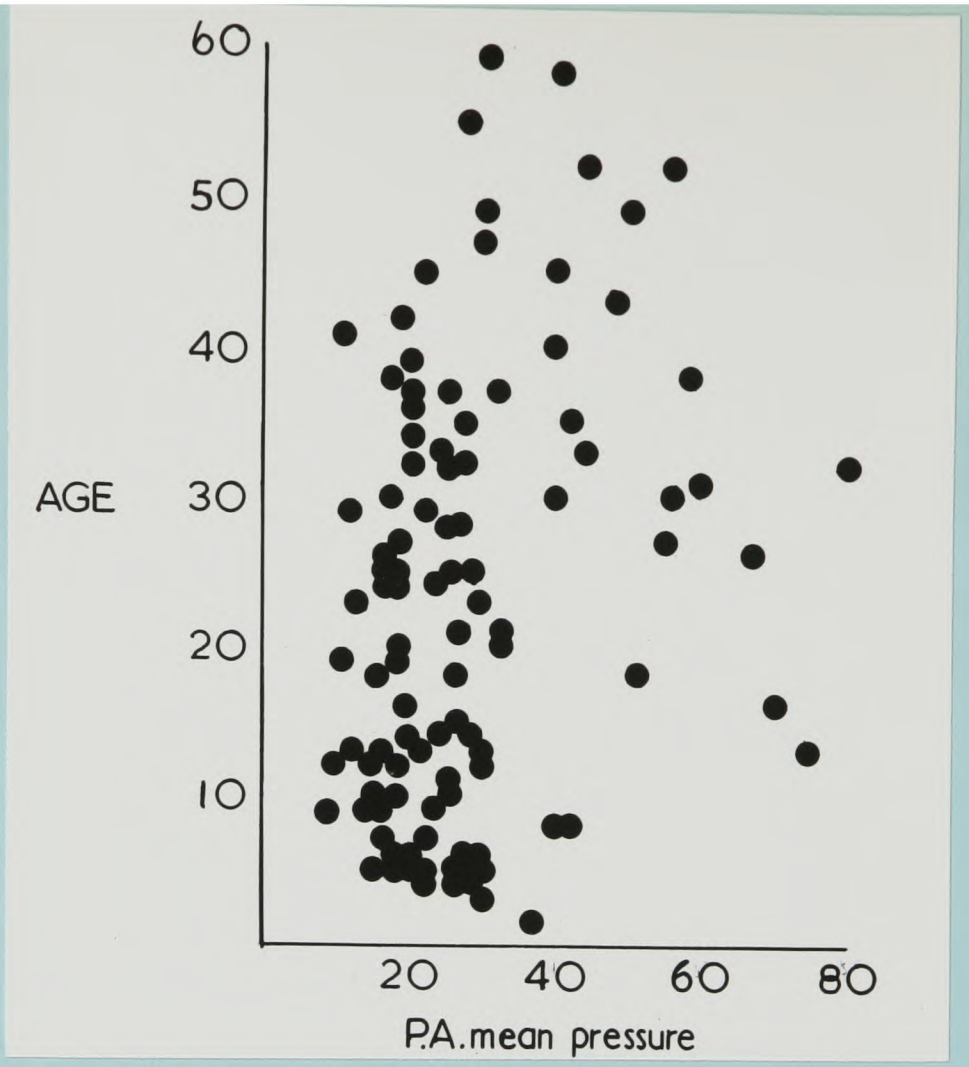


Fig. 3b. Age and pulmonary arterial mean pressure in A. S. D.

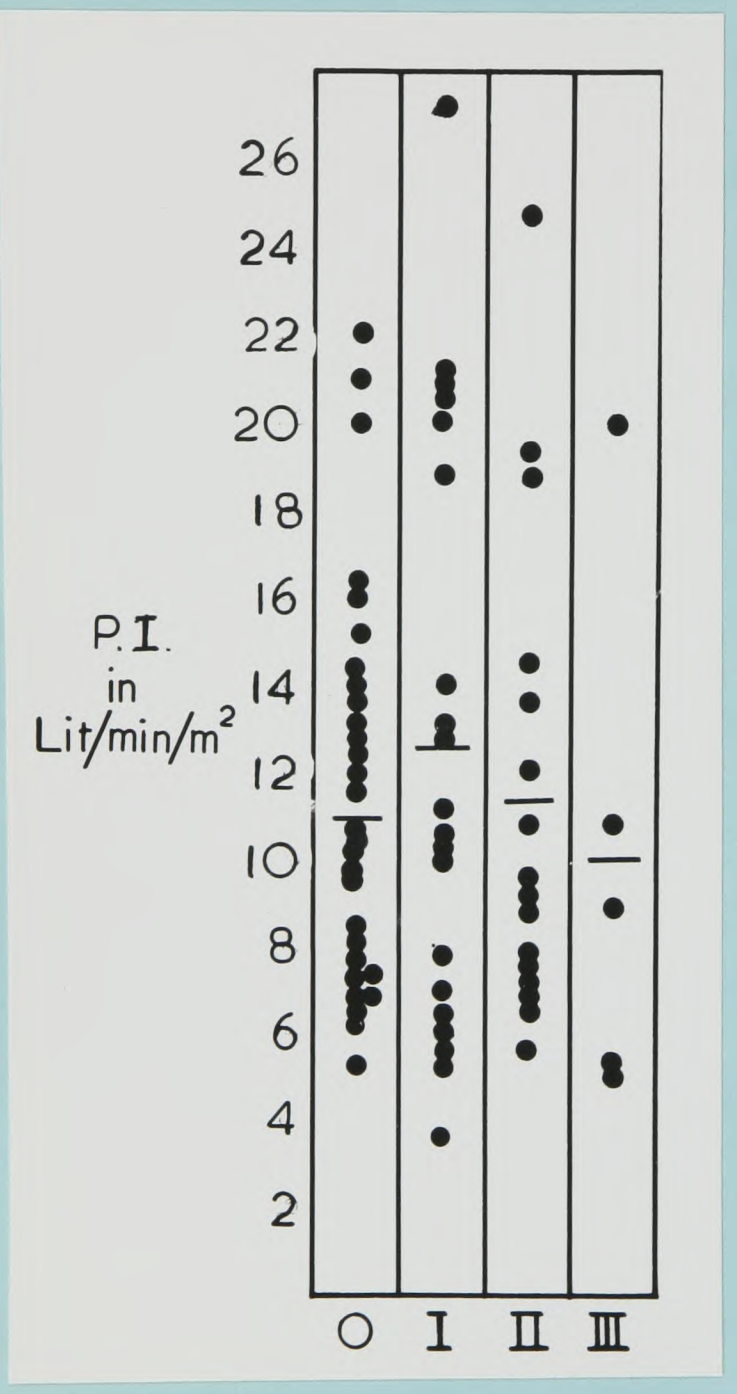
Fig. 3c. Age and total pulmonary resistance in A. S. D.

This grading is similar to that laid down by the New York Heart Association in 1953.

It was obvious that in these cases dyspnoea and fatigue occurred in similar measure. They have therefore not been separated in the analysis. Prior to surgery 10 patients had Grade III symptoms, 23 Grade II and 29 Grade I. Thirty-eight patients were asymptomatic.

It is emphasized that the Denver series is a highly selected one in that all were patients under the age of 45 years who were considered suitable for surgery. Patients with gross elevation of pulmonary vascular resistance were thus excluded. In order to make the data dealing with age more representative, for the purposes of the Figs. 3a-c the English patients from Part II, who were studied from the standpoint of their pulmonary function, have been added to the Denver series. The remainder of the figures relate to the Denver series alone - the difference of altitude makes the two populations not miscible in respect of the haemodynamic data.

Fig. 3a shows the relationship of age to symptoms. It is evident that the asymptomatic patients are the young ones, though the converse is not necessarily true. The average age of Group 0 was 14 years; of Group I, 21 years; of Group II, 34 years and of Group III, 32 years. On the whole, the increasing disability that accompanies increasing years, evident on dealing with a wider and unselected spectrum of patients with A. S. D, is confirmed. That this is probably not due directly to increasing pulmonary artery pressure or pulmonary vascular resistance is shown by Figs. 3b and 3c respectively. However, the average mean pulmonary artery pressures in the



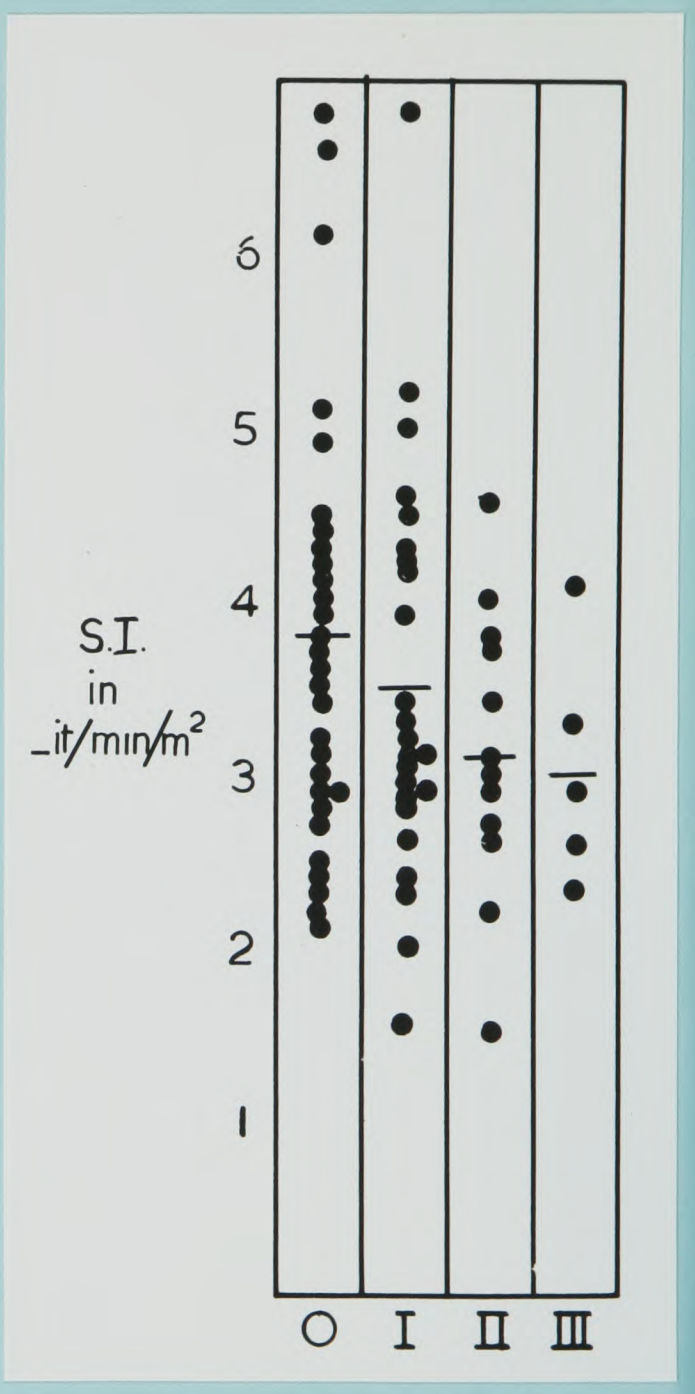


Fig. 3d. There is no relationship between symptoms and the magnitude of the pulmonary flow, but increasing disability is associated with a small but definite decrease in systemic flow.

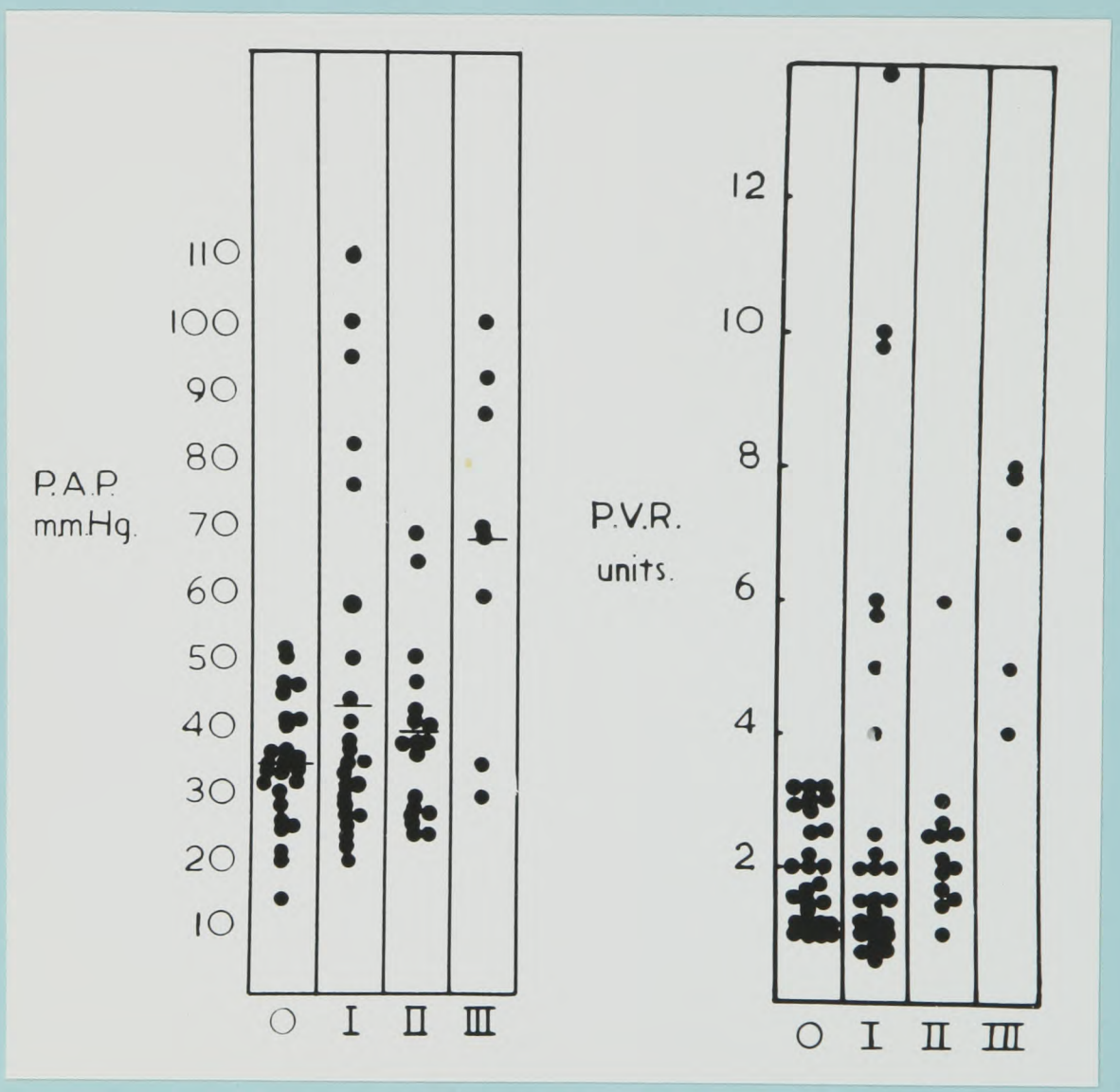


Fig. 3e. Increased pulmonary arterial pressure and pulmonary vascular resistance are broadly related to disability.

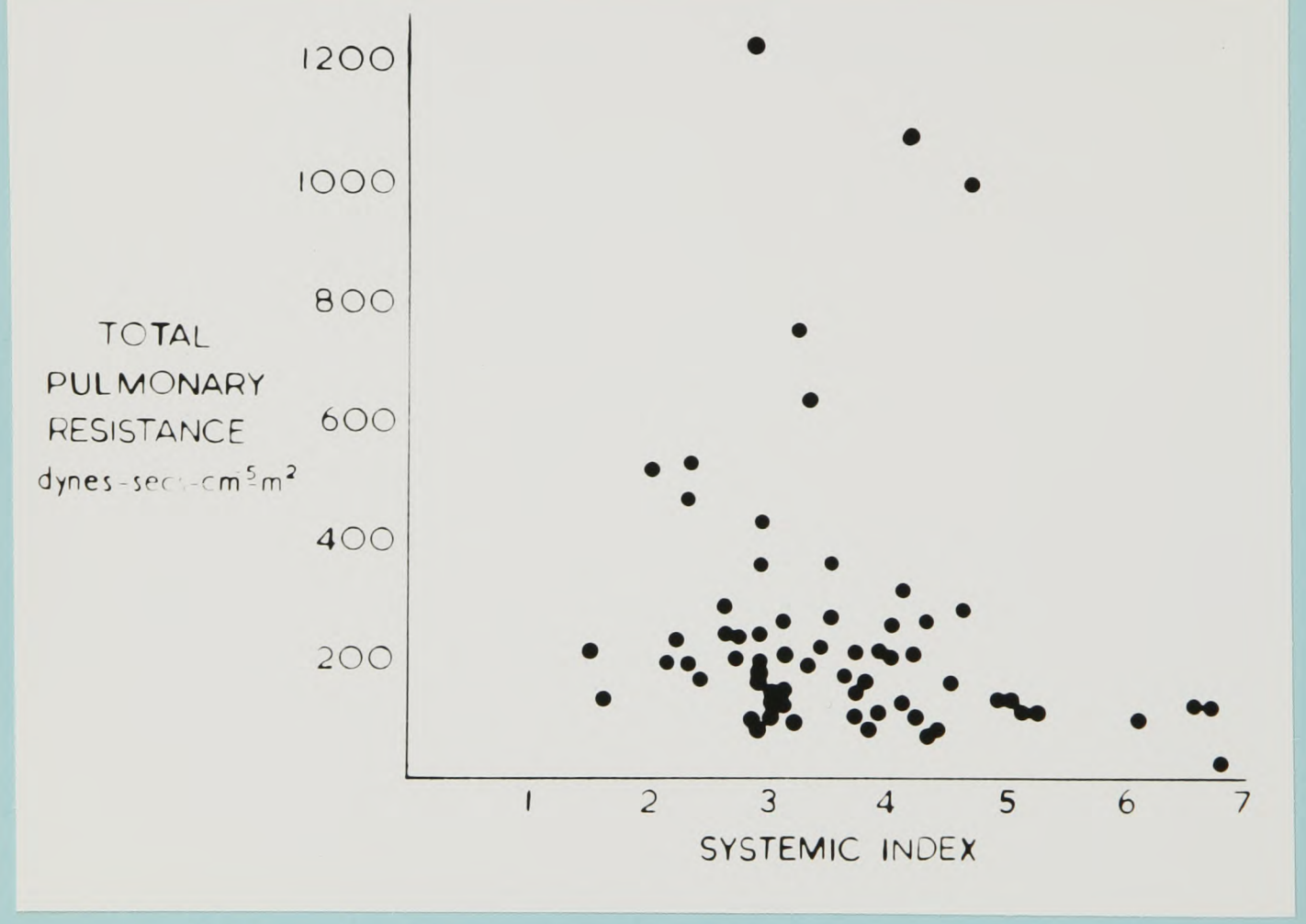


Fig. 3f. There is no obvious relationship between the systemic index and the total pulmonary resistance in the Denver series.

different age groups are as follows: over 50 - 40 mm, 40 to 50 - 32 mm, 30 to 40 - 35 mm, 20 to 30 - 25 mm, 10 to 20 - 25 mm., less than 10 - 25 mm, The pulmonary vascular resistance is also higher over the age of 30 than under it, as seen in Fig. 3c. Below the age of 10 the pulmonary resistance was always less than 300 dynes-sec. - cm^{-5}.-m^{-2}. Resistances above 1000 dynes were seen both in the 10 - 20 and 30 - 40 age groups. As seen in Fig. 3a, however, increasing age is associated with diminishing systemic flow.

In considering symptoms and blood flow it is seen from Fig. 3d that there is no relationship between increasing disability and increasing pulmonary flow, though increasing disability is associated with a falling systemic output. The pulmonary artery pressure, and particularly the pulmonary vascular resistance, show some correlation with increasing disability (Fig. 3e). Thus, all patients with Grade III symptoms had a pulmonary vascular resistance greater than 4, whilst all the asymptomatic ones showed values of less than 3 units. Fig. 3f shows that there is no obvious relationship between the pulmonary resistance and the systemic output, at least in this particular group of patients.

These conclusions, viz. that increasing disability is associated with; increasing age, falli ng systemic output and increasing pulmonary vascular resistance, are also applicable, and more clearly, to the English patients. Reference to Table VI makes this evident.

Results of Surgery

The striking fact that emerged from this follow-up study was that successful surgery could lead to such dramatic symptomatic results. Of 10 patients who were severely incapacitated before operation, six were without dyspnoea; four had

died at or after operation. Of the 23 who were moderately disabled, 16 had lost their dyspnoea and three were improved. Two others had as much incapacity as before, in one case due to persistent arrhythmia, and in the other due to the development of central cyanosis following rerouting of the inferior vena caval blood to the left atrium. Of the 29 patients who were mildly disabled, 26 were without dyspnoea, one died as a result of surgery, and two had as much disability as before; this was due to persistent arrhythmia in one case and was associated with severe pulmonary vascular disease in the other. Thirty-eight patients were without dyspnoea before operation, and of these one died and the remainder remained asymptomatic.

Thus, of the 62 patients who suffered from dyspnoea before operation, 48 had lost this symptom, three had improved, four were no better but had definite reason for this, and six had died as a result of surgery. These figures are shown in Table X.

Table X

Pre-operative disability grade	No. of Cases	Post-operative			
		Unimproved	Improved	Dead	Asympto-matic
III	10	-	6	4	6
II	23	2	19	2	16
I	29	2	26	1	26
0	38	-	-	1	37

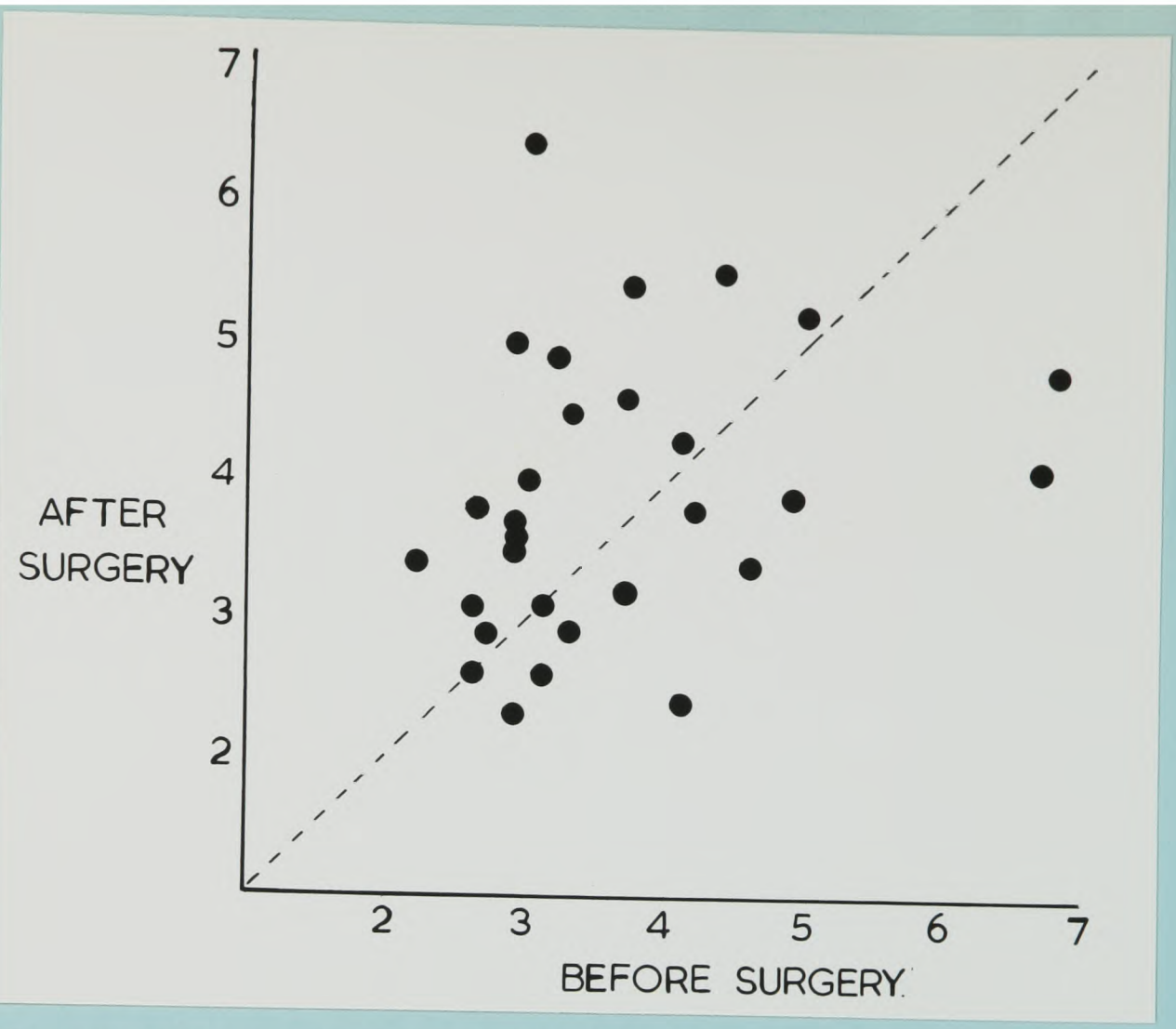


Fig. 3g. The resting systemic output before and after surgery in A. S. D. (L/min./sq. m).

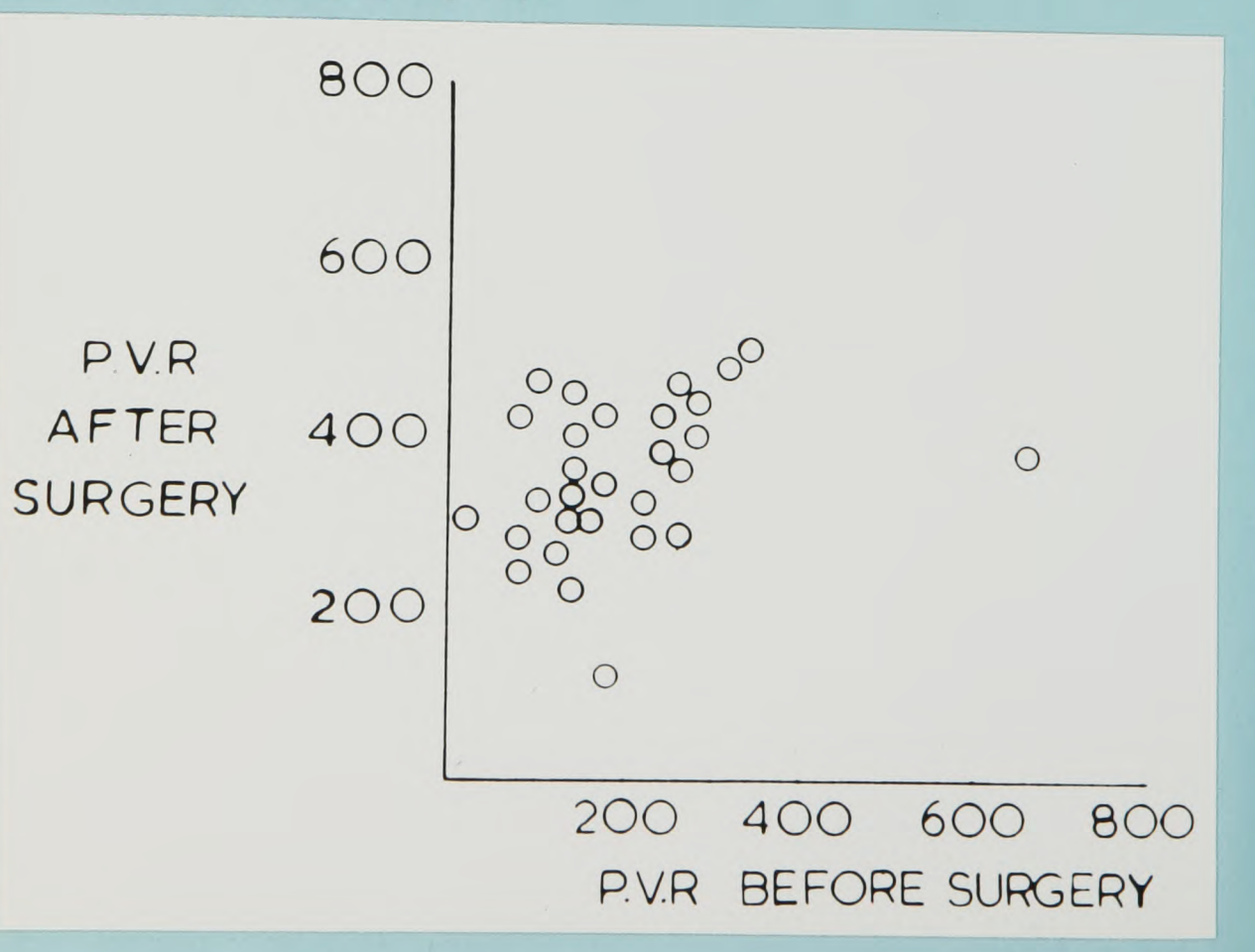


Fig. 3h. Pulmonary vascular resistance in dynes-sec-cm. $^{-5}$-M^{2} before and after surgery in A. S. D.

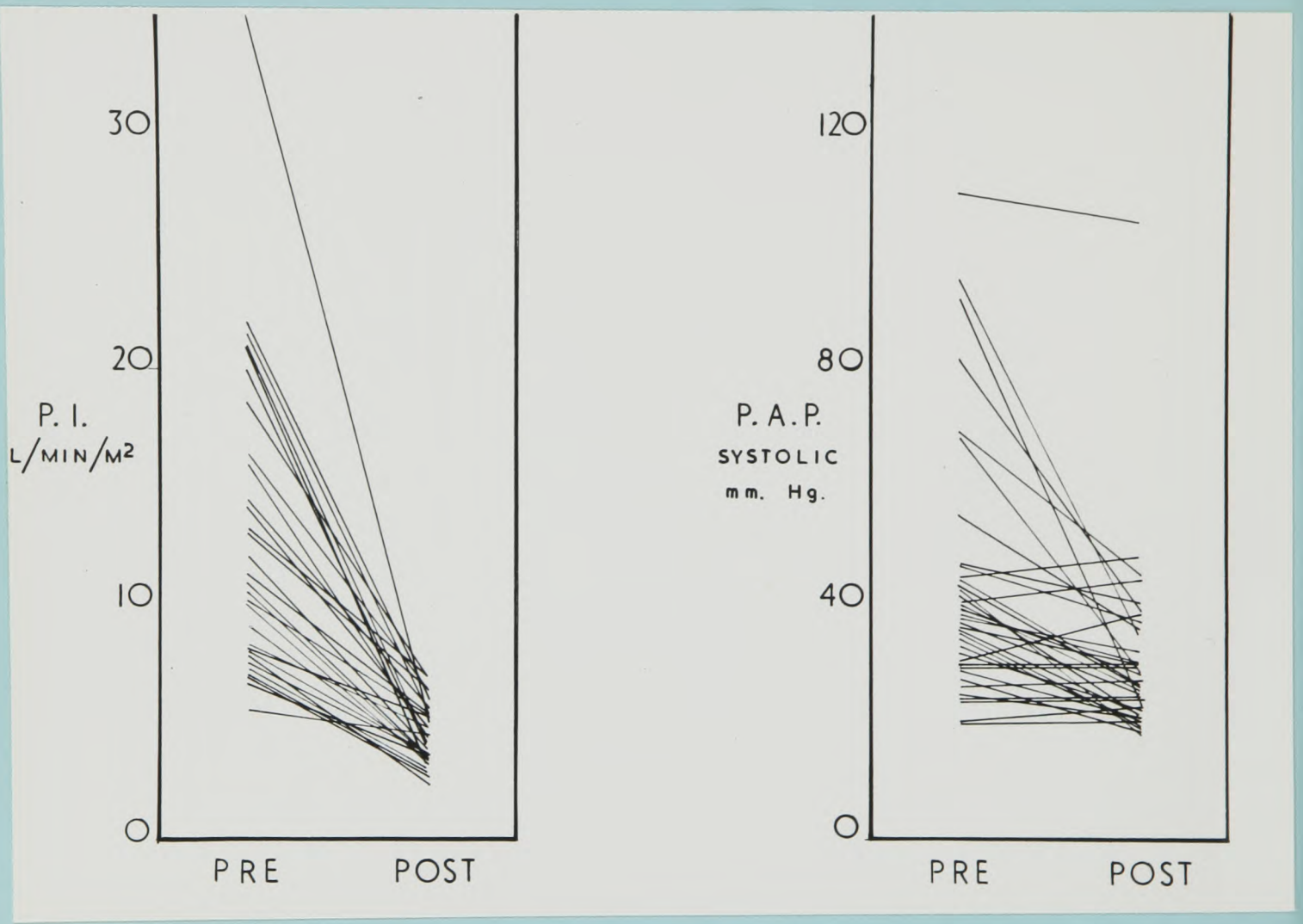


Fig. 3i. **Change in pulmonary index and systolic P. A. pressure as a result of surgery in A. S. D.**

The 42 survivors of surgery were leading normal and active lives. Their rate of improvement after operation is of some interest; following the immediate post-operative period, the gain in strength and well-being was usually rapid, and most of the patients were feeling quite well within two to three months of surgery, though slow improvement continued in many cases up to a year later. This parallels the continued change towards normal of the electrocardiogram (Davies et al. 1960). In a few cases the rate of rehabilitation was remarkable. One jockey, aged 32, for two years had suffered increasing and disabling dyspnoea, and he was riding again three weeks after surgery. A teacher, aged 26, was seen by her medical attendants to climb to the top of a football stadium two-and-a-half weeks after surgery.

The changes in haemodynamics as a result of surgery are shown in Table IX, and Figs. 3g and 3h. No increase was evident in the resting systemic output, and the anticipated small rise in pulmonary vascular resistance was found. The pulmonary blood flow was, of course, reduced to normal dimensions and a fall in pulmonary artery pressure was seen in all cases except one with severe pulmonary vascular disease (Fig. 3i), when it was high.

The following impressions emerge from the above studies :

1. Symptoms in atrial septal defect are very variable, ranging between zero and Grade III dyspnoea and fatigue.

2. The symptoms are on the whole more severe when pulmonary hypertension is present. All cases without symptoms had a low pulmonary vascular resistance and low pulmonary artery pressure. All cases with elevated pulmonary vascular resistance had symptoms.

3. There is no relationship between the severity of symptoms and the measured pulmonary blood flow.

4. There is an inverse relation between severity of symptoms and the resting systemic output.

5. There is a marked and most impressive improvement in symptoms following closure of the A.S.D.

6. There is little change in resting systemic output following closure of the defect. It is unlikely to be sufficient to account for the great change in the patient's condition.

7. Since there appears to be little relation between the magnitude of the pre-operative pulmonary blood flow and symptoms, it is unlikely that the reduction in this flow consequent upon surgery is responsible per se for the improvement in symptoms.

8. The pulmonary vascular resistance rarely decreases after surgery, and in almost all cases there is in fact an increase which is undoubtedly related to the diminution of passive distension of the lung vessels. Therefore, any factor related to this (e.g. Parenchymal lung damage secondary to pulmonary vascular disease) is unlikely to play a great part in the change in symptomatology.

9. Considerable reduction in heart-size occurs after successful surgery. It is doubted, however, if alleviation of purely volume-occupying disturbance of lung by the enlarged heart is responsible for the observed phenomena.

The dyspnoea of patients with atrial septal defect is therefore in many cases reversible and, therefore, not due to permanent changes in the lung. The rapid relief of symptoms following abolition of the shunt and reduction in pulmonary blood flow and pressure suggests that the disturbed pulmonary haemodynamics are directly responsible for the dyspnoea, though the possibility that improved systemic blood flow on the one hand or relief of right ventricular embarrassment on the other may play a part must be considered.

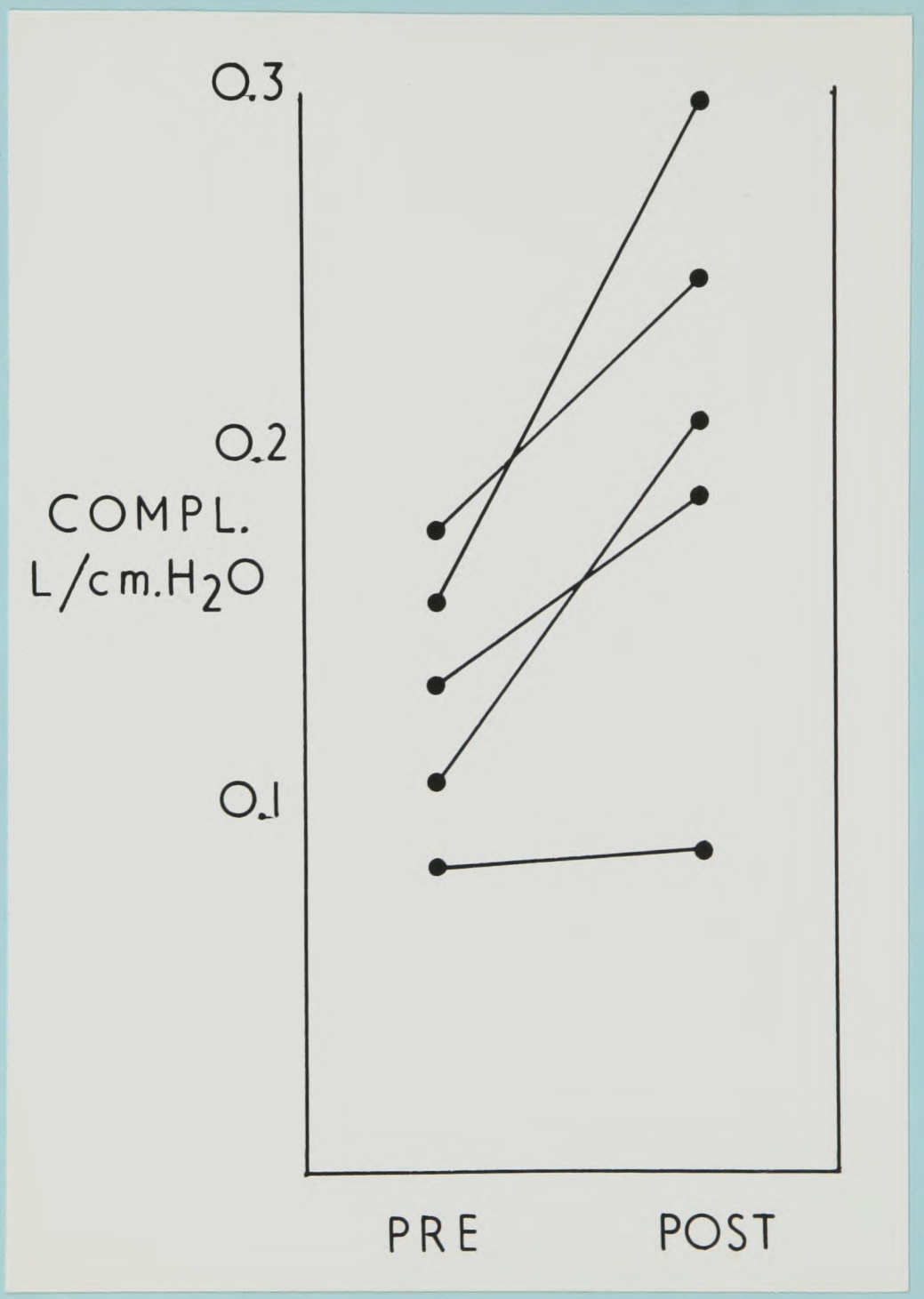


Fig. 3j. The effect of surgery on lung compliance. The post-operative values are those measured at least four months after surgery, when the influence of surgical trauma no longer interferes with the findings.

The effect of surgery on lung function in A.S.D.

This is clearly of importance in determining the reason for the improvement in symptomatology of these patients. Few pre- and post-operative studies are available, and those are shown in Table XI. It is seen that there is little change in the vital capacity and maximal breathing capacity. In every case except one, however, there was a considerable increase in lung compliance, and in two it was almost doubled. Case ET is of particular interest, in that her dyspnoea improved remarkably as a result of operation, yet her spirometry deteriorated - probably as a result of her taking up heavy smoking again after surgery. There was a marked rise in pulmonary compliance. These changes are illustrated in Fig. 3j.

The only patient in whom pulmonary function did not alter (Case PH) nonetheless showed some improvement in symptoms, though some dyspnoea remained.

It would appear, therefore, that improvement in the mechanical aspect of lung function may be an important determinant of the symptomatic benefit that accrues from surgery. It is to be noted that these are resting measurements, and can be only a guide to the values that matter, viz: those on exercise. As will be seen later, changes in haemodynamics of A.S.D. on exercise occur which may adversely affect the compliance. More data are needed before firm conclusions are possible, but these initial results are suggestive that improvement in pulmonary mechanics after surgery in A.S.D. may be of relevance in the understanding of the patients' disability and its relief.

TABLE XI

LUNG FUNCTION BEFORE AND AFTER SURGERY IN A.S.D.

Case Age at operation		Dis-ability	PAP mm.Hg.	FVC % pred.	MBC	FER %	Peak flow	Compl. L/cm.
FM	Pre	II	42/13	100	80	65	240	-
44	Post 12 mths.	0	-	107	92	70	280	0.31
FH	Pre	II - III	40/15	122	130	83	405	-
52	Post 18 mths.	0	-	100	98	75	380	0.23
DB	Pre	III	45/15	79	60	60	220	-
49	Post 12 mths.	I	-	75	53	60	230	0.17
JC	Pre	0 - I	25/10	130	120	83	430	-
15	Post 14 mths.	0	-	120	110	85	480	0.21
JS	Pre	I	30/15	105	110	83	460	-
25	Post 7 mths.	0	-	95	100	80	430	0.129
	Post 14 mths.			110	115	89	440	0.148
ET	Pre	II	55/25	100	77	62	180	0.16
58	Post 8 mths.	0	-	88	49	45	120	0.30
EP	Pre	II - III	80/40	97	90	79	425	0.11
49	Post 1 mth.	0	-	80	85	87	420	0.11
	Post 5 mths.		-	118	112	79	420	0.25
	Post 12 mths.		-	111	111	83	420	0.18
	Post 20 mths.	0	30/17	100	100	82	390	0.20
PH	Pre	II		116	107	96	440	0.086
32	Post 0.5 mth.			76	58	81	270	0.092
	Post 13 mths.	I	-	93	75	85	370	0.082
JH	Pre	I	36/14	100	99	80	400	0.112
26	Post 1 mth.	?	-	72	85	97	400	0.092
SR	Pre	0	34/12	119	110	80	400	0.140
29	Post 1 mth.		-	112	110	88	360	0.198
	Post 12 mths.	0	-	120	122	88	410	0.188
RR	Pre	II		74	78	71	300	0.178
	Post 35 mths.	0	-	100	103	69	360	0.250

CHAPTER IV

EXERCISE STUDIES IN PATIENTS WITH LEFT-TO-RIGHT SHUNTS

EXERCISE STUDIES IN PATIENTS WITH LEFT-TO-RIGHT SHUNTS

Introduction The effect of exercise in patients with left-to-right shunts has been studied by several groups of investigators (Jönsson, Linderholm and Pinardi, 1957; Scébat, Voridis, Renais and Lenègre, 1957; Bruce and John, 1957; Swan, Marshall and Wood, 1958; Stephens, Shafter and Bliss, 1964). The results of these studies are not uniform and, since they are germane to any attempt to understand the disability of such patients, further investigations into this question have been carried out.

Methods Thirty-four patients have been studied, 18 with atrial septal defect (A. S. D), 12 with ventricular septal defect (V. S. D), and four with patent ductus arteriosus (P. D. A).

The study of haemodynamics was performed during cardiac catheterisation in the supine position. Routine observations having first been made, a catheter was left in the pulmonary artery and an indwelling needle in a brachial artery. Spirometry was performed and blood samples taken; the catheter was then withdrawn to the lateral wall of the right atrium and further blood samples were obtained. In patients with A. S. D. a second catheter, having been

placed in the inferior vena cava, was withdrawn to the superior vena cava for further sampling. Paired samples were thus obtained from brachial artery, pulmonary artery, right atrium or cavae for flow determinations by the Fick principle. Dye-dilution curves were also inscribed as outlined below.

The catheters were then replaced in their original sites and the patient was exercised with either a spring-loaded leg exerciser (earlier studies) or a bicycle ergometer (Elema-Schönander - later studies). Pulmonary and brachial arterial pressures were continuously monitored, and after the fifth minute of exercise spirometry was repeated with the same sampling sequence as described above. Dye-dilution curves were also recorded during exercise. The spirometer was of the closed-circuit type (Donald and Christie, 1949) and oxygen consumption was corrected to S. T. P. D. Blood oxygen saturations were measured spectrophotometrically (Unicam model 600).

As representative of mixed venous saturation the mean of right atrial samples has been taken where the shunt was distal to this level, while in A. S. D. the mean of two inferior caval and one superior caval values was taken. Dye-dilution curves were recorded on a Mark II Cambridge dye recorder with a high-resistance input circuit giving a linear response to concentration of dye (Gabe and Shillingford, 1961), Coomassie blue being used as indicator. Special attention was paid to injecting the same quantity of dye at the same site just above the pulmonary valve at rest and on exercise. The curves were replotted and extrapolated on semi-logarithmic paper, and the shunt

calculated as a percentage of the pulmonary flow by planimetry. In cases with large left-to-right shunts, where the primary and secondary circulations could not be separated, the appropriate empirical formula of Carter, Bajec, Yannicelli and Wood (1960) was used:

$$\frac{Q_p - Q_s}{Q_p} \times 100 = 135 \frac{C_{(p + 2BT)}}{C_p} - 14$$

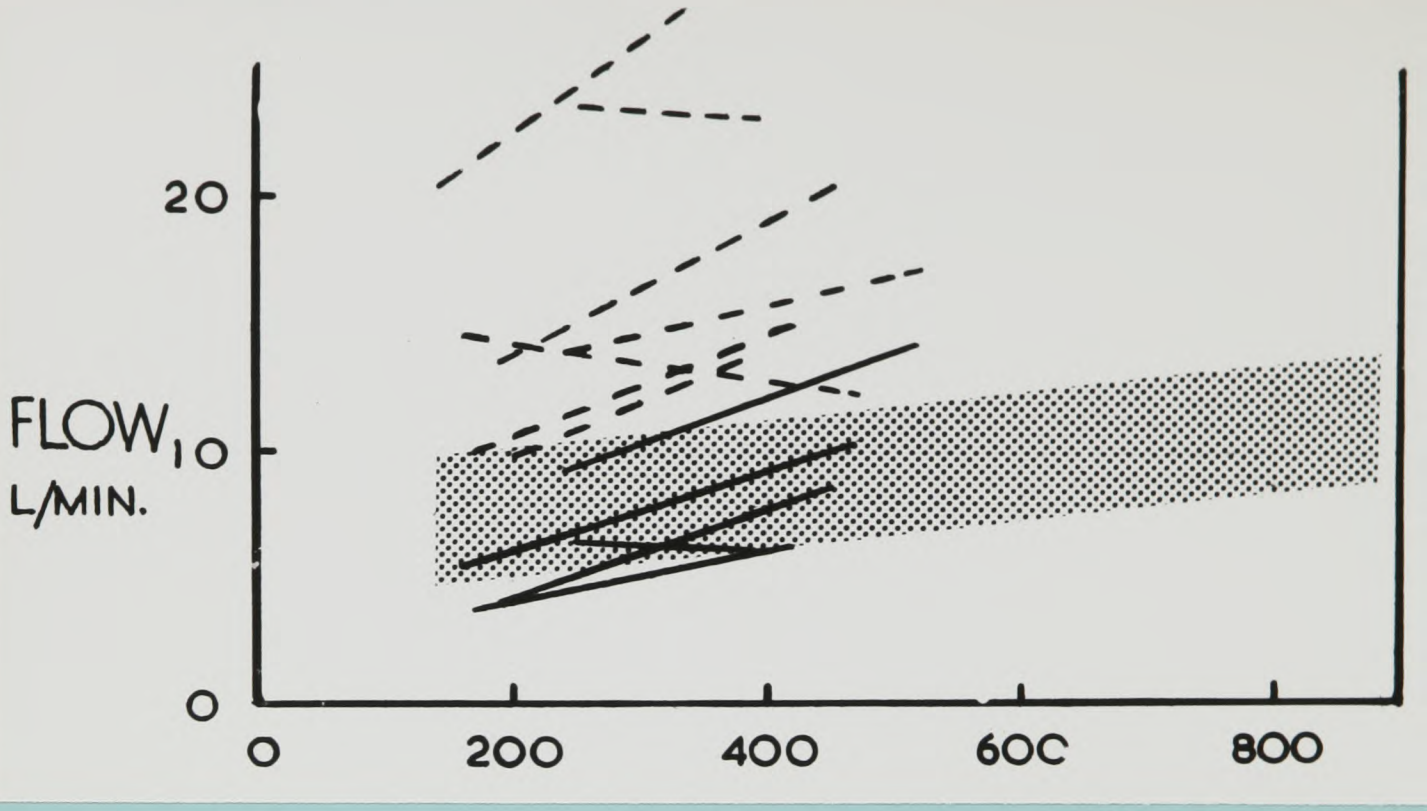
where Q_p represents pulmonary flow, Q_s systemic flow, C_p peak concentration and $C_{(p + 2BT)}$ the concentration at a point twice the build-up time after peak concentration.

Ventilation was measured by means of a Wright respirometer (resistance 2 cm. H_20 at flow of 100 L/min.) at rest and during a steady-state after the fifth minute of exercise, the appropriate corrections being applied for flow rate as described by the makers. A rubber mouthpiece was connected to a low-resistance valve of the Ruben type (dead space 9 ml, resistance during inspiration 2.6 and during expiration 2.8 cm. H_20 at flow rates of 100 L/min).

In parallel with the haemodynamic and ventilatory measurements arterial and venous blood samples were obtained in the third-to-fourth and eighth-to-tenth minutes of effort. These blood samples were analysed for pH, $pC0_2$ and bicarbonate content by the micro-Astrup technique, using the interpolation method of Anderson et al. (1960). Lactate and pyruvate determinations were made on arterial blood respectively by the method of Scholtz et al. (1959) and the modification of the Warburg technique as described by Landon,

Fawcett and Wynn (1962), samples having been transferred immediately to test-tubes containing 0.6 % perchloric acid.

In 10 patients the effects of more severe exercise on the bicycle ergometer were studied in the sitting position. In seven of these, rest and exercise data had been obtained during cardiac catheterisation in the supine position; in the remaining three, only resting data was available. Exercise was begun at a low load (200 Kpm./min), and was increased where possible by 200 Kpm./min. each 10 minutes, usually to maximum exercise tolerance. Measurements of oxygen uptake, ventilation, heart-rate and arterial blood chemistry were made in similar sequence to that outlined above.



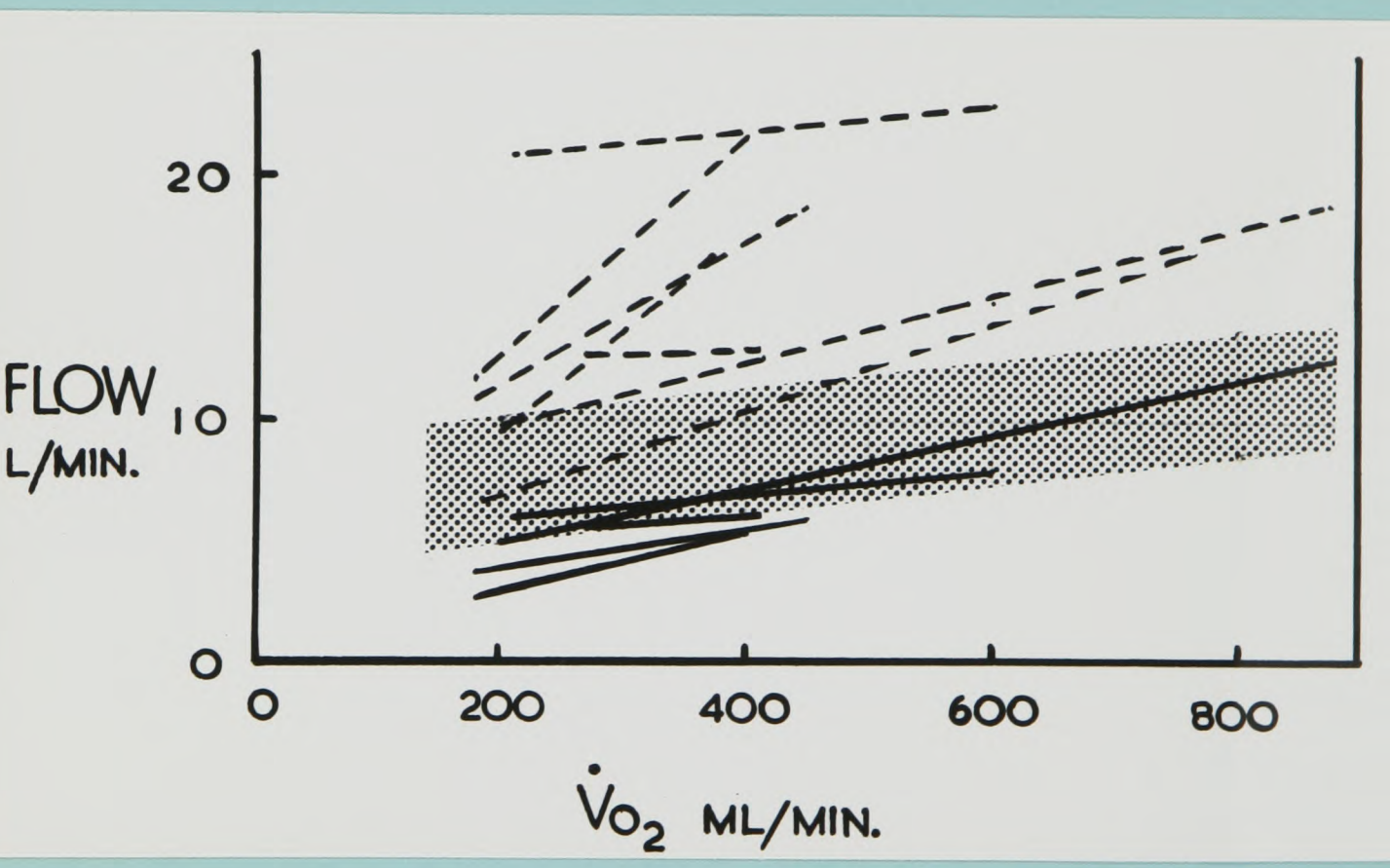


Fig. 4a Systemic (heavy line) and pulmonary (broken line) **flows at rest and on exercise in patients with A. S. D. Above, cases with low pulmonary arterial pressure and below, those with pulmonary hypertension. The shaded areas signify the normal range of systemic flow.**

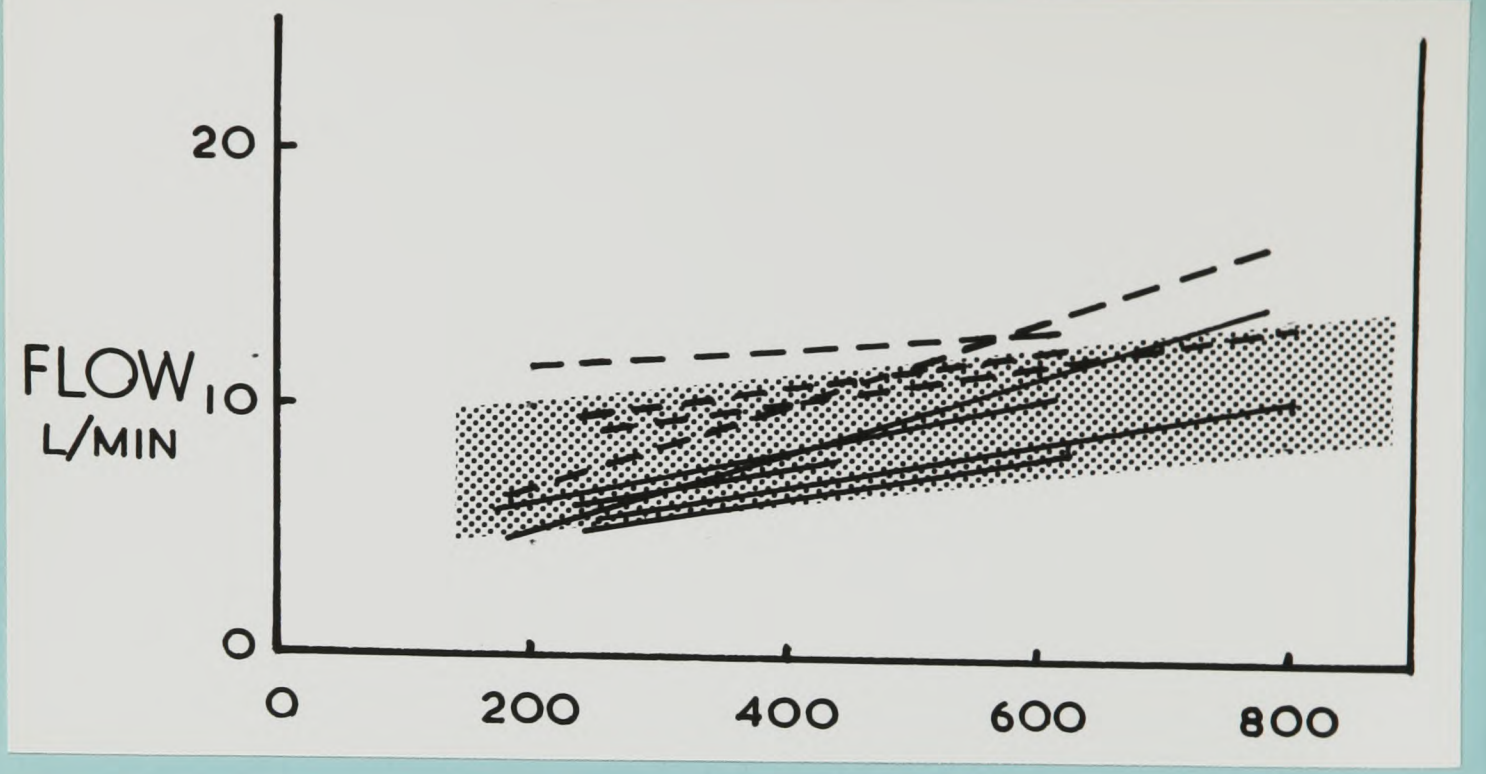
RESULTS

Haemodynamics

These are shown in Table XII in the Appendix. For the purpose of analysis V.S.D. and P.D.A. have been considered together and the two resulting groups (A.S.D. on the one hand, V.S.D. and P.D.A. on the other) have been subdivided into those cases with low, moderately elevated and high pulmonary vascular resistance. The findings will be described in relation to the major groups concerned. In all the subsequent diagrams (Figs. 4a-i) the results of Fick analysis have been used.

Atrial Septal Defect

Amongst these were seven cases with low pulmonary vascular resistance and a pulmonary arterial pressure of 40 mm. Hg. or less on exercise and eight with elevated pulmonary arterial pressure and a large left-to-right shunt. Figs. 4a(i and ii) illustrate the effects of exercise on the pulmonary and systemic flows in these patients. The shaded areas represent the limits of normality of cardiac output during exercise as described elsewhere (Gazetopoulos et al. 1965). It is seen that in uncomplicated A.S.D. the systemic flow varies widely at rest and has a more or less normal slope of increase with



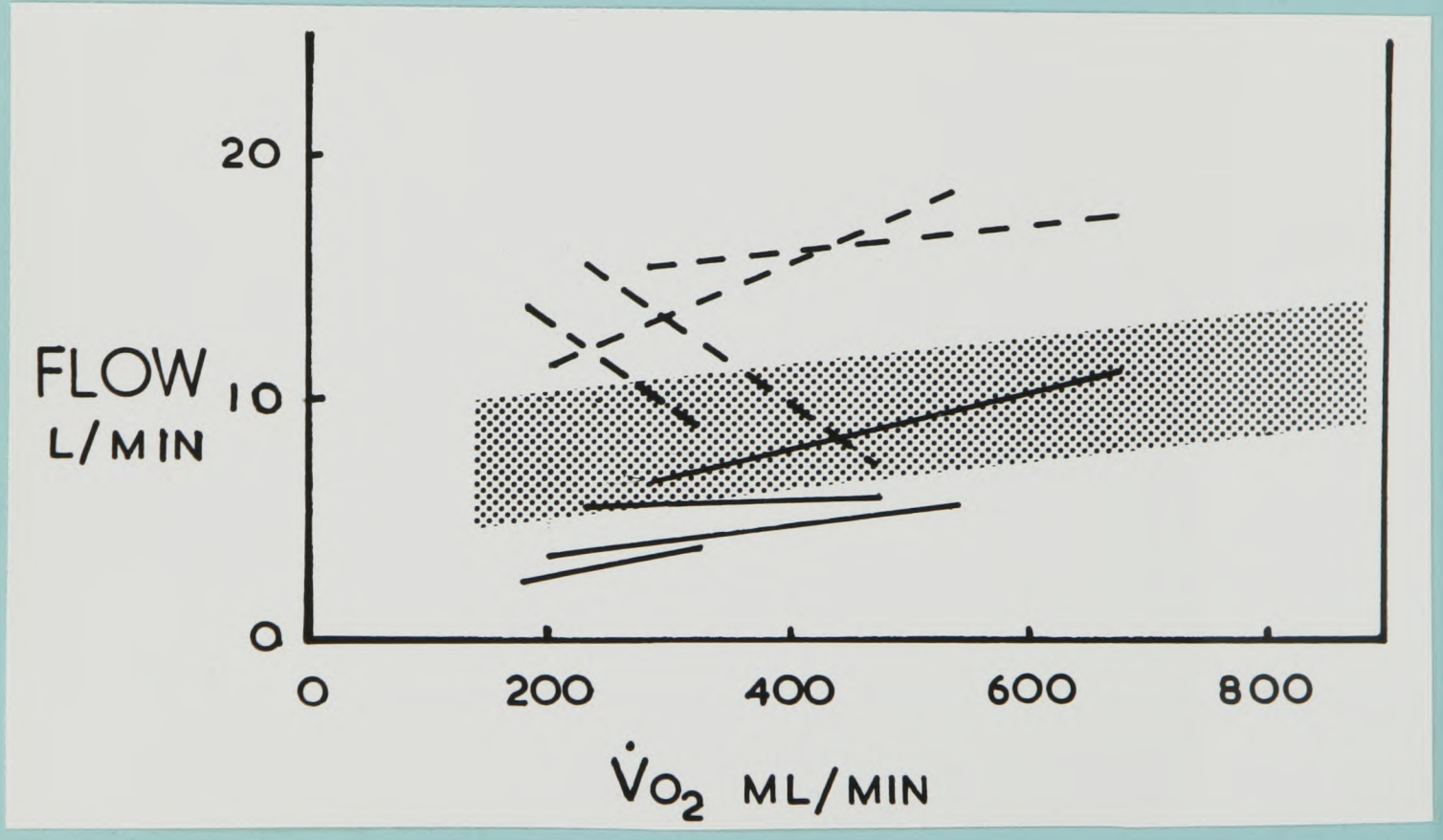


Fig. 4b Results in V.S.D. and P.D.A; designations as in 4a. Above, patients with low pulmonary arterial pressure and below, those with hyperkinetic pulmonary hypertension.

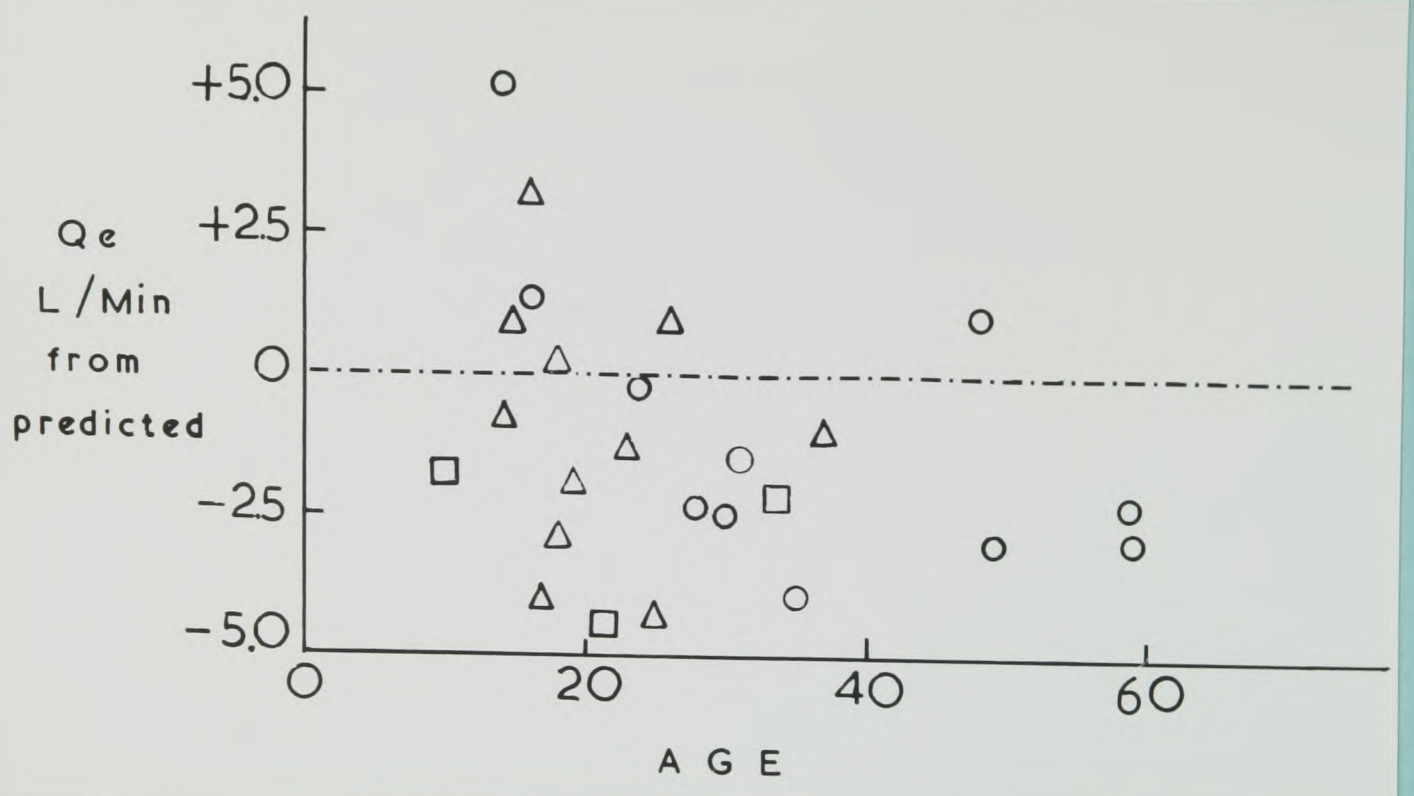
exercise, so that cases with the lower resting values show correspondingly low values on exercise. In the majority of patients the pulmonary flow increased in parallel fashion to the systemic so that the magnitude of the left-to-right shunt remained much the same. Only in one case (AN 4) was a significant diminution of the pulmonary flow observed as a result of exercise.

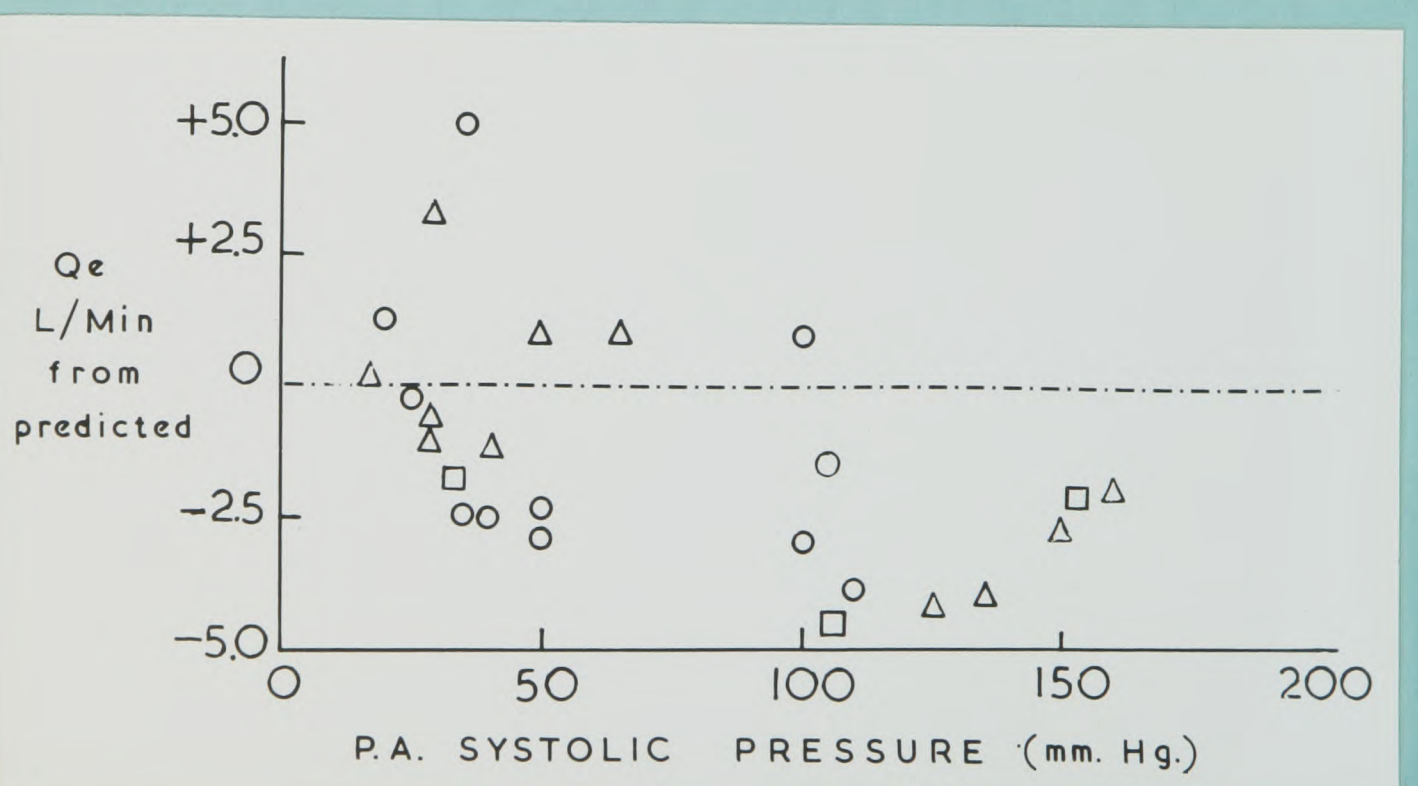
In patients with A.S.D. and pulmonary hypertension, but still with a large left-to-right shunt, the systemic flow was usually in the low-normal or low range at rest and on exercise, the slope of increase with exercise being normal. The pulmonary flow increased in all cases in this group, markedly in some. There was a considerable increase in the left-to-right shunt in two patients (AH 40 and AH 49), the latter having associated moderate mitral stenosis.

Ventricular Septal Defect and Patent Ductus Arteriosus

Of the 16 cases studied, six had low pulmonary arterial pressure and four had hyperkinetic pulmonary hypertension.

The changes of systemic and pulmonary flow in these 10 patients are illustrated in Figs. 4b (i and ii), the limits of normality of systemic flow again being shown. In the group without pulmonary hypertension the systemic flow, as in atrial septal defect, responded normally to exercise. The pulmonary flow increased in a parallel fashion to the systemic and the magnitude of the shunt overall remained unchanged. In the patients with hyperkinetic pulmonary hypertension, on the other hand, the resting and exercising systemic outputs were low in





Figs. 4c and 4d Impairment of effective systemic flow on exercise, expressed as deviation from the mean predicted for the particular oxygen uptake, in relation to age (above) - 4c, and P.A. systolic pressure (below) - 4d.

A.S.D. V.S.D. P.D.A. (in this and following figures)

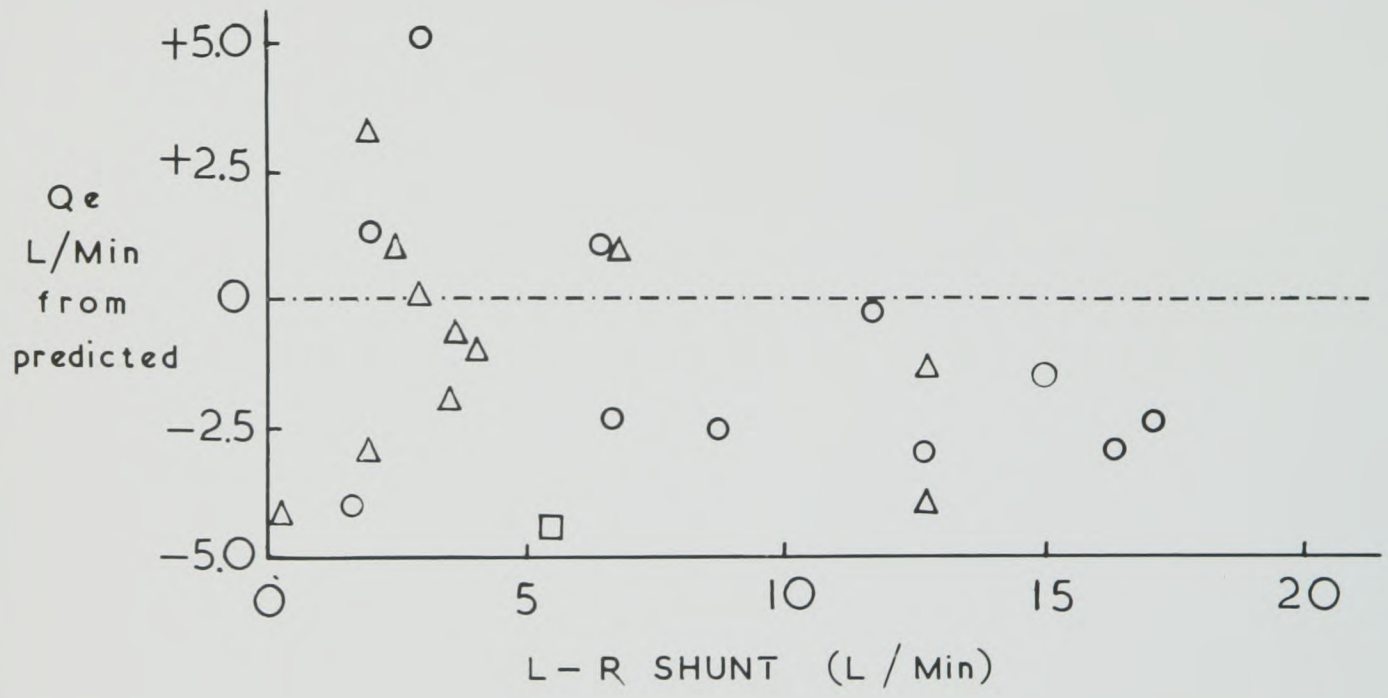


Fig. 4e Impairment of effective systemic flow, in relation to magnitude of left-to-right shunt, on exercise.

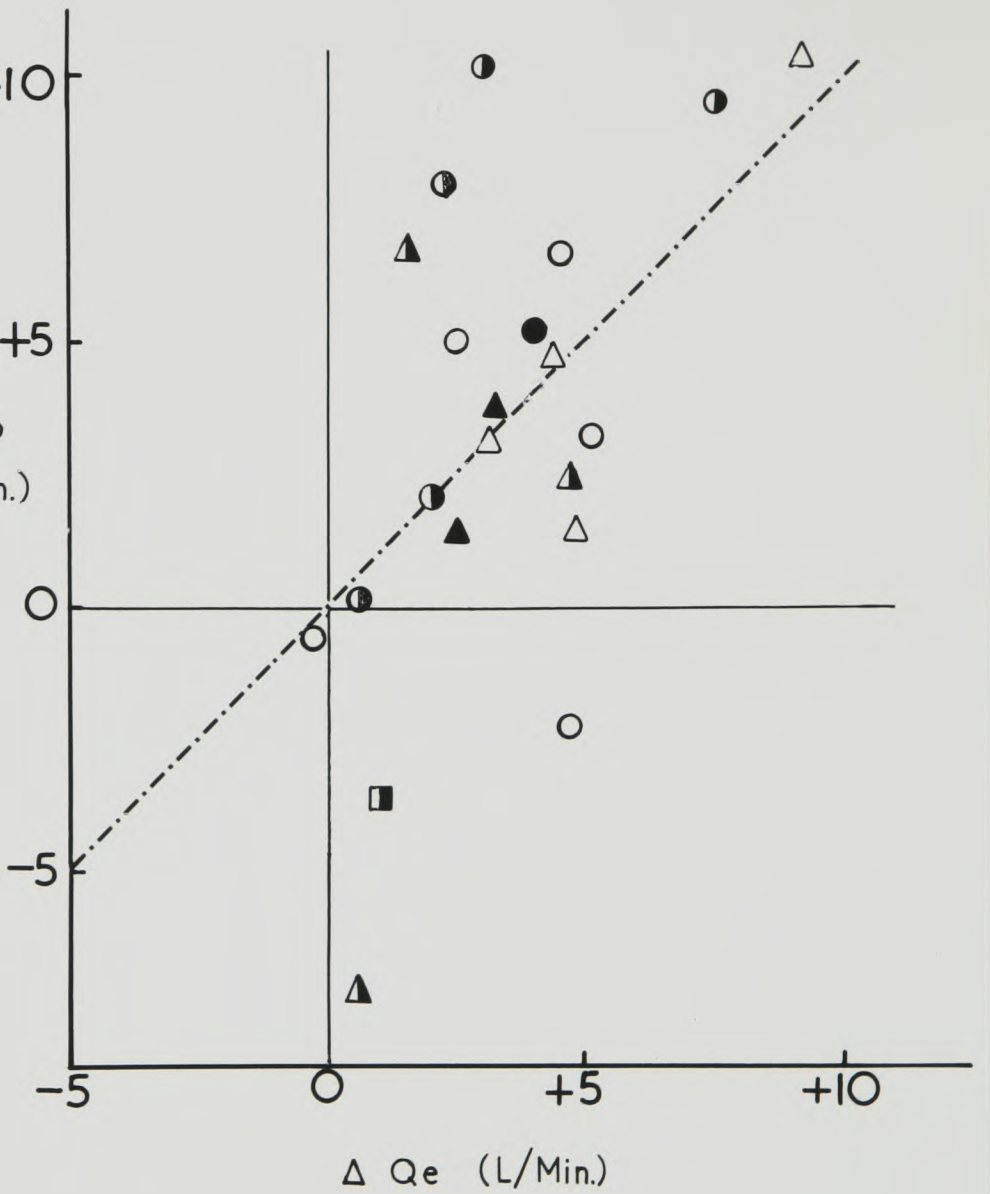


Fig. 4f Changes in pulmonary flow (ordinate) and effective systemic flow (abscissa) on effort. Cases lying above the diagonal line show an increase in left-to-right shunt, and those below, a decrease.
Open symbols represent cases with low pulmonary arterial pressure; semi-solid symbols those with hyperkinetic pulmonary hypertension; solid symbols those with the Eisenmenger state.

three of the four patients. The pulmonary flow increased in two whilst in the other two there was a sharp decrease in pulmonary flow on effort (VH 33 and PH 30). These two were the only patients in whom the indirect left atrial pressure was elevated and in whom a gross reduction in the magnitude of the left-to-right shunt was seen, the findings being confirmed by dye curves. In contrast, case VH 32 showed a considerable increase of the left-to-right shunt. Patients with the Eisenmenger syndrome or co-existing pulmonary stenosis have not been included in Figs. 4a and b, since the haemodynamics are modified by the fixed right-sided resistances. Patients with pulmonary stenosis have been excluded also from all the following figures for simplicity of presentation.

It is seen in Figs. 4a and b that the systemic output, although having a normal slope of increase during exercise, was impaired in a number of cases, particularly if there was pulmonary hypertension. In an attempt to understand the factors determining the impairment of cardiac output we have examined its relationship to age (Fig. 4c), P.A. systolic pressure (Fig. 4d) and the magnitude of the left-to-right shunt (Fig. 4e). On the ordinate of each of these figures is plotted the effective systemic flow in litres/min. above or below the mean normal value for the particular exercise oxygen consumption (Gazetopoulos et al. 1965). It is seen that the older the patient, the larger the left-to-right shunt, or the higher the pulmonary artery pressure, the greater is the tendency for the effective flow to be impaired. In Fig. 4f we have plotted the changes with exercise in the pulmonary flow against those in systemic flow. It is seen that the increase in systemic flow is in most cases associated with an

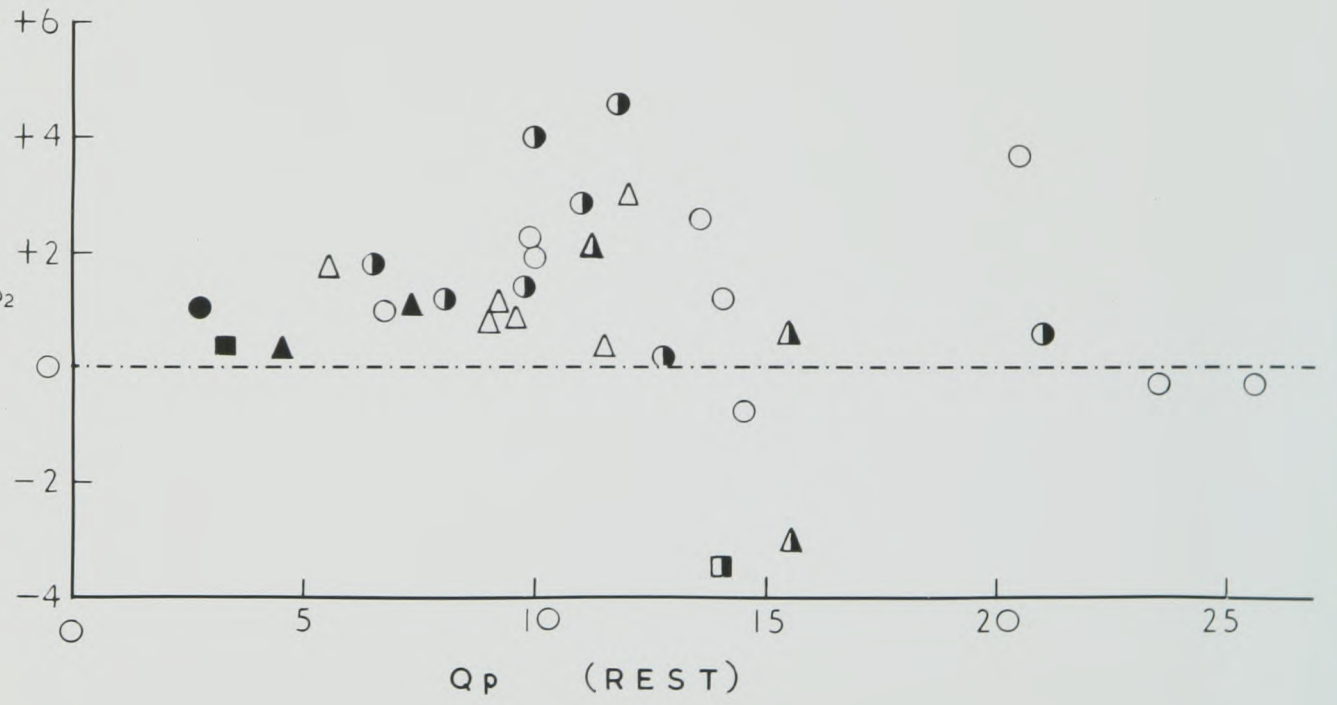
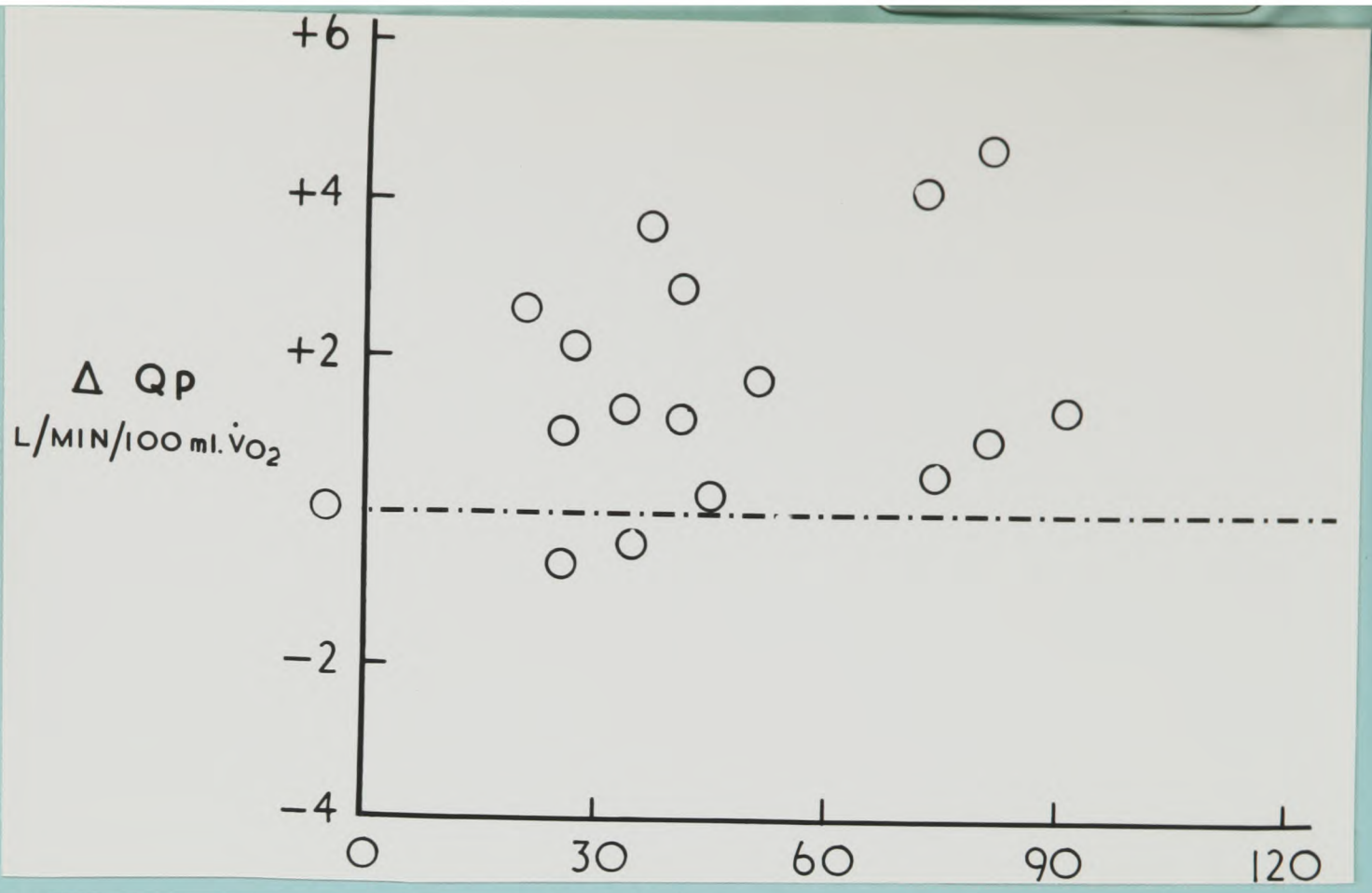


Fig. 4g Change in pulmonary flow on exercise per 100 ml. increase of oxygen uptake in relation to magnitude of resting pulmonary flow. Symbols as in Fig. 4f. It is seen that a high resting pulmonary flow by no means precludes a considerable increase on exercise in some cases.



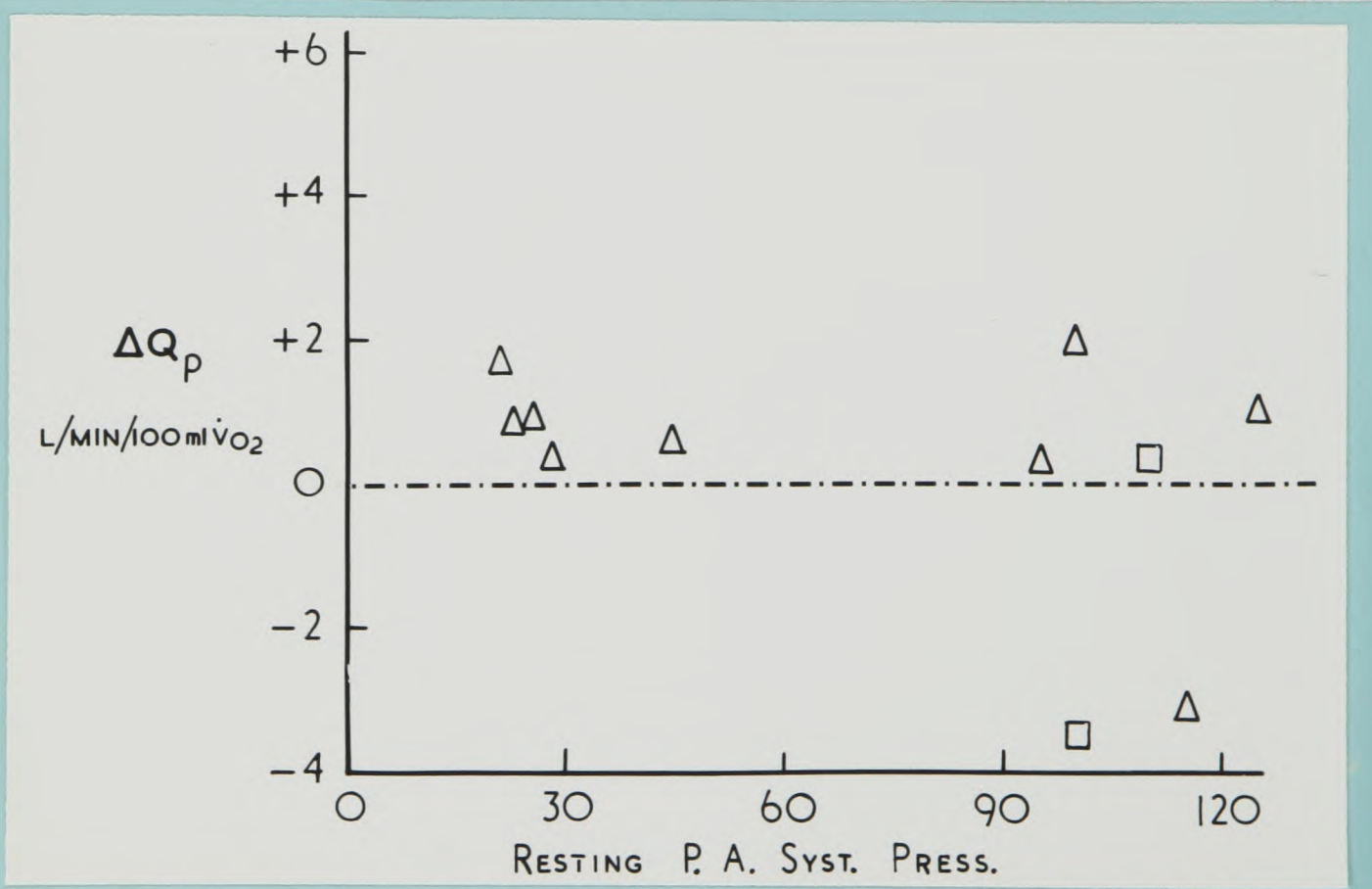
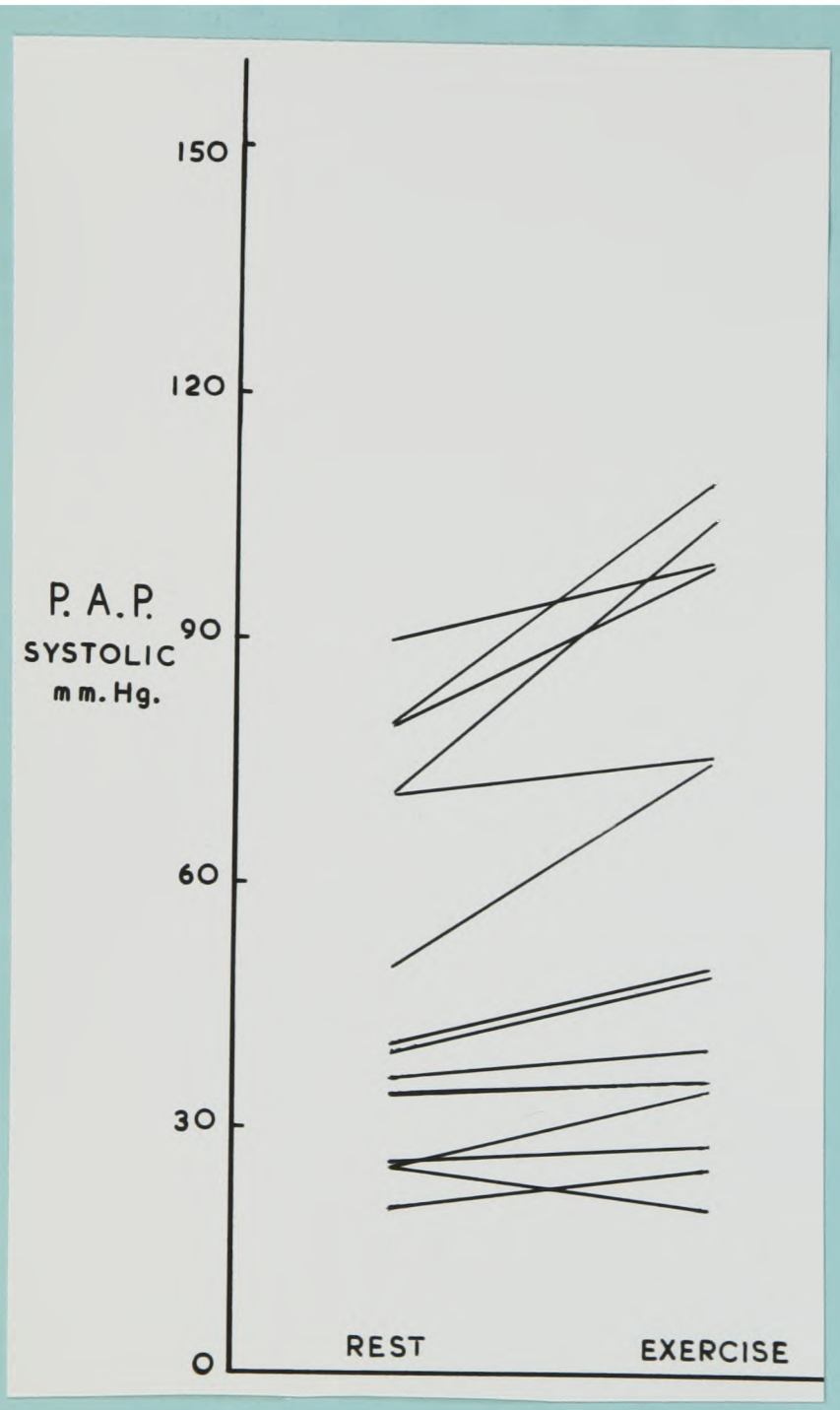


Fig. 4h Change in pulmonary flow on exercise per 100 ml. increase in oxygen uptake in relation to resting pulmonary arterial systolic pressure. Above, A.S.D. and below, V.S.D. and P.D.A. A considerable increase in pulmonary flow occurs in some patients with A.S.D. whose resting pressure is high. In V.S.D. and P.D.A. the response is variable; both cases who showed a marked decrease in flow in the latter group had elevated left atrial pressures.

increase in pulmonary flow (the two patients who showed a marked decrease in pulmonary flow, cases VH 33 and PH 30, have already been discussed). The magnitude of the left-to-right shunt shows a variable pattern of change, but it is clear that there is a significant number of cases in each group in whom the shunt actually increases.

Fig. 4g relates the resting pulmonary flow to the change which occurs on effort. Patients in the Eisenmenger category have a low pulmonary flow which rises little with effort. Case AN 6 on the right of the figure, who had a very large left-to-right shunt due to A. S. D, had relatively fixed haemodynamics at rest and on effort; otherwise it is seen that changes are variable, but the presence of a large resting pulmonary flow does not preclude a further increase with exercise. Fig. 4h (i) relates the magnitude of the change in pulmonary flow to the resting pulmonary artery pressure in A. S. D; it is seen that an elevated pressure was often associated with a rise in pulmonary flow on effort, a tendency which if anything increased at higher pressure (it is to be noted that this applies to the group of patients with hyperkinetic pulmonary hypertension and not to the Eisenmenger state). Fig. 4h (ii) shows the same information applied to V. S. D. and P. D. A. Here the findings are more variable, and in contradistinction to A. S. D. there is an overall tendency for the pulmonary flow to increase less or even to decrease at higher pressures.

The effect of exercise on the pulmonary arterial pressure is also of some interest. It changed little in those cases where it was low, but the higher the resting pressure the greater on the whole was the



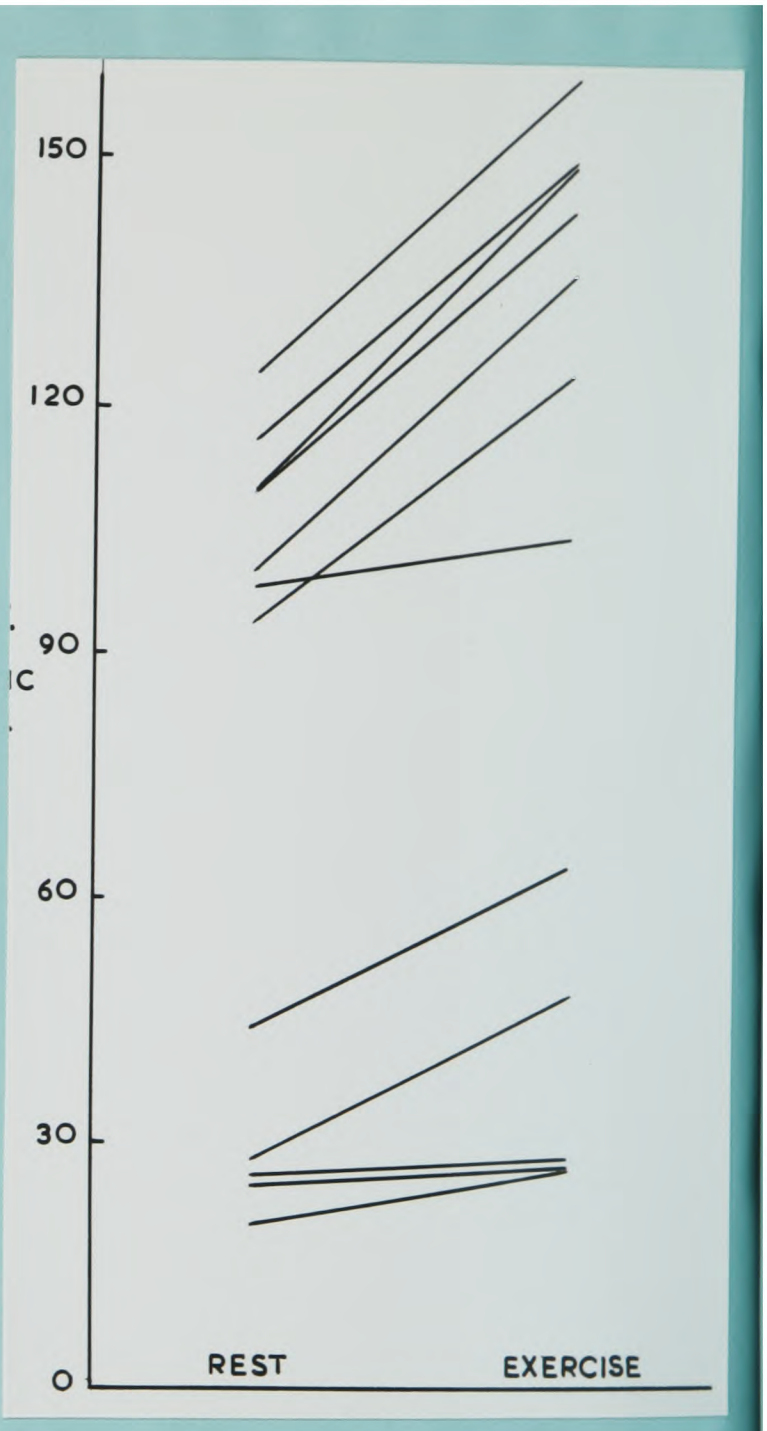


Fig. 4i Changes in pulmonary arterial systolic pressure on exercise. It is seen that both in A. S. D. (left) and in V. S. D. and P. D. A. (right) a high resting pressure tends to be associated with a considerable rise with effort.

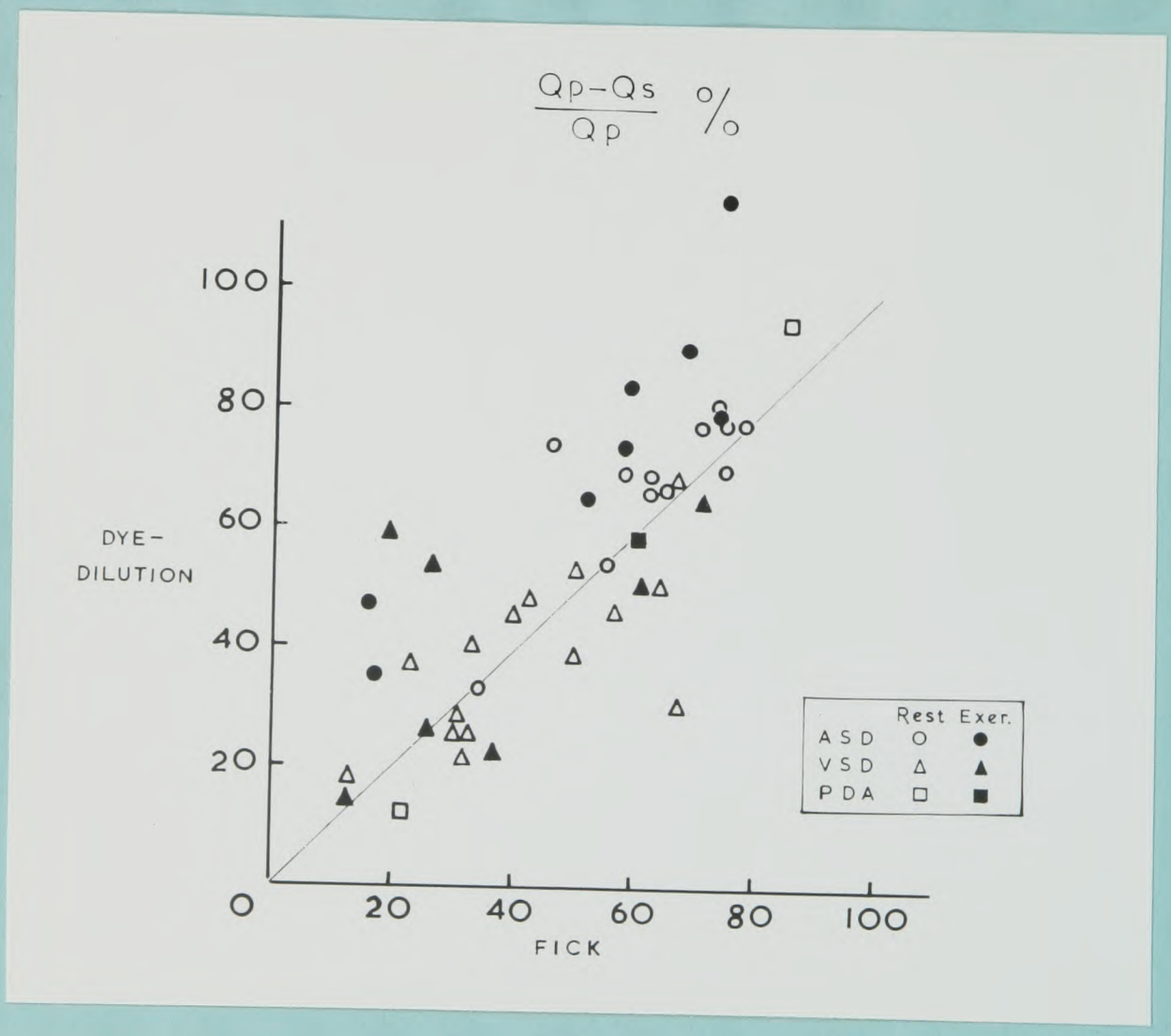


Fig. 4j **Comparison between Fick and dye-dilution determinations** of the ratio of left-to-right shunt to pulmonary flow, at rest **and on exercise.** The dye-dilution calculations give on the whole **higher results than the Fick estimation, especially in A.S.D. on exercise.** This is likely to be due to an over-estimation of exercising **systemic flow in that group, the arterio-venous oxygen difference being probably greater than that calculated from the mean of 2 I.V.C. and 1 S.V.C. values.**

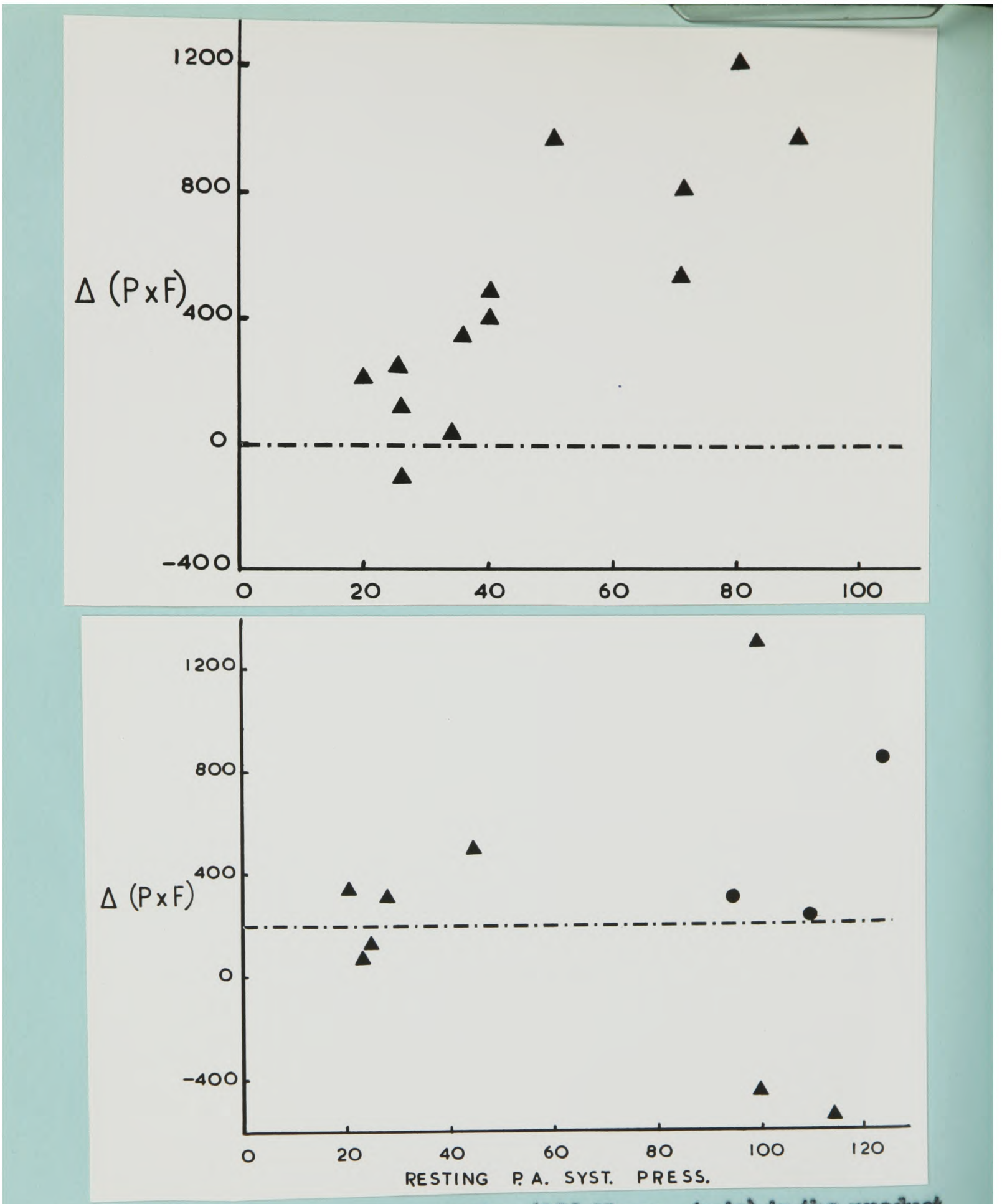


Fig. 4k The increase on exercise (200 Kg. m. /min) in the product of mean pulmonary arterial pressure and pulmonary index in relation to the resting pulmonary arterial systolic pressure.
Above: A.S.D. Relationship highly significant ($r = 0.863$, p .001)
Below: V.S.D. (triangles) and P.D.A. (circles). No relationship is seen.

tendency to rise with effort. This applies to A.S.D. (Fig. 4i (i)) and V.S.D. and P.D.A. (Fig. 4i (ii)).

Dye dilution studies

Table XII shows the left-to-right shunt expressed as a percentage of the pulmonary flow by both Fick and dye-curve calculations, and in Fig. 4j the relationship between the results by the two methods, at rest and on exercise, is expressed. As expected, the correlation is only a rough one, but in general the same pattern of change is observed. The purpose of using the dye-curves was to confirm or refute the conclusions from the Fick determinations. In cases AH 40, AH 45 and VH 32, where we observed a marked increase in pulmonary flow and left-to-right shunt, the dye-curves were confirmatory. In cases AH 4, VH 33 and PH 30, where a marked decrease in those parameters was seen, the dye-curves were also confirmatory of the pattern of change. In a few cases, Fick and dye estimations were contradictory, e.g. cases AN 1 and VN 4. In the former the unusually high systemic flow on exercise suggests that the error lay here.

The product of pulmonary arterial pressure and pulmonary flow has been found to be related to the compliance, and it has therefore been of some interest to examine the changes with exercise in this product. The results in A.S.D. (excluding the Eisenmenger syndrome) are shown in Fig. 4k, and it is evident that the patients with the higher resting pressures show the greater increase in the product P x F on exercise. This relationship is highly significant in A.S.D. ($p < .001$), but not in V.S.D. and P.D.A.

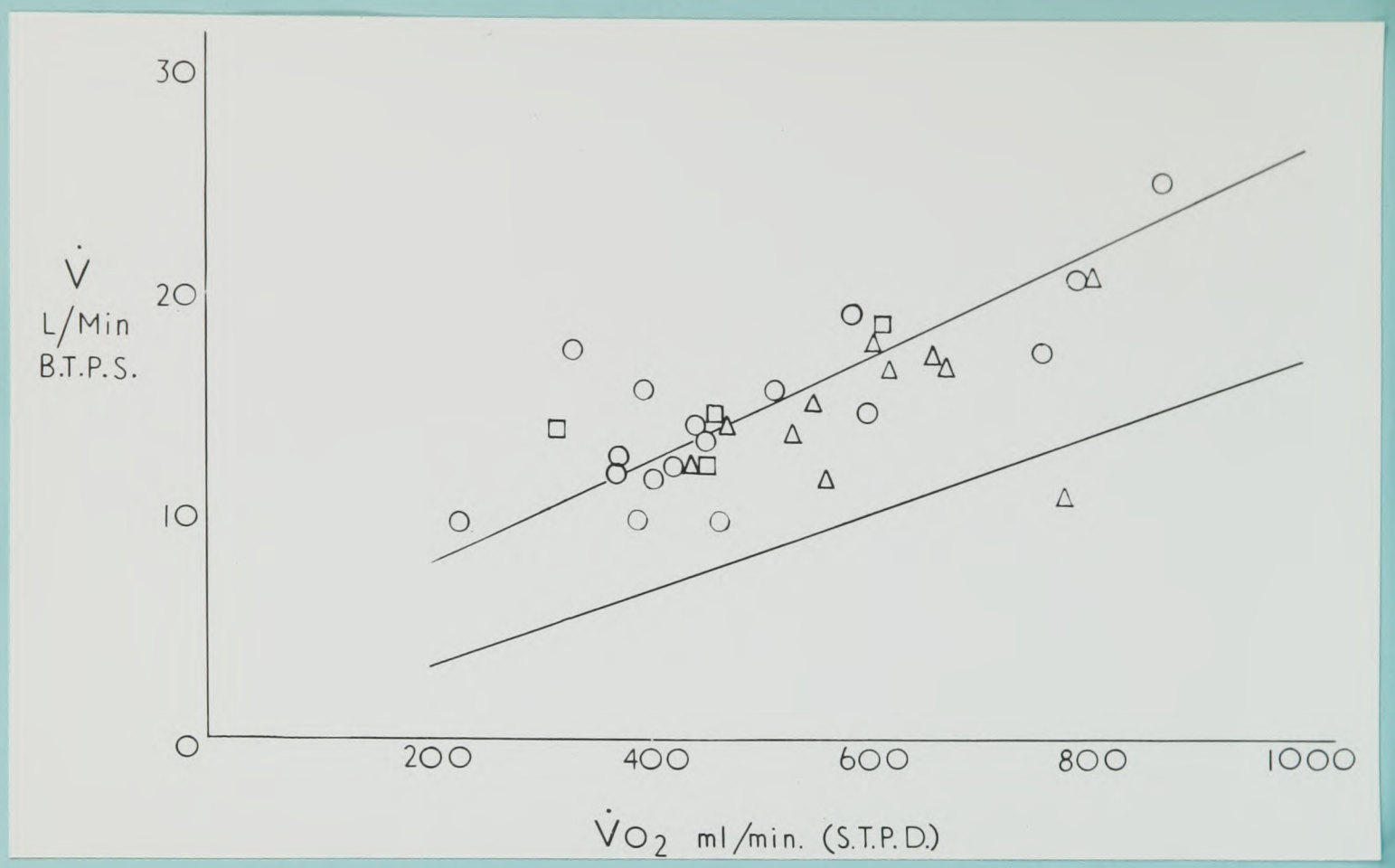


Fig. 5a **Ventilation and oxygen uptake during exercise in the supine position at cardiac catheterisation. The normal limits are shown. (Symbols as in Fig. 4).**

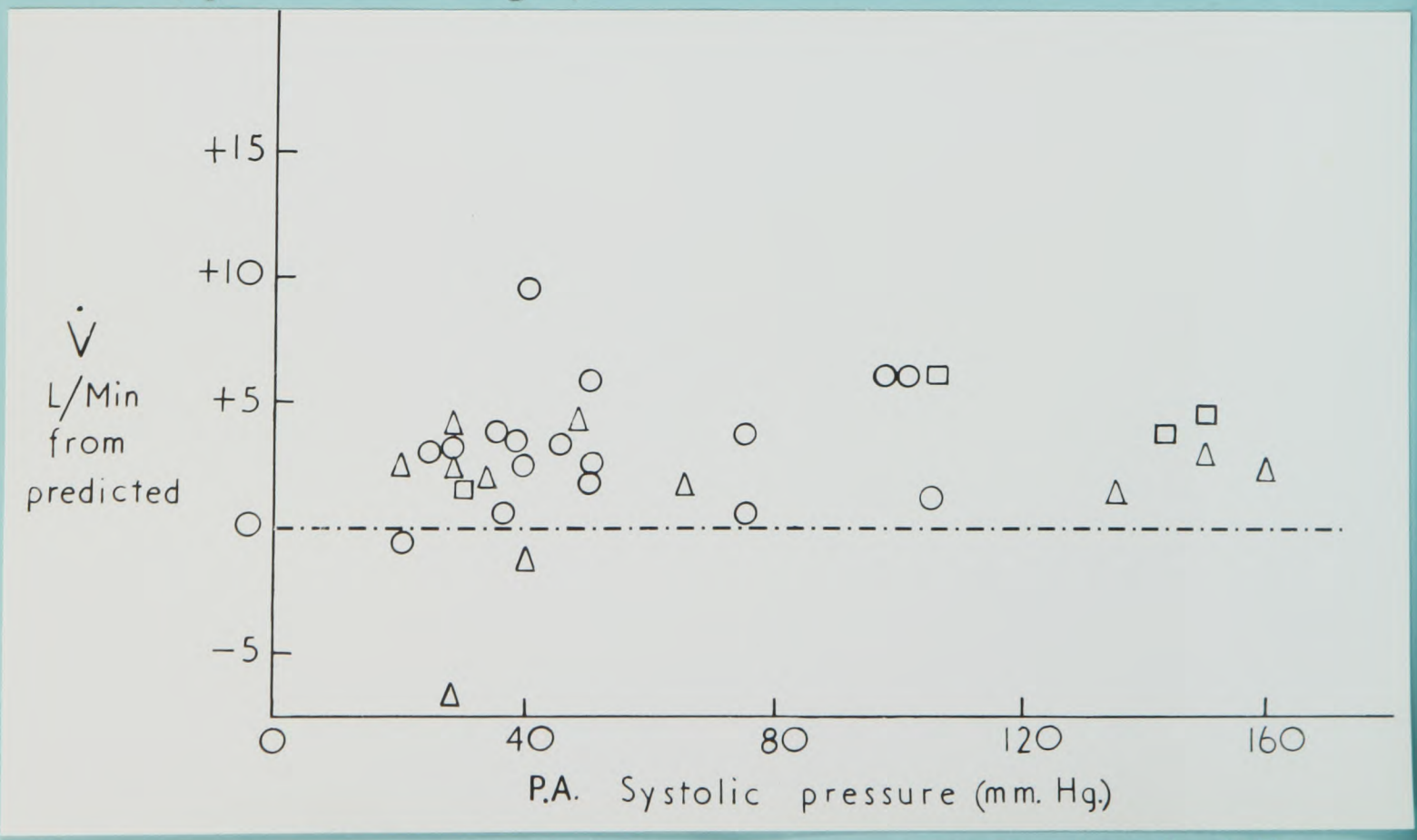


Fig. 5b **Ventilation during supine exercise, expressed as deviation from the mean predicted normal for the given oxygen uptake, in relation to P.A. systolic pressure.**

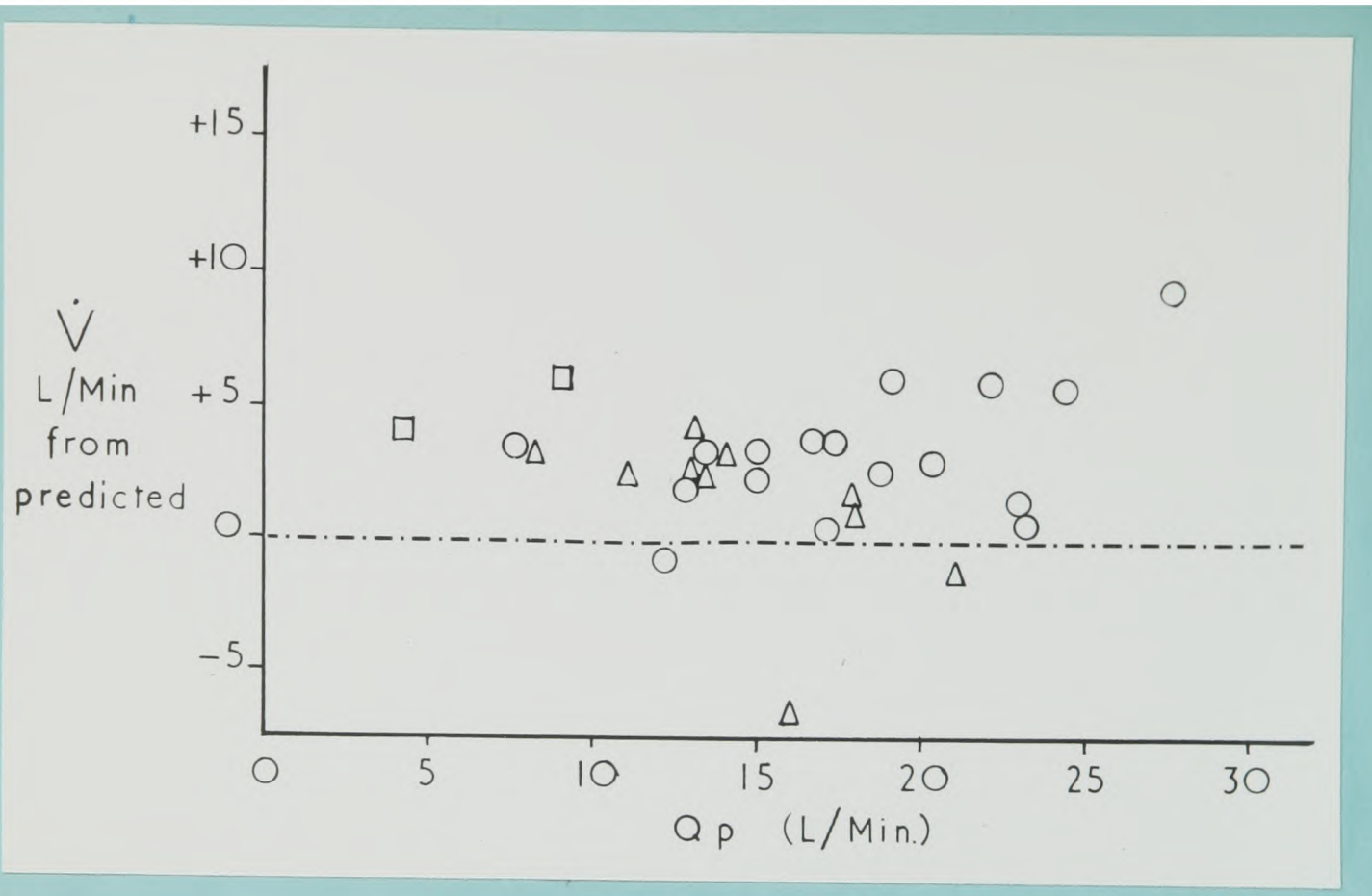


Fig. 5c Excess ventilation and pulmonary flow.

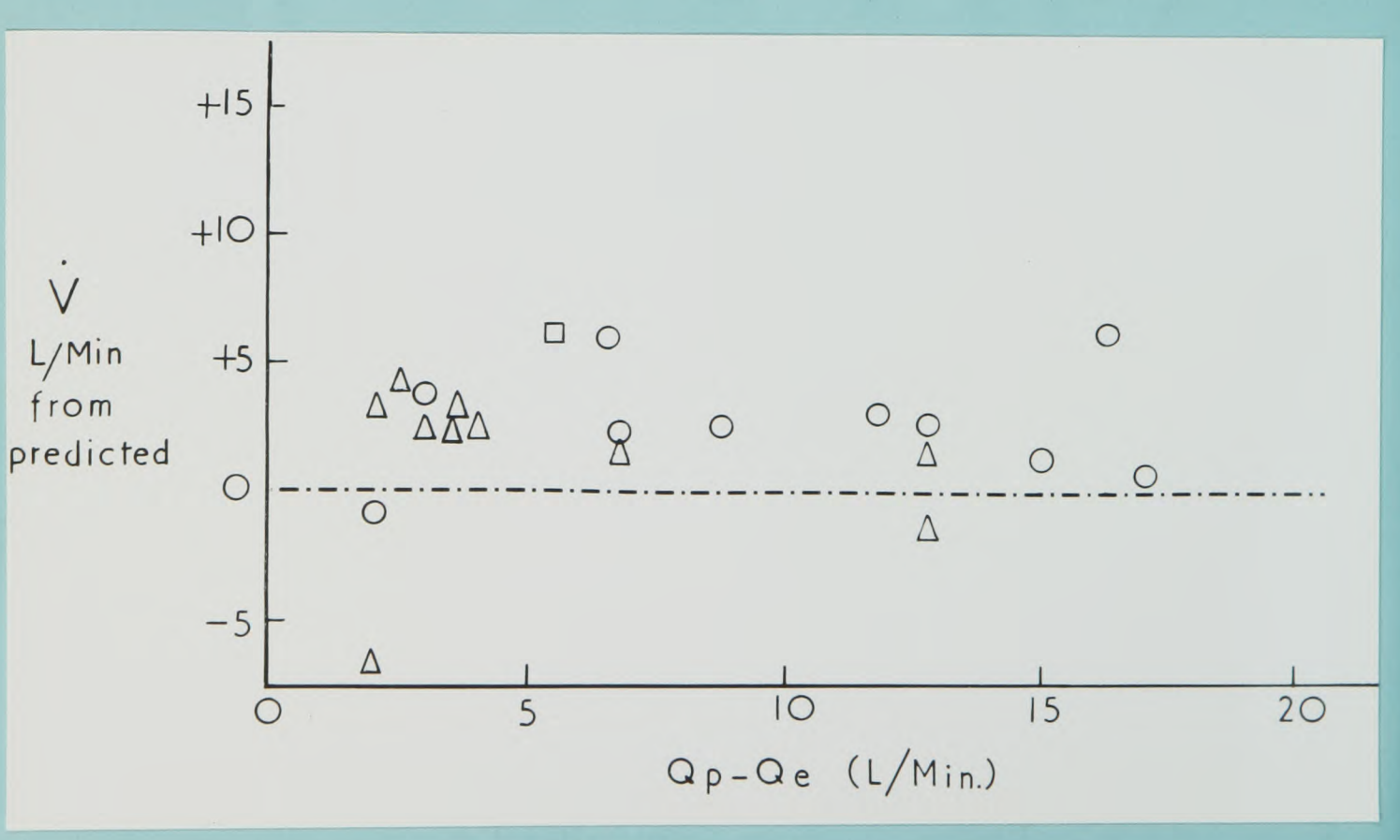


Fig. 5d Excess ventilation and left-to-right shunt.

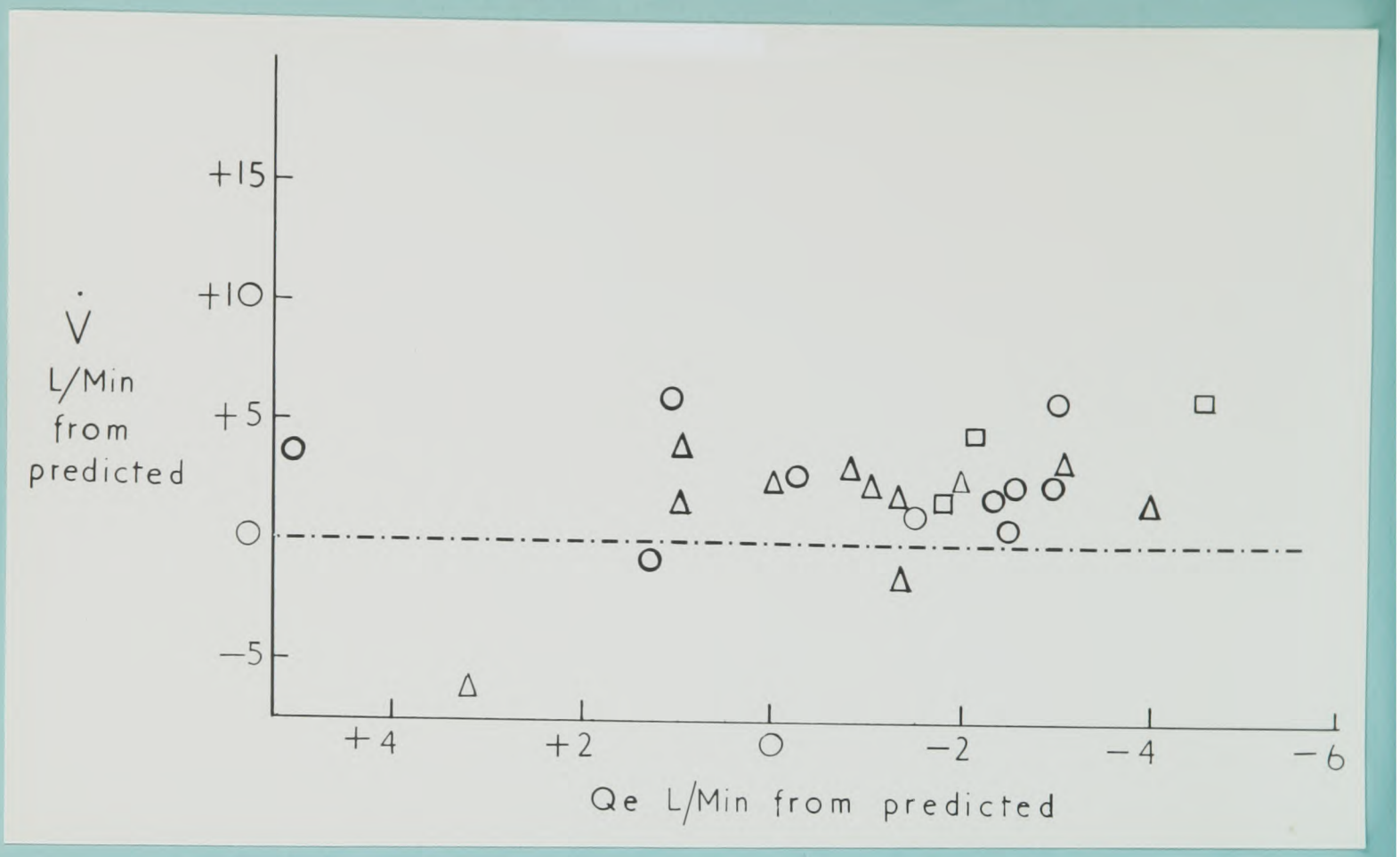


Fig. 5e **Excess ventilation in relation to the degree of impairment of cardiac output, expressed as deviation from the mean predicted for the given oxygen uptake.**

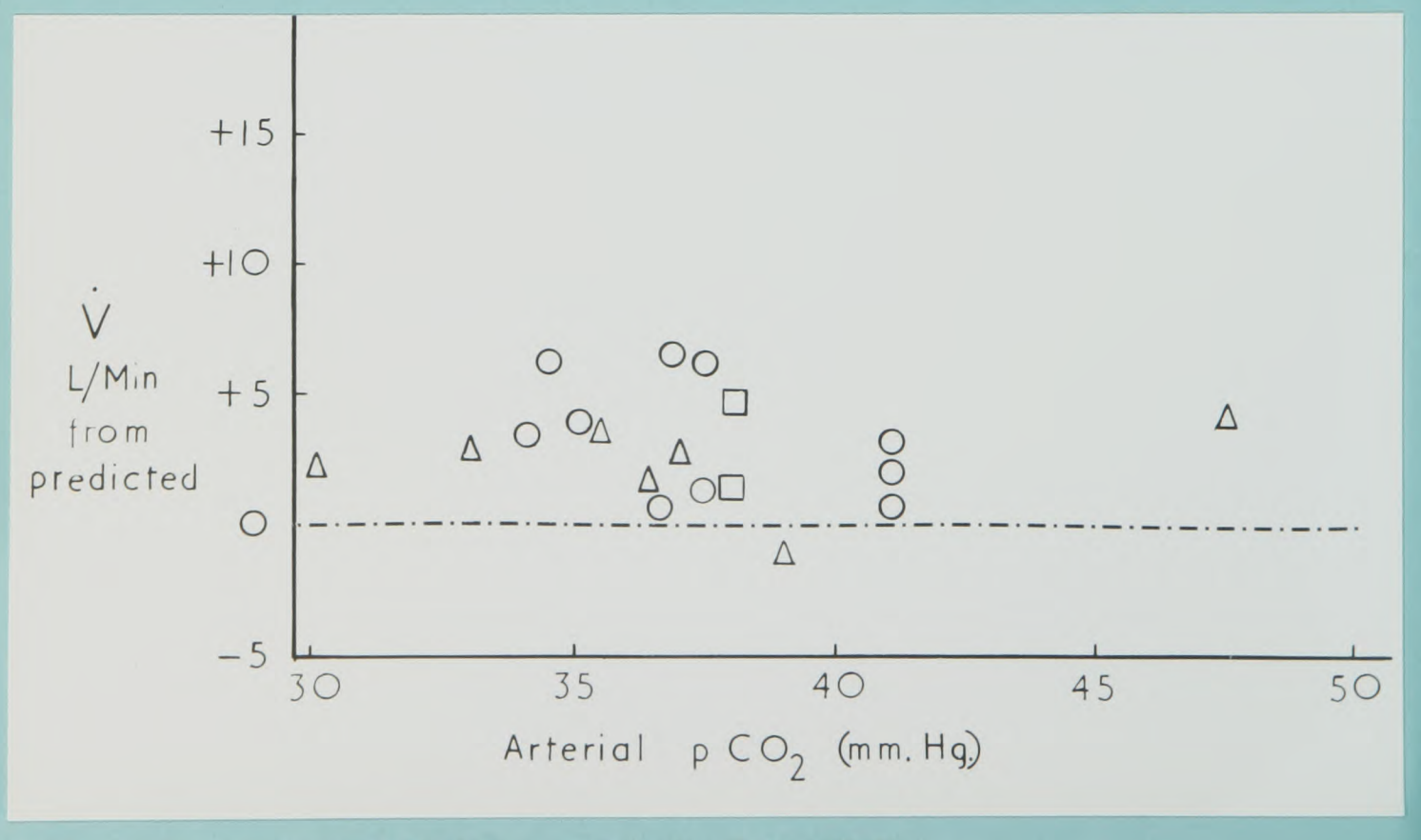


Fig. 5f **Excess ventilation and arterial PCO_2.**

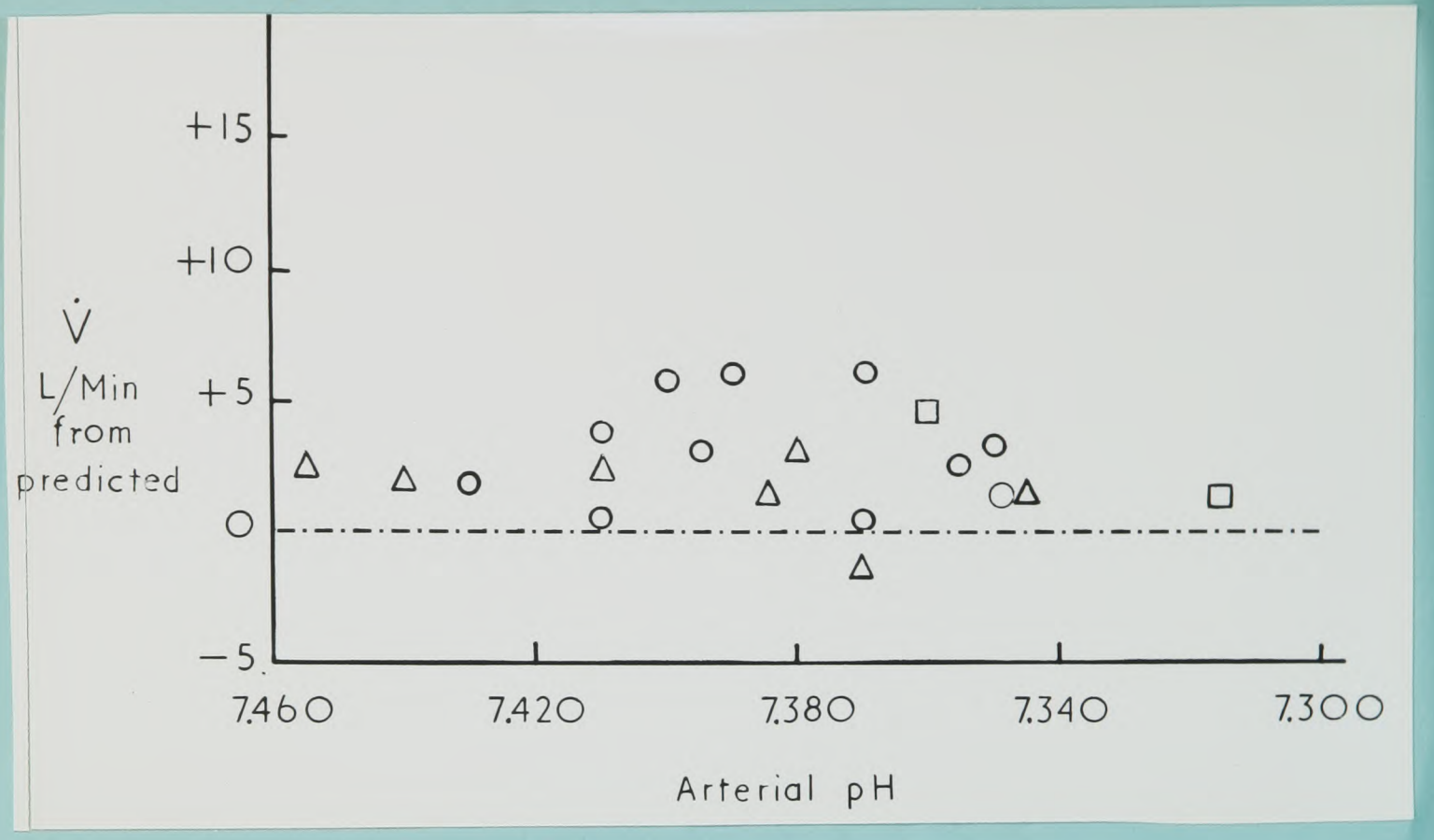


Fig. 5g Excess ventilation and arterial pH.

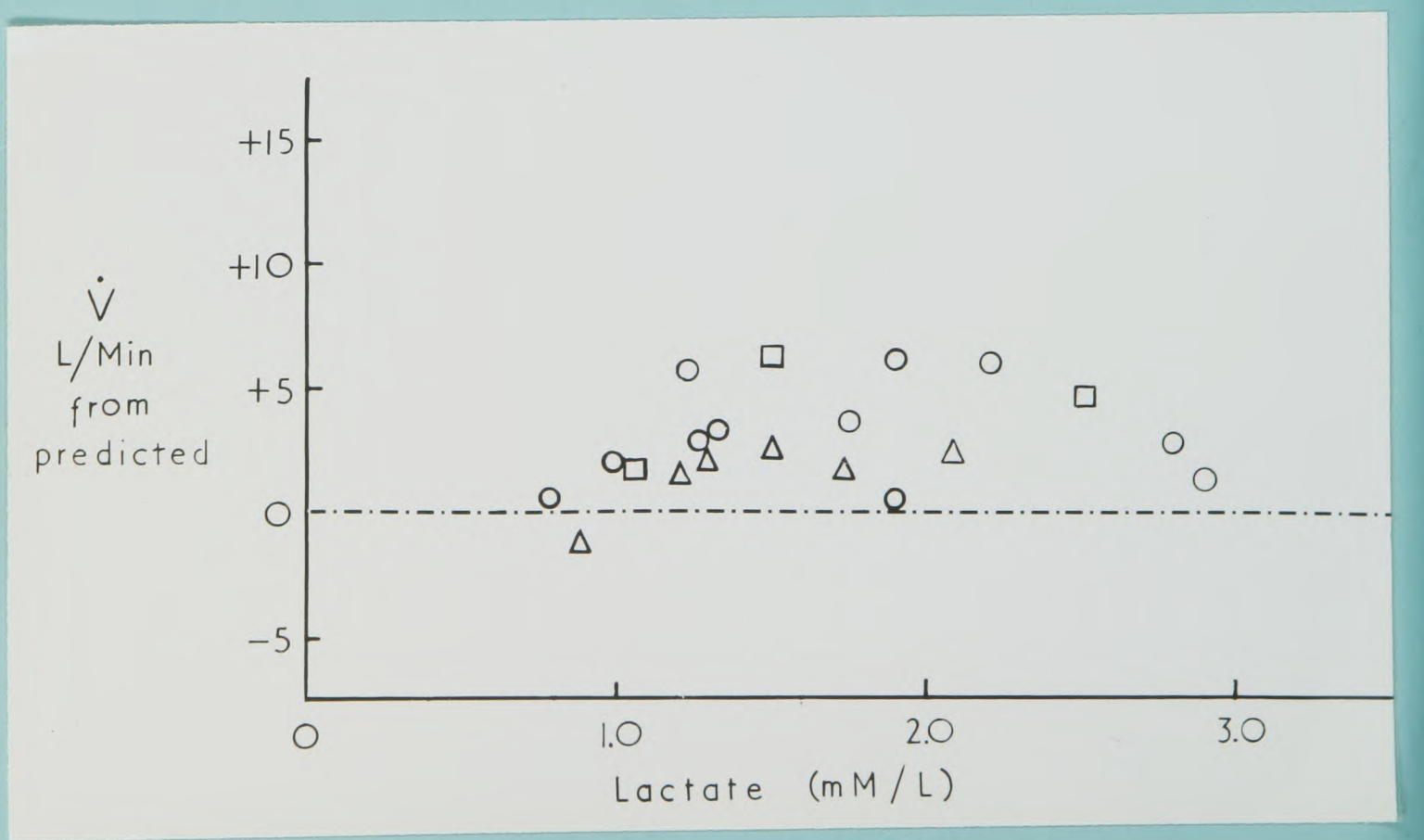


Fig. 5h Excess ventilation and arterial lactate.

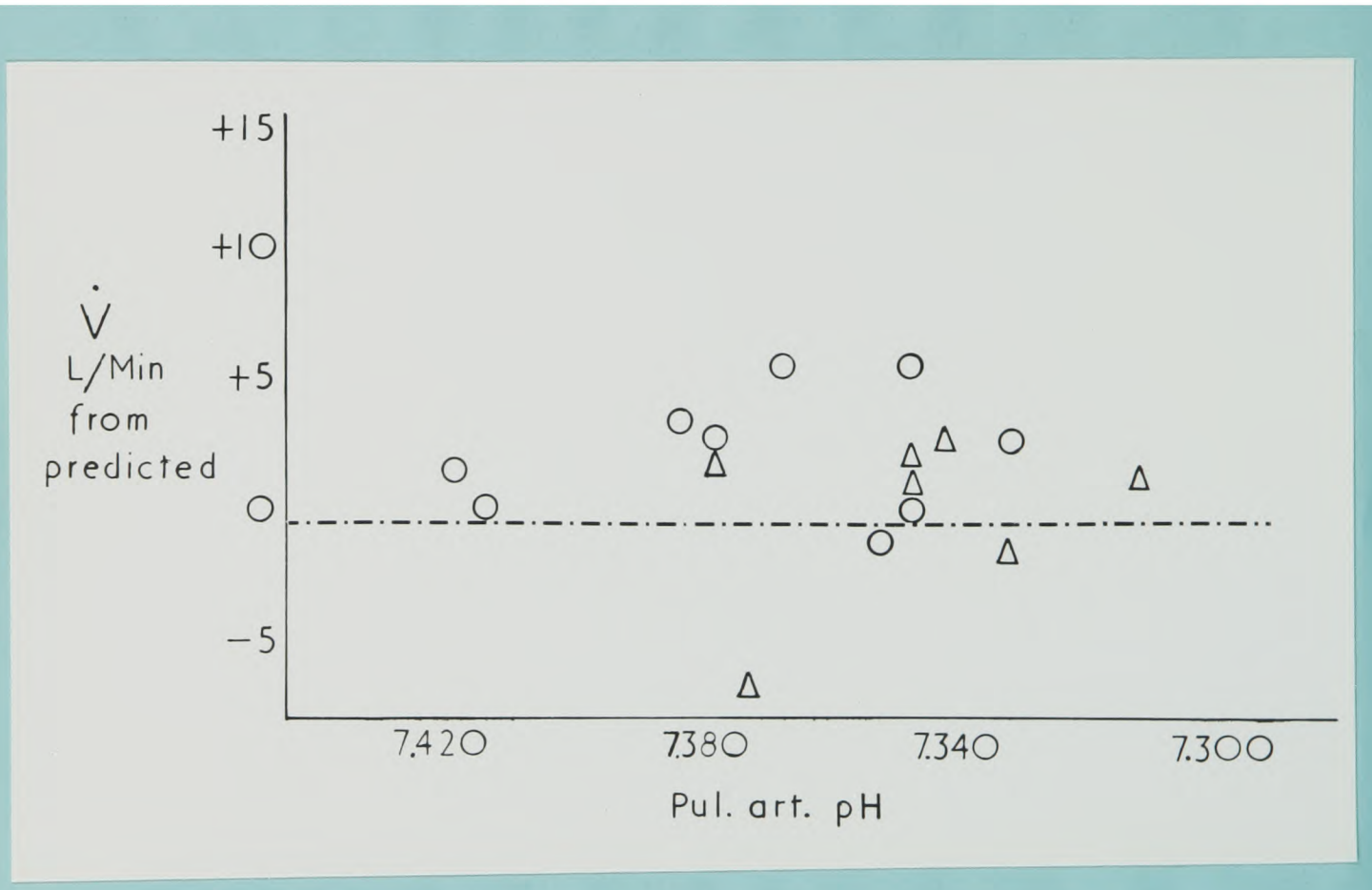


Fig. 5i **Excess ventilation and pulmonary arterial pH.**

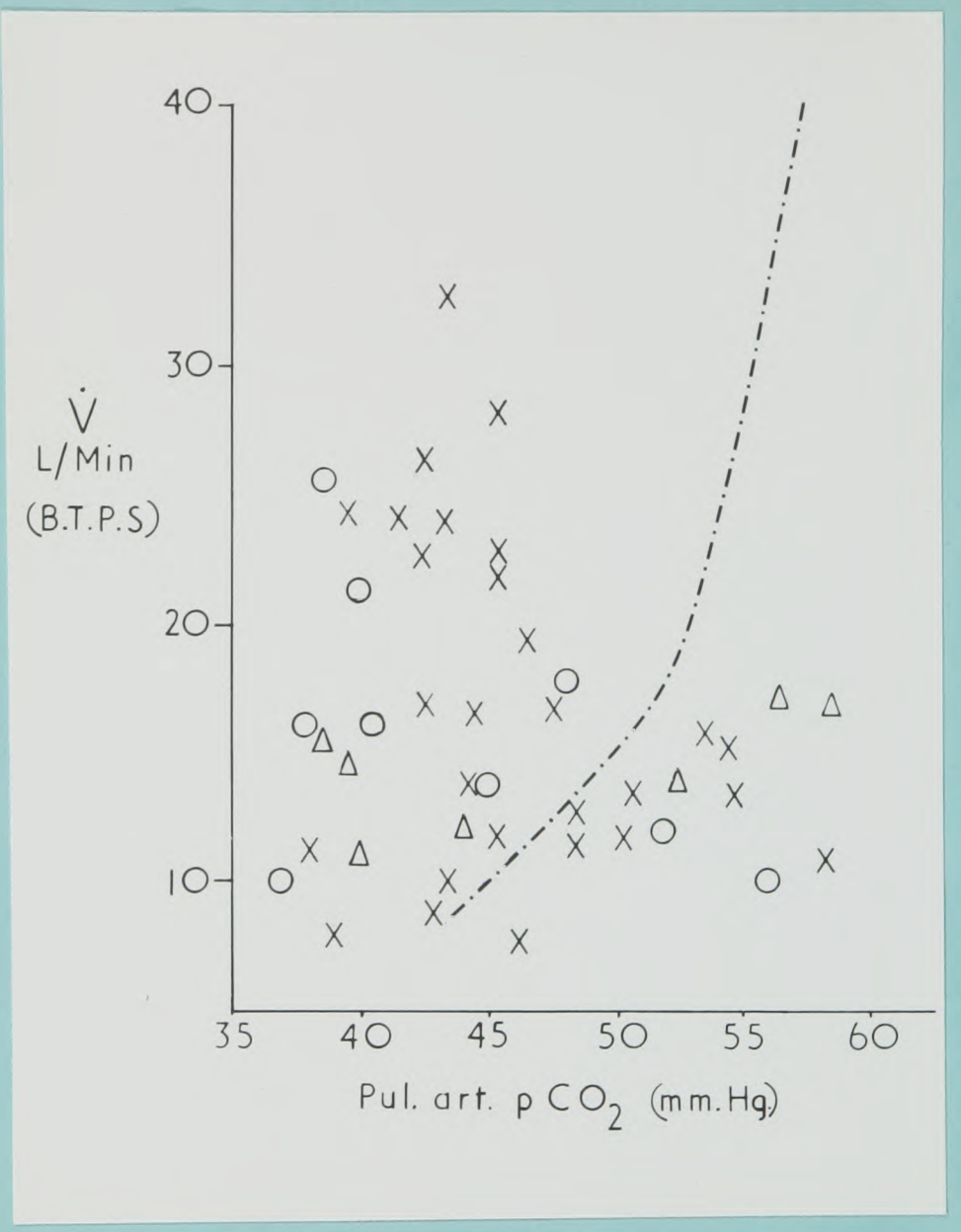


Fig. 5j Ventilation and pulmonary arterial PCO_2. Xs represent patients without septal defects (Gazetopoulos et al. 1965a). Otherwise, symbols as above. The broken line represents the normal $\dot{V}$ - mixed venous PCO_2 relationship from Riley et al. (1963). High ventilation is associated with lower values of PCO_2.

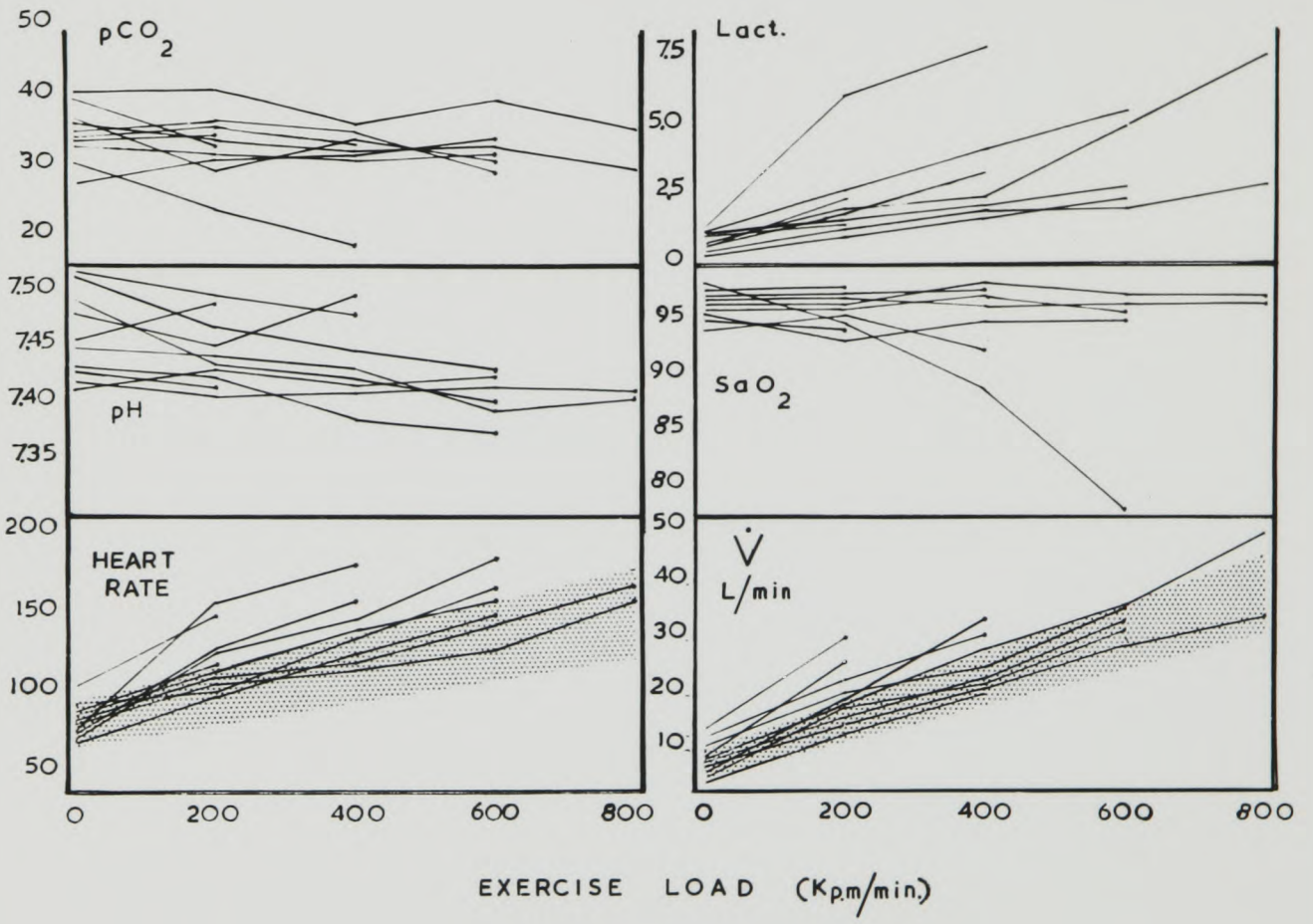


Fig. 5k Ventilation, heart-rate and blood chemistry during exercise in the upright position with stepwise increase in load. The normal ranges are shown by the shaded areas. Excessive ventilation is often seen, and the blood chemistry changes as a result of this.

Ventilation and Blood Chemistry

Mild supine exercise

Table XIII shows the ventilatory response at rest and on exercise in the supine position, and Table XIV the arterial and venous blood chemistry (both in Appendix).

Fig. 5a relates the ventilation to the oxygen consumption, the limits of normality being taken from the literature and our data from this laboratory. It is seen that the ventilation was excessive in most patients. Three showed slight arterial desaturation on effort due to an associated small right-to-left shunt; their ventilatory response did not seem to be unusual on this account.

Figs. 5b, c and d, show the deviation of ventilation from the mean normal for the given oxygen uptake plotted against the pulmonary arterial pressure, the pulmonary flow, and the left-to-right shunt. Fig. 5e illustrates the deviation of exercise ventilation from normal in relation to the degree of impairment of cardiac output (i.e. deviation from the mean predicted value for the given oxygen uptake). No clear relationship can be discerned between ventilation and any single haemodynamic parameter; the same applies to pulmonary vascular resistance and the próduct of pulmonary arterial pressure and pulmonary flow.

Figs. 5f and g, show the arterial pCO_2 and pH, measured in the second half of exercise, plotted against the excess ventilation. A number of patients is seen to be hypocapnic, in accordance with their tendency to hyperventilate. Despite this, the pH fell in most cases as a consequence of lactic acidaemia. Fig. 5h relates the arterial lactate concentration to the excess ventilation; there is some suggestion that the patients with the higher lactates tend to have the greater ventilation, but the relationship is not significant ($p > 0.1$).

Figs. 5i and j, illustrate the changes in blood gases on the venous side of the circulation. It appears that neither the venous nor the arterial blood chemistry varies in such a manner as to exert an influence on the ventilation, rather do their changes seem to be consequent on the ventilation.

Upright exercise

Table XV gives the findings in subjects exercised in the upright position with stepwise increases in load. Fig. 5k illustrates the changes in the main parameters studied; in the lower part the ventilation and heart-rate in the steady-state are shown, and above them the pH, pCO_2, oxygen saturation and lactate concentration at the end of each 10-minute period.

Four of the patients (cases AN 5, AH 39, AH 45 and VH 34) were able to exercise only at lower levels (200 - 400 Kpm./min.), and in all these dyspnoea was the limiting factor. Ventilation was excessive, and the blood chemistry again showed changes consequent on hyperventilation. In two of them (cases AH 45 and VH 34), elevated pulmonary venous pressure could have been a stimulus to ventilation,

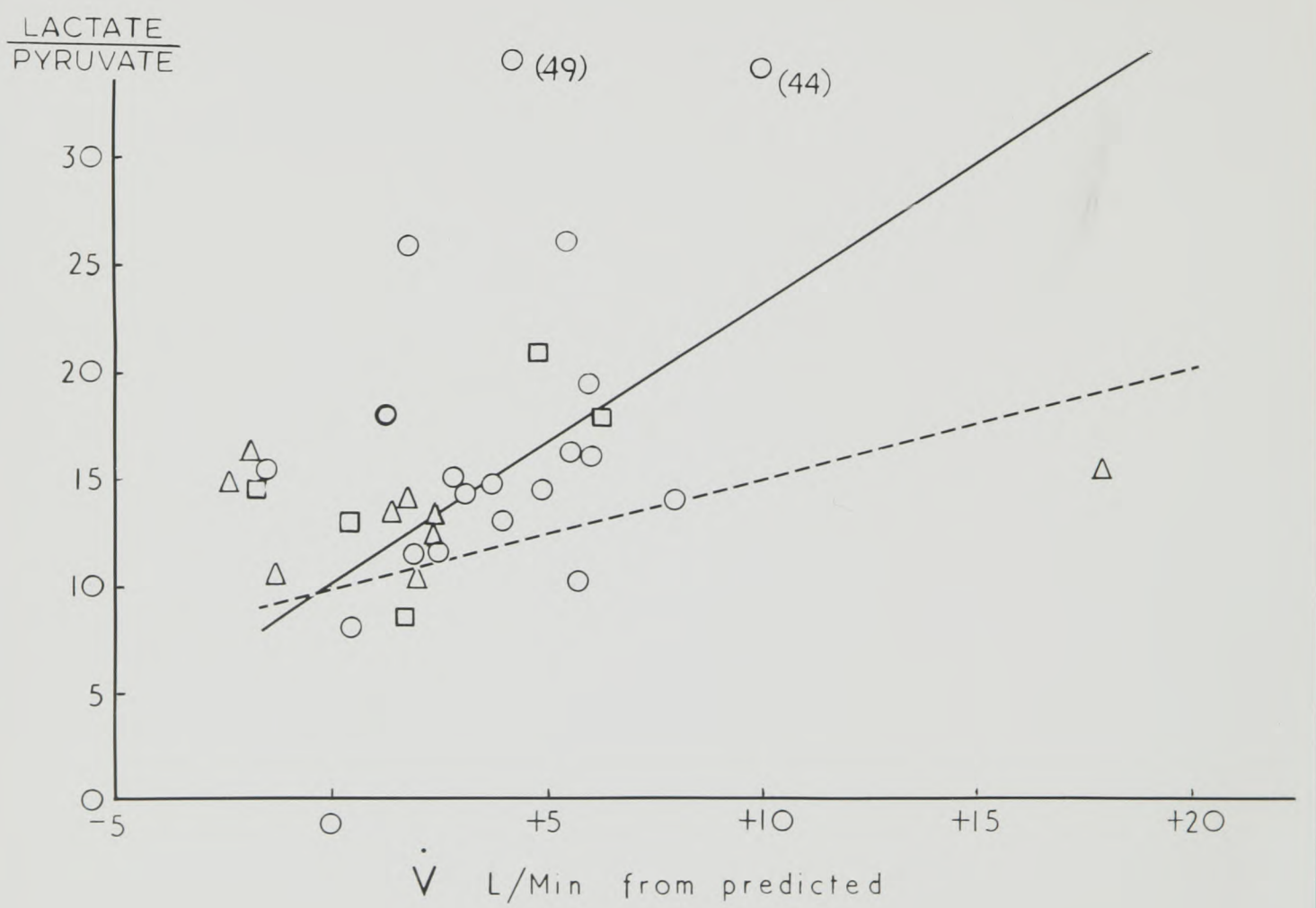


Fig. 51 **Lactate/pyruvate ratio and excess ventilation in all patients with oxygen uptakes below 1200 ml./min.**

but in the other two it was normal (it is of interest that both these patients - AN 5 and AH 39 - showed severe respiratory embarrassment after surgery, as a result of which they died).

The other patients were able to reach higher exercise loads and, in some, fatigue rather than dyspnoea appeared to be the limiting factor. A few patients with high pulmonary arterial pressure and increased pulmonary blood flow were able to reach moderate exercise loads (600 Kpm./min.) without impressive hyperventilation.

The arterial lactate concentration was excessive in some patients, as were the lactate/pyruvate ratios. In Fig. 51 the latter have been plotted against the excess ventilation in all patients, both in the supine and upright positions. For comparison the mean response of patients with pulmonary valve stenosis (solid line) and mitral stenosis (broken line) have been included; (details of the latter are not included in the thesis). Patients with left-to-right shunts show a variable response, but most cases behave in a manner similar to pulmonary stenosis, indicating that impaired cardiac output is probably playing a part in the ventilatory response.

DISCUSSION

The difficulties inherent in performing accurate measurements of flow and vascular resistance in patients with left-to-right shunts are well known. When the pulmonary arterial oxygen saturation is high and the pulmonary arterio-venous difference is low, small errors in measurement lead to large errors in calculated flow by the Fick principle. To obtain a truly mixed venous sample in atrial septal defect is virtually impossible, since the inferior vena caval blood itself is far from well-mixed at any site near the heart, and the proportions of inferior and superior caval flows can only be guessed at. In this study, 1/3 (2 I.V.C. + 1 S.V.C) has been taken as a rough approximation. Furthermore, early recirculation on the dye-curves often makes it impossible to separate the secondary curve from the primary systemic circulation. For these reasons the data must be interpreted according to the merits or demerits of the methodology, and it was hoped that measurements by both techniques would yield more representative results.

Current opinion appears to be that where there is a left-to-right shunt, exercise diminishes its magnitude. However, there are certain a priori reasons why this should not always be so, and particularly why the effect may not be the same in different types of lesions.

In trying to anticipate the results of exercise, the following line of reasoning may be followed; the factors which might be expected to influence the amount of shunting are -

(a) The pressures in the chambers of the heart and in the great vessels

(b) The resistances of the pulmonary and systemic circuits

(c) The rate of the heart, and the stroke output of the ventricles

(d) The filling resistances of the two ventricles

(e) Whether the shunt is systolic, diastolic, or both.

If these variables are known, it should be possible to predict broadly the effect of exercise on the shunts.

Ventricular Septal Defect

Here several possibilities exist, each presenting its own problem. First, the small defect, which carries inevitably a left-to-right shunt since the right ventricular pressure is always low. Second, the medium-sized defect with a left-to-right shunt and moderate elevation of the pulmonary artery pressure. Third, the large defect with systemic pressure in the right ventricle, but a dominantly left-to-right shunt, the pulmonary vascular resistance being well below the systemic. Fourth, the large defect with a balanced shunt, the pulmonary vascular resistance being of the same order as the systemic resistance. Fifth, the V.S.D. associated with pulmonary stenosis.

In the first and second groups, the main resistance to left-to-right shunting is at the site of the defect, in the third and fourth groups it is in the vessels of the lung, and in the fifth it is at the site of the right ventricular outflow obstruction. In the first, second, fourth and fifth groups this resistance is virtually fixed in magnitude, whilst in the third a change of resistance in pulmonary vessels lends a potential for variation.

By making an abstraction, it is possible to ascribe a resistance in units to the smaller defects which enables us to compare it with the systemic resistance. The flow from left ventricle, assuming this to be entirely systolic, would pass through the defect or through the aortic valve in inverse ratio to the respective resistances. A simple example serves to illustrate the changes expected. If the systolic flow is 6 L/min. and the pulmonary flow 9 L/min, the left-to-right shunt is 3 L/min. The left ventricular output is thus distributed in the ratio 2 : 1 between aorta and V. S. D, the resistance of the defect being then 32 units. If on effort the systemic blood pressure remains the same, but the flow doubles, the systemic vascular resistance will halve to 8 units, and since the V. S. D. resistance remains constant at 32 units, the shunt will be one-quarter of the systemic flow - again 3 L/min. So long as the systemic pressure remains the same, therefore, the shunt will be constant. Any increase in systemic pressure associated with exercise will thus lead to an increase in the absolute volume of shunt and, as is seen to be so in Fig. 4a (i), this is what happens. In symbolic terms, Q_S is the systemic flow, R_S systemic resistance, S the shunt,

r the defect resistance, and P_S the mean systemic pressure -

$$S = Q_S \quad \frac{R_S}{r}$$

$$\text{Since } Q_S = \frac{P_S}{R_S} \qquad S = \frac{P_S}{r}$$

Since r is fixed, S will be constant for constant P_S and will increase with rising P_S.

This reasoning may be expected to apply to Groups I and II, and to Groups IV and V when the right-sided resistance is high and constant. Effort will then increase the absolute amount of left-to-right shunt, whilst diminishing its proportion to systemic flow. It will of course not apply if the size of the defect diminishes with contraction of the heart or if the right ventricular outflow obstruction is variable.

If the right-sided resistance is low but the defect large, as in hyperkinetic pulmonary hypertension, the bulk of the right-sided resistance lies at pulmonary vascular level and is usually of the order of 5 - 8 units. Increase of left ventricular output, again distributed in inverse ratio to the respective circuit resistances, will pass preferentially through the defect, since at all time the right-sided resistance is lower than the systemic. Furthermore, the ratio of shunt to systemic flow will increase in this group. That this can happen in fact is seen from the response of Case VH 32.

It is appreciated that this over-simplified line of reasoning cannot be expected accurately to fit all the facts, but at least gives ground

for the feeling that an increase in left-to-right shunt might occur with exercise in V.S.D. Any increase in pulmonary vascular resistance with exercise will, however, minimise this tendency and it is of some interest that the only two patients in this group who showed a decrease in left-to-right shunt had also an elevated left atrial pressure. One of these two (case VH 33) had clinical signs suggestive of coexistent mitral stenosis. Whether or not in these two cases there was an element of reactive pulmonary hypertension secondary to a raised left atrial pressure is not known, but it remains a possibility to account for their anomalous behaviour. The same would obtain in any other situation where there is impairment of filling of the left ventricle. Similar principles must apply in P.D.A.

Atrial Septal Defect

The situation is essentially different from that of V.S.D. since the communication is between the two low pressure chambers. It is likely that much of the shunt occurs in diastole, as evidenced by the diastolic flow murmur which is a constant feature of those cases with a large shunt. It would seem probable therefore that one of the main factors promoting a shunt is the sucking effect of the right ventricle in diastole rather than the positive driving force of the increased left atrial pressure. The diastolic volume of the right ventricle, when there is a shunt, is very large indeed, and this suction must exist if the ventricle is to expand in diastole. Its place in the haemodynamic control in A.S.D. cannot well be denied if nature is to continue to abhor a vacuum.

The bulk of the flow through the tricuspid valve takes place in early diastole (Wiggers, 1950; Rushmer, 1961) and it is possible that

tachycardia, by increasing the total diastolic time of rapid filling, could augment the total minute volume of the shunt rather than diminish it. The lowering of left atrial pressure in response to a fall in systemic vascular resistance has been documented by Berglund (1955). This effect would be unlikely to play a major part in reducing the shunt on exercise in A. S. D. and a case can thus be made for expecting the shunt to increase rather than decrease with effort, particularly if there is coexisting mitral stenosis (case AH 45) or increased resistance to left ventricular filling; dysfunction of the left ventricle in A. S. D. has been discussed by Dexter (1956) and Davidsen (1960).

Several studies have been reported in the literature of the haemodynamics at rest and on exercise in patients with left-to-right shunts. Brotmacher and Deuchar (1956) and Weidman et al. (1957) have shown, usually in young patients, a normal resting systemic output in the absence of cardiac failure. However, impairment of cardiac output is seen in older patients with large shunts (Kjellberg et al. 1959). Scébat et al. (1957) confirmed these findings in 63 cases of A. S. D, 27 of V. S. D. and 52 of P. D. A. and presented exercise data in 14 of A. S. D, 3 of V. S. D. and 4 of P. D. A, all with low pulmonary vascular resistance. In A. S. D, the mean systemic index increased from 3.72 to 9.42 L/min./sq. m, whilst the left-to-right shunt decreased in all cases, the mean values at rest and on exercise being 8.6 and 3.8 L/min./sq. m. In three cases of V. S. D. the mean systemic index increased from 4.69 to 6.52 L/min./sq. m, and the left-to-right shunt decreased in two cases and was unchanged in the third. In three cases

of P.D.A, the systemic index increased from 5.24 to 7.95 L/min./sq. m; the left-to-right shunt increased in two cases and decreased in the other one. These authors concluded that the rise of systemic flow on effort was normal, and suggested that the important factor determining the magnitude of shunts between the two circulations is the lateral pressure at right-angles to the main direction of the blood stream; since the increase in speed of flow of the systemic circuit is greater than that of the pulmonary circuit the tendency to left-to-right shunting will be less. This would appear to be a rather dubious concept, particularly where the communication is at atrial level and the shunt does not depend primarily on the pressure gradient between the atria; also where it is at ventricular level and anatomic considerations would seem to dominate. The total abolition of large shunts on exercise in two of the patients with A.S.D. in Scébat et al. 's series, and the findings of a higher-than-normal systemic output in this condition make the conclusions acceptable with some difficulty.

Jönsson et al. (1957), studying patients with A.S.D, concluded that the pulmonary flow increased with stepwise increase of exercise load in such a fashion that the shunt remained unchanged or decreased somewhat. Plotting their data in our Fig.4f and supposing with them a normal slope of increase of systemic flow, a small overall increase in left-to-right shunt would be apparent rather than a decrease, though we have not comparable data at maximal exercise levels.

Swan et al. (1957) studied the haemodynamics during supine exercise in 30 patients with septal defects. Their data show that there were nine patients in the Eisenmenger category; in these the pulmonary flow remained essentially unchanged, whilst the increase in systemic flow was less than normal. Where the pulmonary artery pressure was low, the pulmonary flow behaved in a manner similar to that of our cases, i.e. some overall increase, while there was a small rise in the magnitude of the left-to-right shunt with exercise in the six cases where this could be calculated. In eight patients with hyperkinetic pulmonary hypertension, the pulmonary flow increased little in six patients with V.S.D. and P.D.A, whilst in two with A.S.D. there was a greater increase. The left-to-right shunt in the three cases of P.D.A. and two of V.S.D. showed some decrease. These authors conclude that patients with large left-to-right shunts may show little change in pulmonary vascular dynamics with effort, no further stress thus being thrown on the over-burdened pulmonary circulation. This conclusion is not confirmed when applied to the group of cases with A.S.D. and hyperkinetic pulmonary hypertension.

Bruce and John (1957) studied patients with A.S.D, V.S.D and P.D.A. at rest and on exercise in the upright position, measuring only the pulmonary flow. They found a larger increase in this than the anticipated rise of systemic flow, indicating an increased left-to-right shunt with effort. These authors conclude that the upright posture explained their differences from Swan et al. (1957).

Stephens et al. (1964) described the effects of exercise in the upright position in patients with left-to-right shunts. Eight had V.S.D. and

one P.D.A. Five cases (C1 - C5) had normal pulmonary artery pressure and pulmonary vascular resistance; in three of these the systemic flow increased normally, the pulmonary flow increased to a lesser degree, and the absolute volume of the left-to-right shunt diminished. In one other (case C4) the increase of systemic flow was less, whilst the pulmonary flow and left-to-right shunt increased markedly; in case C5 there was a small increase in left-to-right shunt, both pulmonary and systemic flow increasing together. Case C6 had moderate pulmonary hypertension, but a small shunt which increased a little on exercise. Case C7 was the only one with truly hyperkinetic pulmonary hypertension and here the pulmonary flow diminished in the face of a normal increase of systemic flow with virtual abolition of the left-to-right shunt (this patient had the highest wedge pressure). In the last two cases with the Eisenmenger complex there was a small increase in systemic flow, a small increase in pulmonary flow, and there was little change in the left-to-right shunt. In the last four cases a significant right-to-left shunt appeared. Again, the increase of pulmonary artery pressure was greater in those cases where it was already elevated.

The lack of uniformity of data reflects in large part the difficulties of accurate measurement of flow and pressure. The previous impressions that the economy of the pulmonary circulation was protected in the presence of large shunts by lack of further change on exercise has not been borne out by these studies, especially where atrial septal defect is associated with hyperkinetic pulmonary hypertension. This situation is most commonly found in older patients,

and we have been impressed with the considerable rise that can occur in the pulmonary flow with effort in such patients, associated with a significant increase in the pulmonary artery pressure. This may be linked to their increased dyspnoea on effort via the changes in compliance, as already discussed, but other factors such as lung damage and impairment of systemic flow also operate in this group.

In V.S.D. and P.D.A, with the exception of case VH 32 who showed a marked rise in left-to-right shunt and pulmonary blood flow on exercise, the impression has been that the same tendency has not been present. It is possible that the elevated left atrial pressures in this situation, of which we have seen evidence in case VH 33 and case PH 30, may increase the reactive element of the pulmonary vascular resistance, and hence diminish the tendency to increase the left-to-right shunt. The presence of mitral stenosis or filling difficulty of the left ventricle in such patients would also operate to diminish this tendency, in contra-distinction to the situation in A.S.D.

Firm conclusions about the control of ventilation are more difficult to draw. The problem is complicated enough in normal subjects, and a fortiori the situation is complex in patients with left-to-right shunts in whom pulmonary plaeonaemia, pulmonary hypertension, heart-failure, lung damage and impairment of systemic flow may co-exist - each a potential determinant of hyperventilation.

Pulmonary plaeonaemia may be present without symptoms and with a demonstrably normal ventilatory response to exercise (e.g. cases AN4, AN6 and VN3), but this is not always so (case AN7). When pulmonary hypertension supervenes in patients with left-to-right shunts, dyspnoea

is usually present and hyperventilation observed on effort (cases AH 44, AH 45, PH 30). It does not appear that pulmonary hypertension per se is an important direct causal factor in hyperventilation, and patients are often seen in whom severe pulmonary hypertension is associated with a normal ventilatory response to exercise (cases AH 44, AH 43 and VH 32).

In these studies, therefore, the pattern of ventilatory response to supine exercise has been variable, but neither high pulmonary flow nor pulmonary arterial hypertension seem to be powerful independent determinants of hyperventilation. The same variability of response is seen in upright exercise.

The influence of pulmonary venous hypertension on the ventilation has been discussed elsewhere (Gazetopoulos et al, 1965). Elevation of left atrial pressure has been found in a minority of patients in this study; in atrial septal defect this is a usual accompaniement of co-existing mitral valve disease or of failure of either ventricle. In ventricular septal defect or patent ductus arteriosus the presence of mitral stenosis or of left ventricular failure leads to pulmonary venous hypertension. In two patients (cases AH 45 and VH 34) the elevation of left atrial pressure was considerable and both showed marked hyperventilation. Usually, however, the pulmonary venous pressure remains low in patients with septal defects at rest and on effort (Jönsson et al, 1957, Stephens et al. 1964) and only exceptionally would the pulmonary venous pressure appear to provide a significant ventilatory stimulus in this group of patients.

Impairment of systemic output has been proposed as a stimulus to ventilation (McIlroy, 1959), but various authors (Cotes, 1955; Arnott, 1963; Sloman and Gardenia, 1964), as well as ourselves (Gazetopoulos et al. 1965), have failed to find a satisfactory demonstrable relationship between reduced output and the ventilation in different types of heart disease. We have found lactate levels and lactate/pyruvate ratio to be somewhat higher on effort in patients with left-to-right shunts than in normal subjects, but the significance of this in terms of the ventilation remains uncertain. Likewise, the changes in arterial and venous gases are likely to be the result of hyperventilation rather than the cause of it.

CHAPTER V

EXERCISE STUDIES IN PATIENTS WITH RIGHT-TO-LEFT SHUNTS

STUDIES IN PATIENTS WITH SEPTAL DEFECTS AND RIGHT-TO-LEFT SHUNTS

The role of chemical factors in the control of ventilation has been the subject of inquiry ever since Lavoisier at the end of the eighteenth century discovered that oxygen and carbon dioxide are intimately related to respiration. The effects, separately and together, of hypoxia, hypercapnia, and acidaemia have been investigated both in health and sickness.

In the commoner forms of heart disease where dyspnoea is prominent there are often disturbances of lung function due to the altered pressure-flow relation in the lungs, as for example in rheumatic valvular disease, left ventricular failure, or pulmonary hypertension. This makes it difficult to assess with confidence the respective contributions of lung damage on the one hand and chemical changes in the blood on the other in the causation of effort disability. When the pulmonary vascular bed is 'protected' by the presence of pulmonary stenosis, however, the variable factor of lung damage associated with pulmonary hypertension is not present. It is then easier to assess the significance of non-pulmonary factors in the genesis of effort dyspnoea.

Shortness of breath on effort is usually considerable and is often severe in cyanotic congenital heart disease. This section is concerned with the changes observed in these patients when they were actually dyspnoeic.

Patients and Methods

Twenty patients with cyanotic congenital heart disease have been studied, and of these 13 had Fallot's tetralogy, the severity ranging from acyanosis at rest in six, to a resting oxygen saturation of only 58 per cent in one. Four patients had the Eisenmenger syndrome as defined by Wood (1958), two of them with ventricular septal defect, one with ventricular septal defect and patent ductus arteriosus, and one with atrial septal defect. Two patients had pulmonary valve stenosis and atrial septal defect, and one had transposition of the great vessels with pulmonary stenosis. Details are given in Table XVI. In cases C12, C16 and C17 Blalock anastomoses had been performed at the ages respectively of 10, 11 and 11 years; in the first two the shunt had become inadequate. Cases C3 and C9 underwent infundibular resection at the ages of 11 and 16 years, the former with great and lasting relief; in the latter case restenosis of the outflow tract of the right ventricle had occurred with reappearance of former symptoms.

For clarity of presentation the cases have been placed in three groups according to their resting arterial oxygen saturation. This appears to be a satisfactory arrangement since with few exceptions they fall into this pattern with respect to their clinical disability and the changes that we have observed on exercise. Group I consists of cases C1-7, with a resting arterial oxygen saturation greater than 90 per cent. All fell within the designation of 'acyanotic Fallot's tetralogy' except case C7; this patient had an 'Eisenmenger ASD'. Group II consists of cases C8-15, having a resting arterial oxygen saturation between 80 and 90 per cent (inclusive). Group III consists of cases C16-20, with resting arterial oxygen saturations less than 80 per cent.

TABLE XVI

DETAILS OF 20 CASES OF CYANOTIC CONGENITAL HEART DISEASE

Groups	Case No. Sex& Age	Diagnosis	Resting art. O_2 sat. %	Hb (g./100 ml.)	Disability	B.S.A.
I	C 1 M 38	Fallot	97	14.7	II	1.7
	2 M 29	Fallot	96	17.8	I	1.9
	3 M 19	Fallot	93	15.6	I	1.7
	4 M 18	Fallot	94	17.3	I	1.7
	5 F 18	Fallot	95	14.5	I	1.5
	6 F 16	Fallot	94	13.4	I	1.5
	7 M 35	ASD Eis.	97	16.5	I	1.9
II	C 8 F 41	PS + ASD	90	15.0	II	1.6
	9 F 27	Fallot	90	17.8	II	1.2
	10 M 34	Fallot	86	17.0	II	1.7
	11 F 23	Fallot	87	15.3	II	1.4
	12 F 26	Fallot	90	16.4	I - II	1.7
	13 M 13	Fallot	90	17.2	I	1.3
	14 M 25	VSD Eis.	86	17.8	II	1.7
	15 F 28	VSD + PDA Eis.	84	17.7	II	1.5
III	C 16 M 23	Fallot	58	22.4	III	1.6
	17 M 26	Fallot	75	19.0	II	1.6
	18 F 23	VSD Eis.	75	17.1	II - III	1.4
	19 M 15	Transpos. + PS	54	24.0	III	1.4
	20 F 26	PS + ASD	75	21.3	II	1.6

The resting arterial oxygen saturation was measured immediately before bicycle or step exercise, except in cases C8, C9 and C20, where only catheter data are available. Disability grades according to New York Heart Association (1953).
BSA = Body surface area in square metres (DuBois and DuBois, 1915).

Exercise studies were originally performed during the course of cardiac catheterisation, using a spring-loaded leg exerciser in the supine position. While this yielded data of considerable interest, it soon became apparent that the exercise level was too low to produce dyspnoea. Accordingly,

more strenuous forms of exercise, using standard step tests and the bicycle ergometer, were adopted.

For the cardiac catheterisation all patients were premedicated, usually with Omnopon® and scopolamine. Samples of blood for oxygen and metabolic studies were taken at rest and between the sixth and eighth minute of steady leg exercise, pulmonary and systemic flows being estimated by the Fick principle. The ventilation was measured from the spirometric tracing obtained after the fifth minute of exercise and corrected to BTPS.

For the step and bicycle exercise the patient was not prepared in any way apart from the insistence that he should have been resting for the previous hour. The nomogram of Hugh-Jones and Lambert (1952) was used to estimate the exercise level on the steps, though this gives only a modest approximation of the work output at lower levels; the same can be said of the bicycle ergometer. Particular attention was paid to the maintenance of a steady level of exercise.

Under local analgesia a Cournand arterial needle was introduced into either the brachial or radial artery. After an interval of three minutes a resting blood sample was withdrawn, and measurements made of resting ventilation, oxygen uptake, and heart rate. The type of exercise was then commenced which was considered most appropriate to the case being studied, and continued until dyspnoea was present, as judged by the patient's statements and the evidence of considerable hyperventilation and tachypnoea. The level of effort chosen depended on the severity of the clinical disability; if after 10 minutes at the given level

there was no dyspnoea, the exercise load was increased by 100 - 200 kg. m./min. In a few cases the effects of walking before the other levels of effort were assessed.

Blood samples were withdrawn usually in the fourth and tenth minute of exercise at each level. Of the 10 ml. taken, 6 m. were immediately transferred to test-tubes containing·6% perchloric acid for lactate and pyruvate estimation. The remainder of the blood sample was analysed for pH, PCO_2, and bicarbonate content. Oxygen saturation was measured in a Brinkman haemoreflector. PO_2 was calculated from the nomogram of Severinghaus (1958).

It was intended to measure ventilation in all cases, but in the more disabled patients interference with respiration by the mouthpiece made this unsafe at higher ventilatory levels. Where measurements were made, a Wright anemometer was used and the expired air was collected in a Douglas Bag for analysis by the Haldane method. The ventilation was measured between the fifth and tenth minute of each exercise level. When measurements of ventilation were not made dyspnoea was assessed on a clinical basis as severe (Grade III), moderate (Grade II), or mild (Grade I).

There were no untoward effects from these tests, apart from feelings of nausea either during or after the exercise in a few cases. It is stressed that during such studies the patient must be watched carefully at all times and the exercise terminated as soon as there are any signs of distress. This is particularly so in the Fallot group, where severe dyspnoea may appear very quickly after a period of apparent comfort at the same exercise level. Where necessary, information derived from the study of other patients in this laboratory over the past five years has been drawn upon.

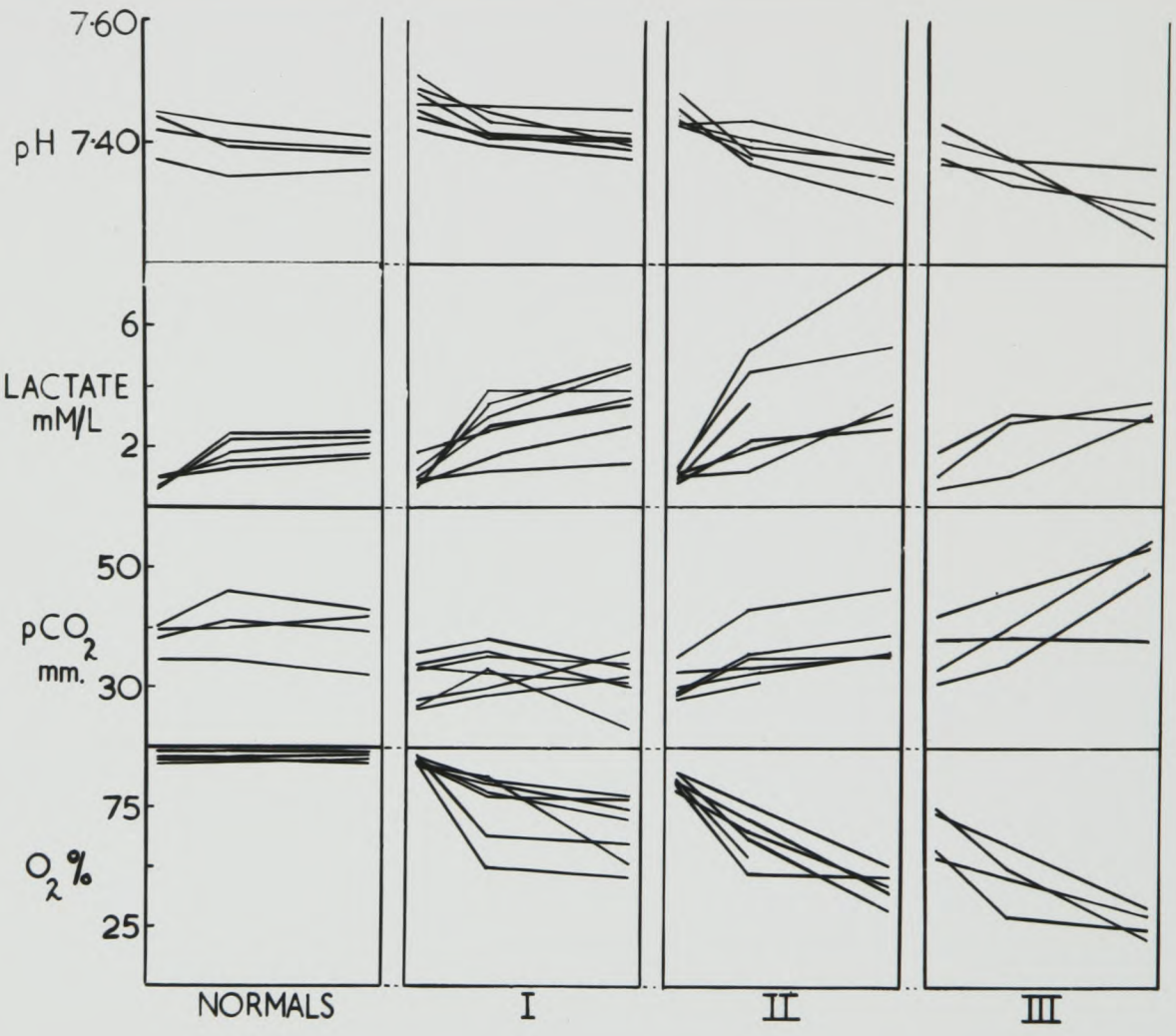


Fig. 6a Changes in arterial oxygen saturation, PCO_2, lactate, and pH on exercise in normal subjects and three groups of patients with cyanotic congenital heart disease. Group I, resting arterial oxygen saturation above 90 per cent; Group II, 80 - 90 per cent; Group III, below 80 per cent. The first point represents the resting value, the second that after approximately three minutes of exercise, and the third that at the highest level of exercise when dyspnoea was present.

RESULTS

The data obtained are presented in Tables XVII and XVIII in the Appendix. Table XVII shows the results of exercise during cardiac catheterisation, and Table XVIII those at bicycle, step, or walking exercise.

Figure 6a summarizes the changes in the main factors studied at higher exercise levels where dyspnoea was present.

Arterial Oxygen

(a) At rest This depended on the nature and severity of the lesion. In four out of five cases in whom arterial oxygen estimations were made both during cardiac catheterisation and before bicycle or step tests, there were differences in the resting saturations on the two occasions. The values at catheterisation were lower in three cases, by 10 per cent in case C7, 16 per cent in case C18, and 6 per cent in case C4; case C3 showed no difference, while case C14 had a slightly higher level at catheterisation.

(b) During exercise The arterial oxygen saturation fell in all cases. At catheterisation the fall was modest; during bicycle or step exercise very low values were seen at times, e.g. 25 per cent in case C16, and 20 per cent in case C17. Table XIX shows the saturations and partial pressures of oxygen that were found in the arterial blood at the peak of exercise, which represents in almost all cases the point at which it had to be terminated.

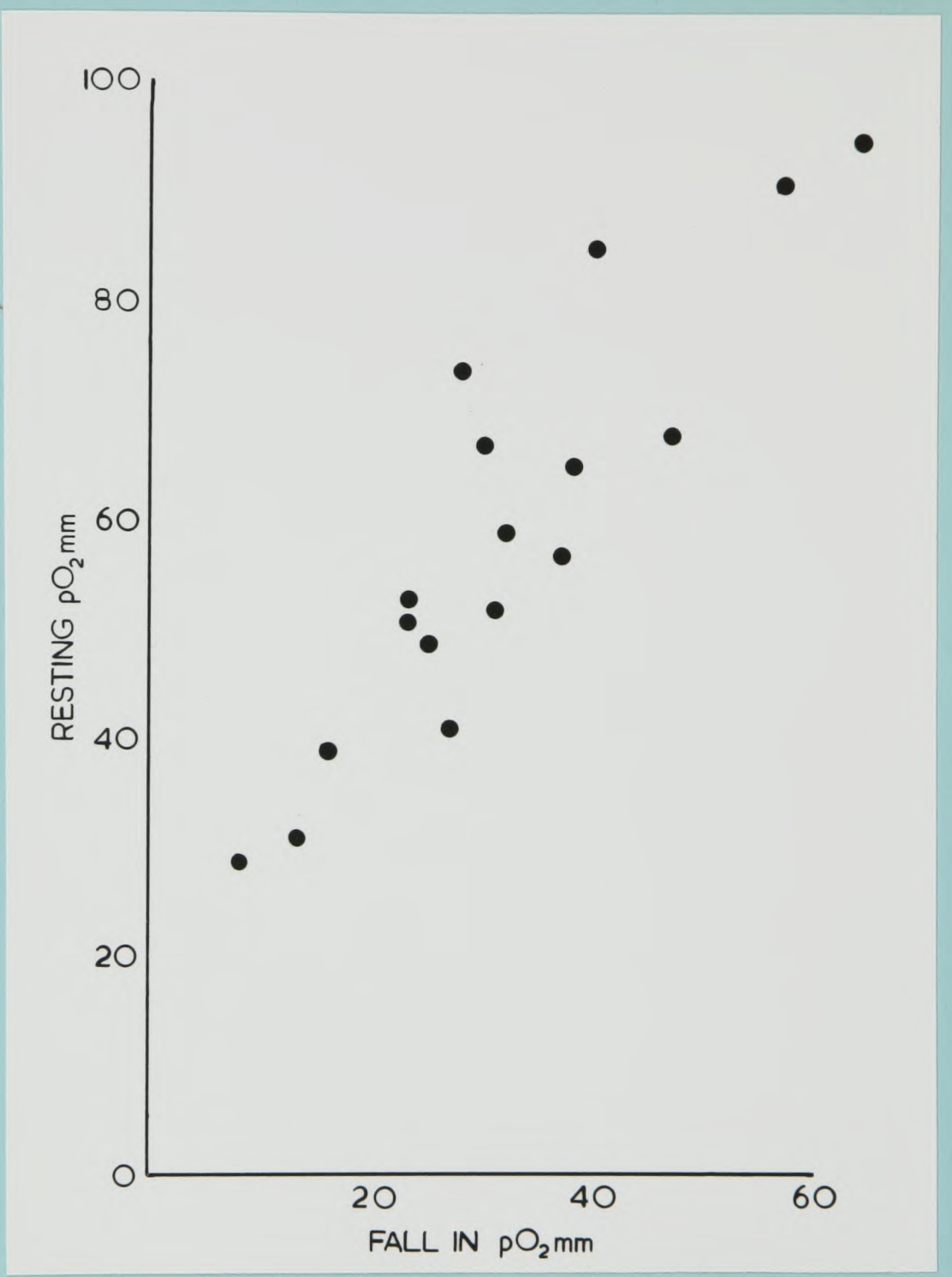


Fig. 6b The relation between the resting arterial PO_2 and the fall below that value which occurred when exercise was continued to the point of dyspnoea.

TABLE XIX

Case No.	1	2	3	4	5	6	7	10	11	12	13	14	15	16	17	18	19
Rest art. O_2 %	97	96	93	94	95	94	97	86	87	90	90	86	84	58	76	75	54
Rest art. PO_2 (mm.)	95	85	67	73	74	65	91	52	53	59	57	51	49	31	41	39	29
Exercise art. O_2 %	60	80	81	47	81	51	66	40	55	51	33	46	43	25	20	34	32
Exercise art. PO_2 (mm.)	31	45	37	26	46	27	34	21	30	27	20	28	24	18	14	23	21

Arterial O_2 saturation and partial pressure at rest and at peak of exercise in subjects exercised to point of dyspnoea.

The lowest saturation seen was 18 per cent in case C16, corresponding to a PO_2 of 14 mm. (Table XVIII). This occurred shortly after the cessation of exercise. Symptoms varied considerably in relation to the level of arterial oxygen, from cases C1 and C2 who were incommoded when their saturations were 60 and 80 per cent respectively, to case C17 who was content to carry on when his arterial oxygen saturation was 20 per cent. Clearly the oxygen saturation is not the only factor that determines disability.

Figure 6b shows the fall in partial pressure of arterial oxygen on exercise as a function of its resting value. It enables us to derive an approximate estimate of the level that might be attained during exercise leading to dyspnoea in any cyanosed patient whose resting level is known. For example, if the resting saturation were 80 per cent (PO_2 of 45 mm. at pH 7.4), the exercise value would be likely to fall to around 35 - 40 per cent (PO_2 of about 22 mm. at pH 7.3) before dyspnoea would prevent the patient from exercising any further.

The average arterial PO_2 on effort in Group I was 35 mm. Hg, in Group II 25 mm. Hg, and in Group III 22 mm. Hg, the resting values being 79, 54, and 35 mm. Hg. respectively. There was thus a fall of 44 mm. in Group I, 29 mm. in Group II, and 13 mm. in Group III.

On cessation of exercise, the rise in arterial saturation was usually prompt. In case C16, however, the level continued to fall for several minutes before rising again. Eight minutes later it fell once more (Table XVIII). Both these episodes were accompanied by manifestations of excessive vagal activity, viz: nausea, sweating and bradycardia.

Arterial PCO_2

(a) At rest At cardiac catheterisation the values were very variable, ranging from 33 mm. in cases C4, C7, and C9, to 38 and 42 mm. in cases C8 and C3, to 47 mm. in case C14.

Before the bicycle or step tests the circumstances were very different in that the patients were not sedated and there was necessarily a measure of anxiety accompanying the insertion of the arterial needle, the measurement of ventilation, etc. The PCO_2 values found in the patients were lower than those usually seen under similar conditions in normal subjects and in others without central cyanosis. It would be tempting to relate this to the fact that there is in most of them a lowered arterial oxygen tension, since hypoxaemia has been so widely held to be responsible for hyperventilation and consequent

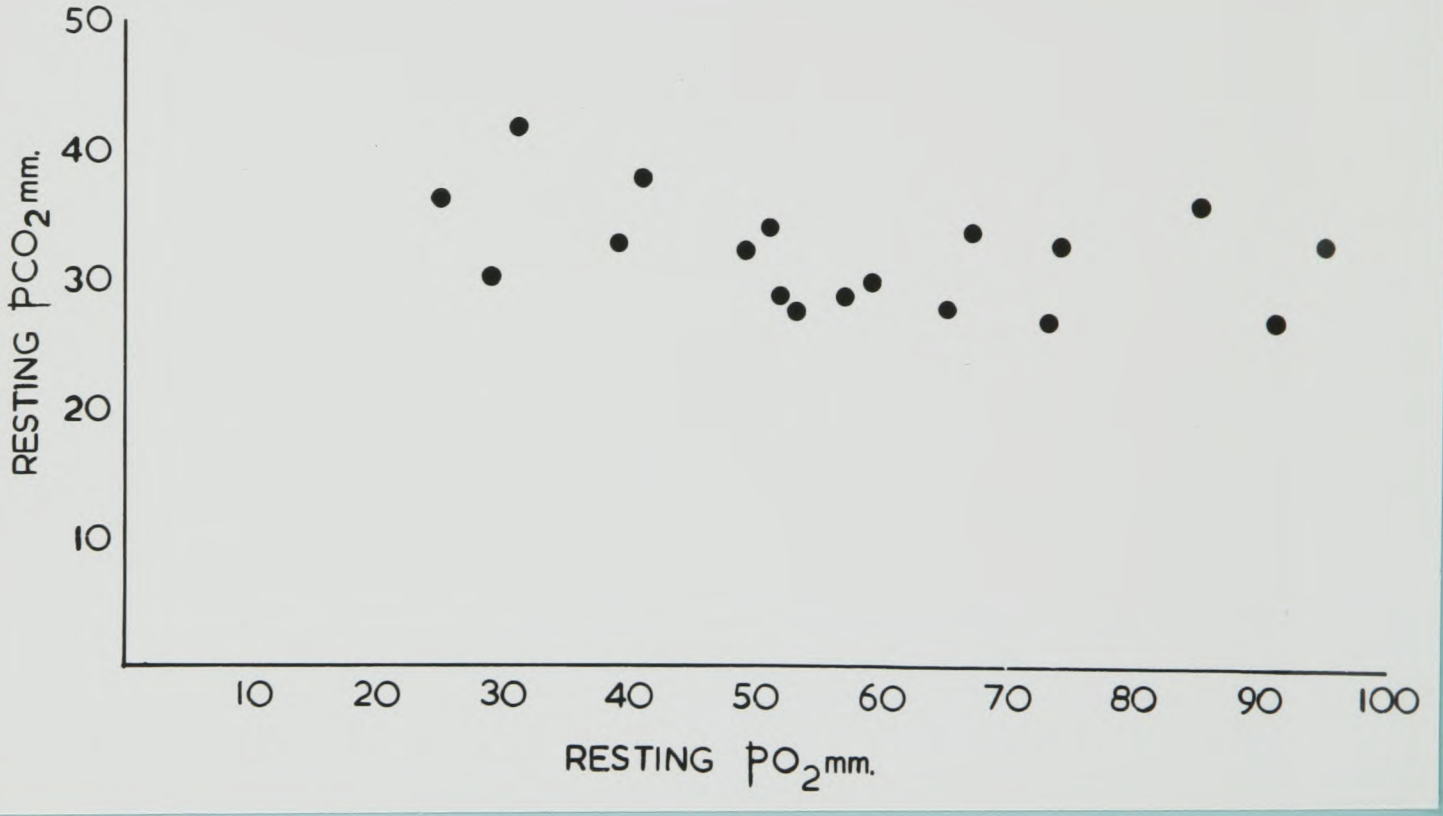


Fig. 6c The resting PCO_2 in relation to the degree of arterial hypoxaemia.

hypocapnia (Morse and Cassels, 1953). However, on examining the relation of the arterial oxygen to the CO_2 levels, it is clear that the more cyanosed patients do not in fact have the lower values of PCO_2 (Table XVIII, and Fig. 6c). All that can be said is that the cyanosed patients had on the whole a lower arterial PCO_2 than normal, but that the lowering was not proportional to the degree of hypoxaemia.

The finding of a lower-than-normal arterial PCO_2 in a patient with a right-to-left shunt must mean that the pulmonary venous PCO_2 is particularly low. This was measured during cardiac catheterisation in case C20, with severe pulmonary stenosis and reversed inter-atrial shunt, and shown to be 26 mm. Hg. Gootman, Scarpelli and Rudolph (1963) have recorded the pulmonary venous PCO_2 in hypoxic patients and found it to be low (18 - 27 mm. Hg).

(b) On exercise The behaviour of the arterial PCO_2 during exercise was significantly different in the three groups (Fig. 6a & Table XVIII). In Group I, the acyanotic group, the level rose initially and then fell below the resting value. In Group III, the most cyanosed, there was a progressive rise in PCO_2, uninterrupted by any fall. In Group II the pattern of change was intermediate between that of the other two groups.

Campbell (1934) found a diminished output of carbon dioxide in the early minutes of exercise in patients with heart disease. Davison, Armitage and Arnott (1953) found a delay in the ventilatory response in the early minutes of exercise in patients with cyanotic congenital heart disease, and noted that there must be considerable retention of

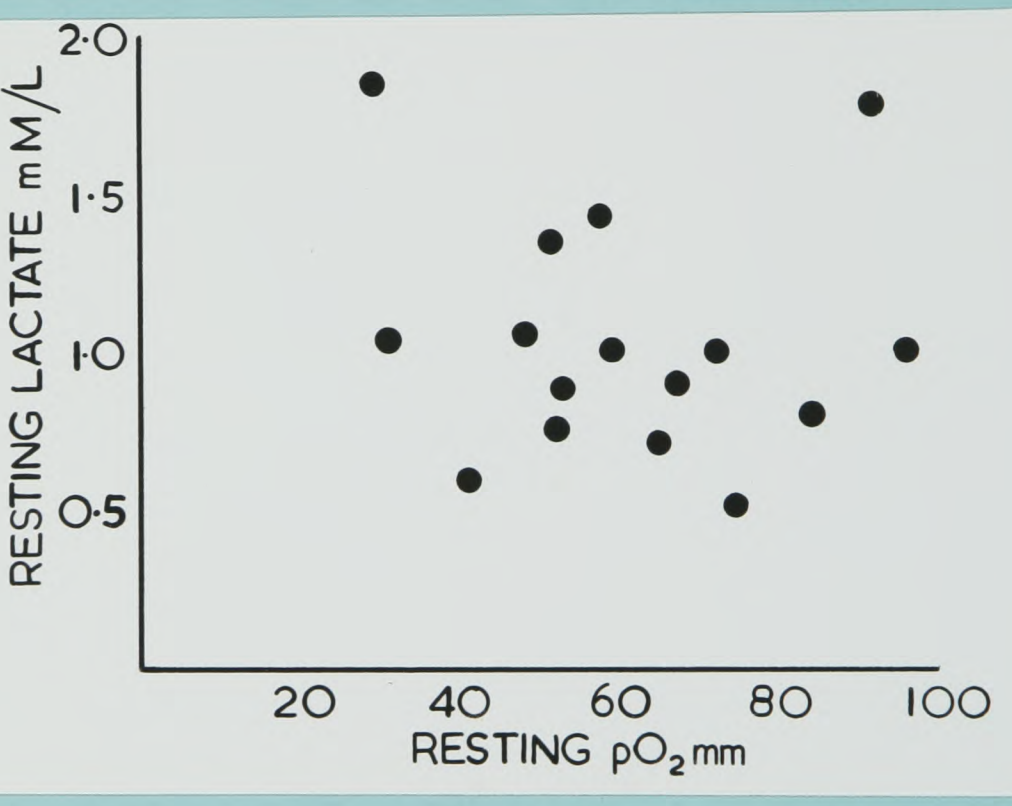


Fig. 6d The resting arterial lactate concentration related to PO_2.

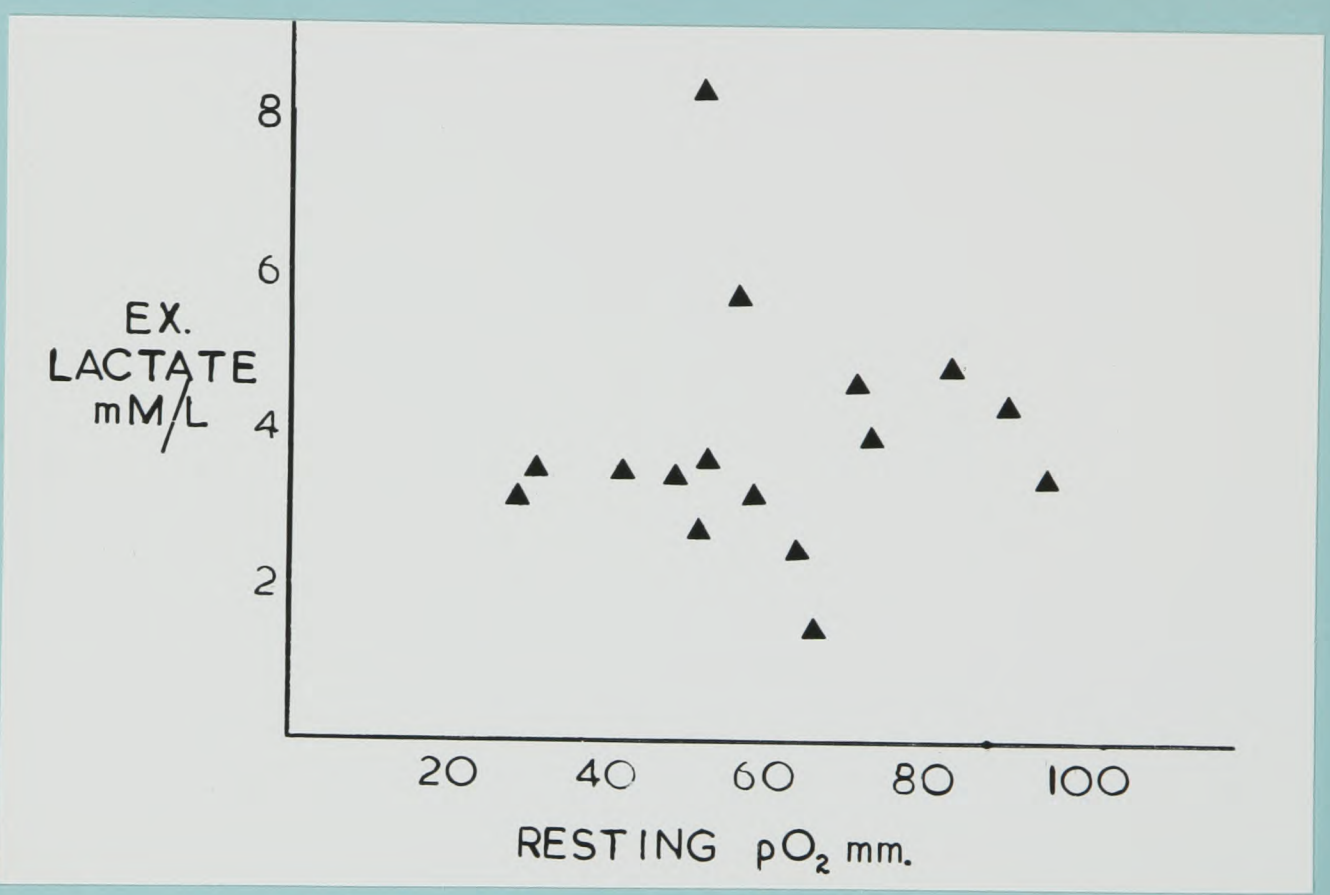


Fig. 6e The exercise arterial lactate concentration related to the resting PO_2.

CO_2 at this time. We have confirmed an early rise of arterial PCO_2, but must note that it occurred not only in cyanosed patients but also in normal subjects (Rahn and Otis, 1949; Suskind et al. 1950; Matell, 1963).

Arterial Lactate and Pyruvate Concentration

(a) At rest These were on the whole within the normal range, confirming the findings of Hallock (1939) and Havel and Watkins (1950). Fig. 6d shows that there is no relation between the actual level of PO_2 and arterial lactate concentration.

(b) On exercise Arterial lactate and pyruvate tended to be a little higher than those of normal subjects at the same exercise level (Davies and Gazetopoulos, in the Press). The most striking feature, however, was that the most profound hypoxaemia could exist with only a slight increase of arterial lactate, as in cases C16, C17 and C19. This is surprising in the light of the known association between oxygen lack and lactate production (Hill and Lupton, 1923; Meakins and Long, 1927; Jervell, 1928; Huckabee, 1958). Presumably the fact that the intensity of effort was limited by other factors in severe cases, as will be discussed later, was responsible for the low lactate levels which tended to be lower in the most disabled group (Fig. 6e). The peak lactate levels were attained at the point of maximum effort in these patients, and we never saw a late release after the end of exercise.

Pyruvate rose in the usual fashion, the maximum values being reached a few minutes after the end of exercise. The actual levels reached were not remarkable.

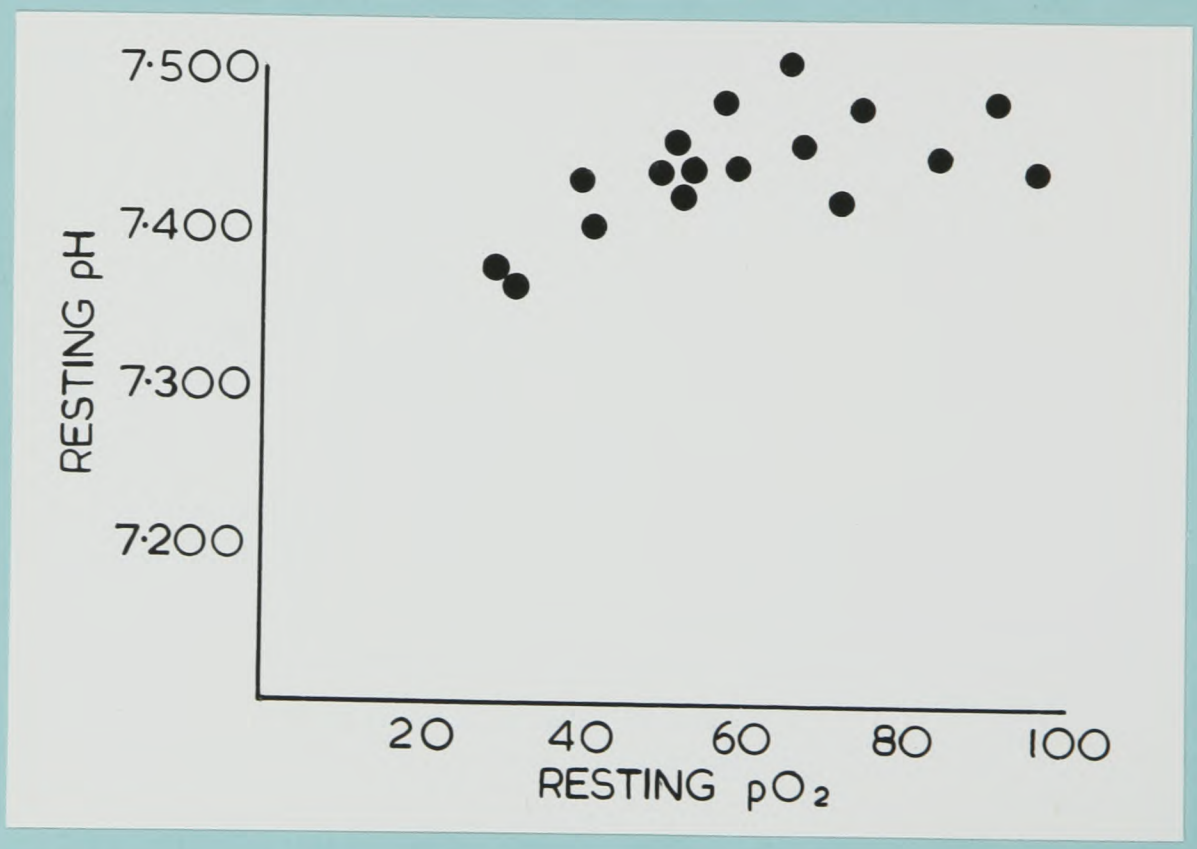


Fig. 6f The pH and PO_2 in the arterial blood at rest.

Arterial pH

(a) At rest These were within the upper normal to alkalaemic range, though there was some tendency towards acidaemia in the more hypoxaemic patients (Fig. 6f). Of these, case C16 had a higher than usual resting PCO_2, while case C19 had a somewhat raised blood lactate. These findings are in keeping with those of Bing et al. (1948) and Morse and Cassels (1953).

(b) On exercise The arterial pH fell in all cases except three in the acyanotic group. The levels reached were lowest in the most disabled patients. It is of considerable interest that since the lactate levels were low in the latter group, the acidaemia was in the main hypercapnic rather than metabolic in origin. The lowest value seen was 7.24 in case C18, who had Eisenmenger's complex.

Ventilation

(a) At rest It has been widely accepted that patients with cyanotic congenital heart disease hyperventilate at rest, in the sense that their minute volume of ventilation is higher than normal. Bing et al. (1948) found that this was so in 29 out of 30 cases, that the arterial PCO_2 and alkaline reserve were reduced, and that the arterial pH was normal. There appears to be some lack of agreement, however, in the published figures for normal subjects. Baldwin, Cournand and Richards (1948) and Matheson and Gray (1950) stated that in resting young adults the average ventilation was 4.0 l./min./m^2, but Bucher (1949) found in 27 cases an average of 6.3 and Shephard (1955) gave the figure as 4.2. Shephard found that the minute ventilation

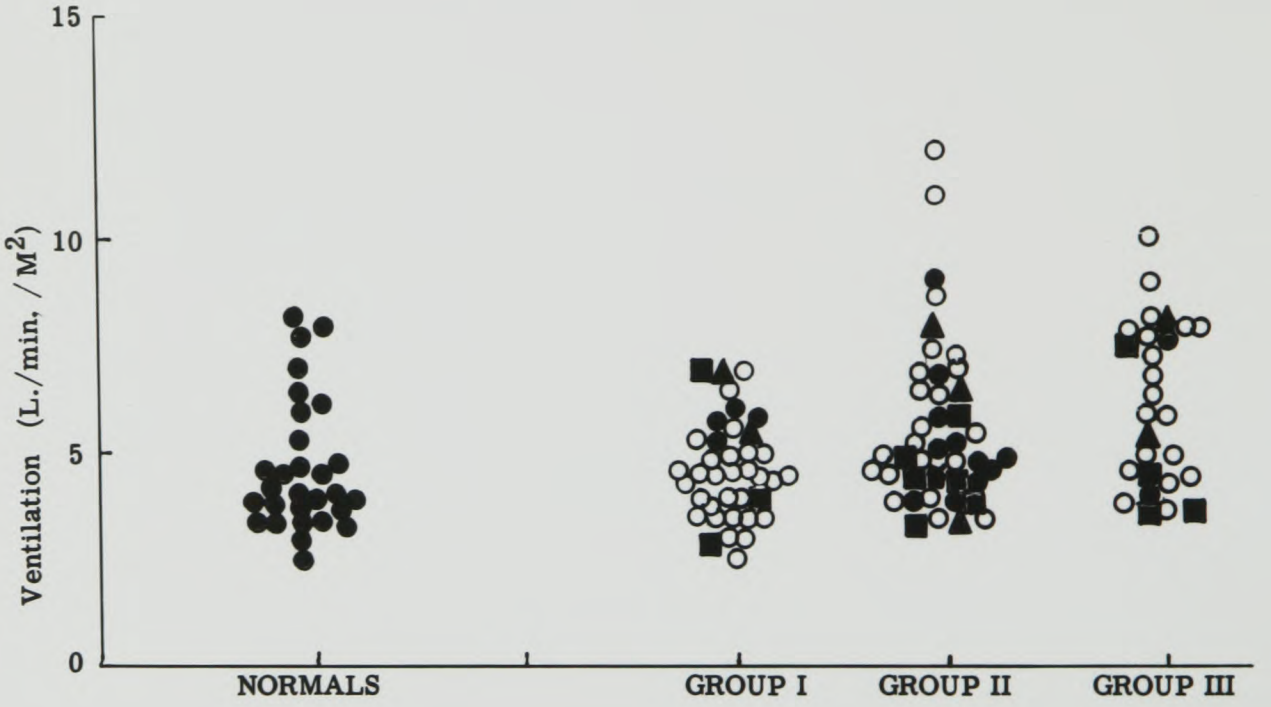


Fig. 6g The resting ventilation in normal subjects and in three groups of patients with cyanotic congenital heart disease. Open circles represent Fallot's tetralogy; closed symbols, Eisenmenger syndrome.
(Circles: V.S.D. Squares: A.S.D. Triangles: P.D.A.)

was increased in most forms of congenital heart disease, both in the cyanotic group and in the acyanotic group with increased pulmonary blood flow. Davison et al. (1953) confirmed the resting hyperpnoea of cyanosed patients, though they doubted whether hypoxaemia was the main factor responsible.

In an attempt to clarify this, we have examined the records of ventilation in a large number of patients during cardiac catheterisation. Normal subjects have been compared with cyanosed patients in the Fallot and Eisenmenger groups. Fig. 6g shows the results. It is seen that there is a slightly higher mean level of ventilation in the cyanosed group, but the difference is not significant (mean 4.7 in normals as against 5.5 in the cyanosed patients). The difference between the means in these groups is not significant ($p > 0.2$). Here, allowance must also be made for the fact that there is a higher proportion of small people, young and undersized, in the severer groups, the ventilation per square metre being of course greater in smaller subjects (Shock and Soley, 1939; Mannheimer, 1949). In the sedated state, therefore, there is scant evidence of hyperventilation, in the sense of increased minute ventilation, in patients with cyanotic congenital heart disease.

Without sedation the resting ventilation also seems to be within the normal range, though we would not wish to draw firm conclusions from the relatively few measurements that we have at our disposal. We have reservations about accepting the frequently-quoted statements about the resting hyperventilation of cyanotic congenital heart disease, though it is conceivable that under conditions of stress the patients may

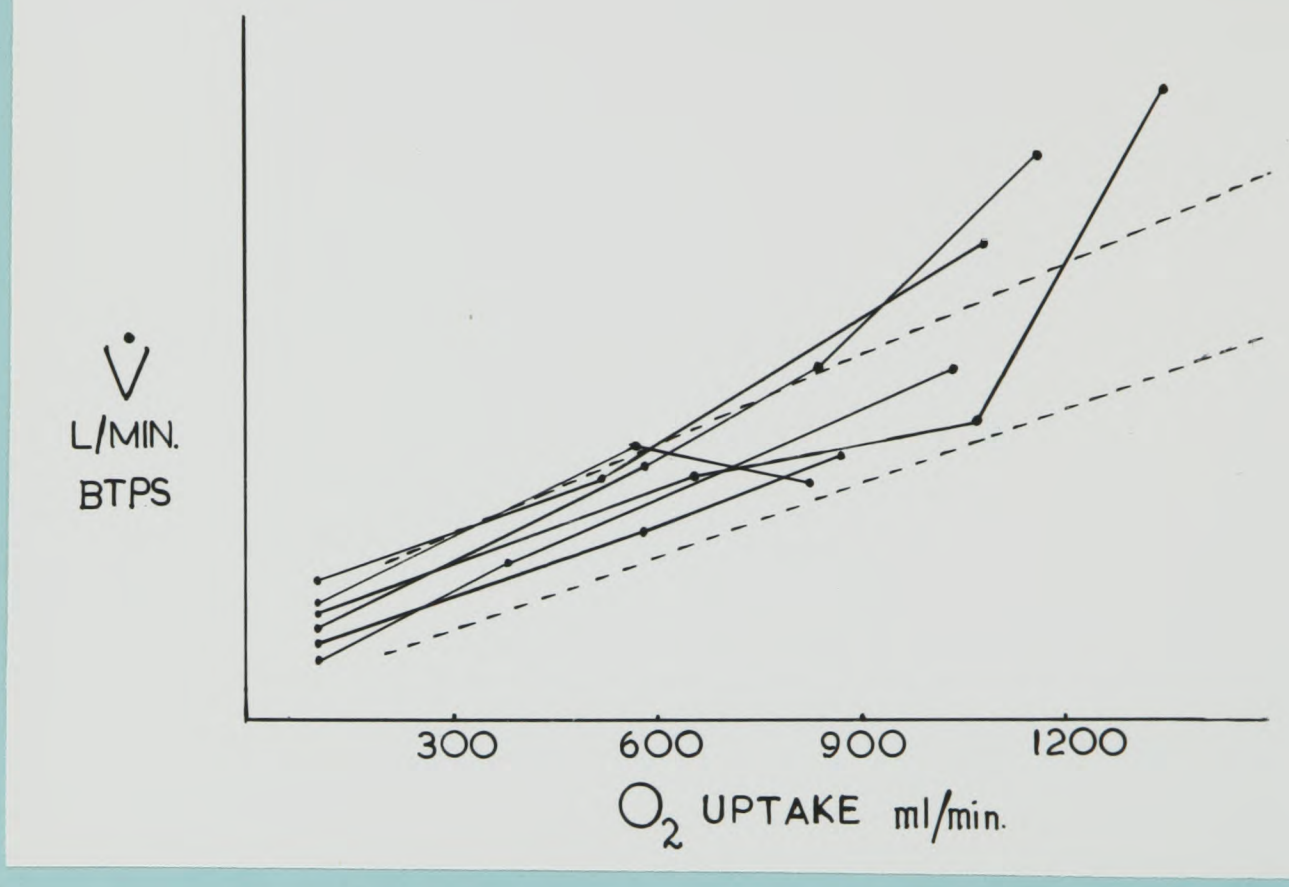


Fig. 6h The ventilation in relation to the oxygen uptake in six cases of Fallot's tetralogy at rest and on exercise. The dotted lines represent the limits of normality obtained from patients studied in this laboratory and from published cases ($\dot{V}$ = ventilation in l./min).

show an excessive ventilatory response as compared with normal subjects. Patients with Eisenmenger syndrome are not apparently separated from the Fallot group in respect of their resting ventilation.

(b) On exercise The first relevant observation is that, as in normal subjects (Åstrand, 1960), the amount of exercise rather than its type is the more important in determining the ventilation. This is well seen in case C4 (Table XVIII), where the ventilation at similar levels of exercise can be compared, first at catheterisation and then during walking; also in case C17 ventilation while walking and during the lowest level of bicycle exercise is seen to be comparable (leg exercise has always been used during these studies).

A second general observation is that in most cases the ventilatory response is normal up to a certain level of exercise. Above this level the ventilation is greater than expected. With others we use for this the term 'relative hyperventilation'.

This is seen clearly in patients exercised at more than one level. Fig. 6h shows that in patients with Fallot's tetralogy the relation between ventilation and oxygen consumption is normal at values of $\dot{V}O_2$ (oxygen uptake) less than about 800 ml./min. STPD. Above this relative hpyer-ventilation occurs. The more severe the cyanosis the lower is this 'critical level' (i.e. the level at which relative hyperventilation begins). Generally the acyanotic group was able to attain an exercise level of 400 - 600, the intermediate group 300 - 400, and the most severe cases less than 300 kg. m./min, but there was a notable exception in case C17 with a functioning Blalock anastomosis which will be discussed later.

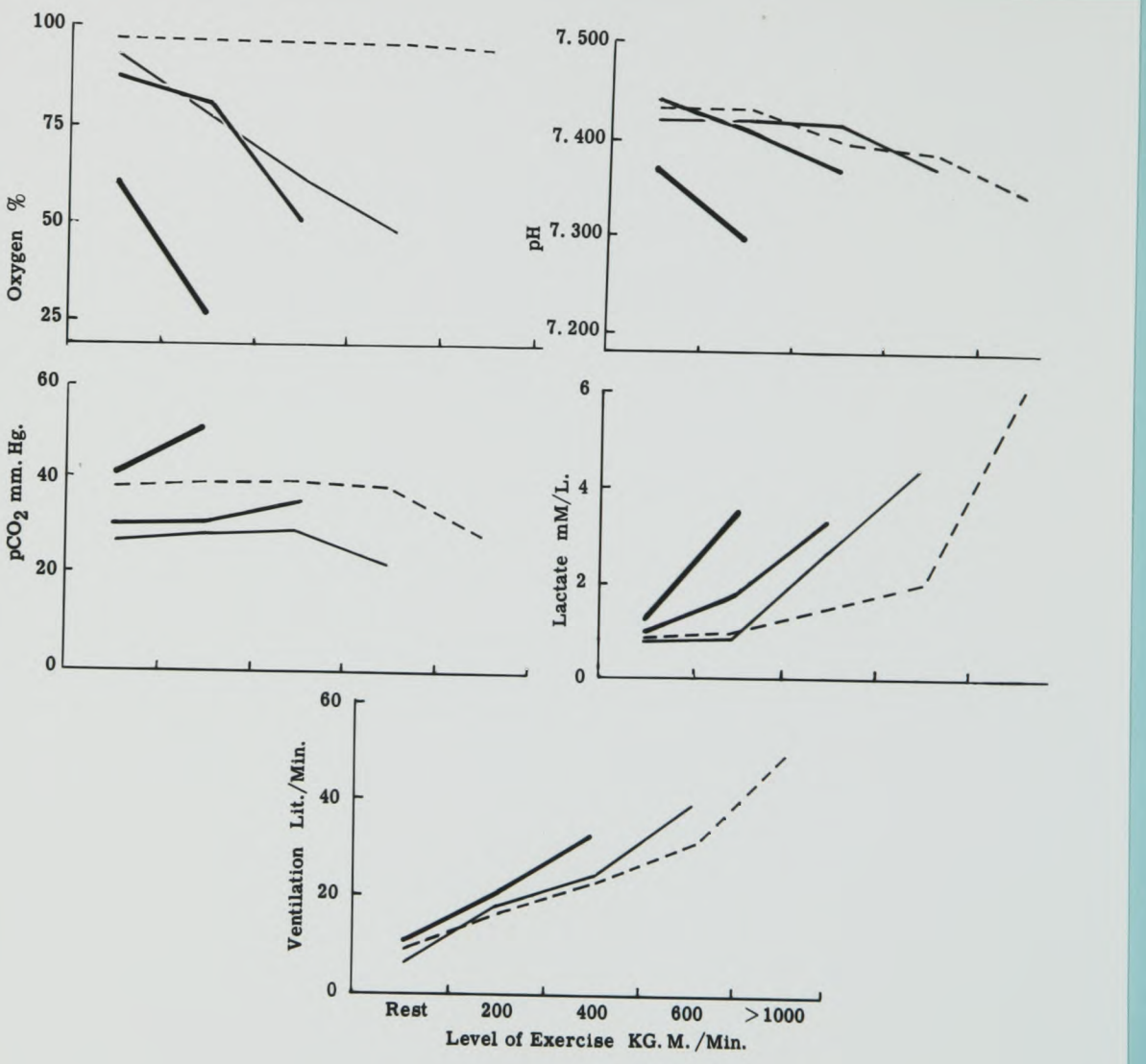


Fig. 6i Changes in arterial oxygen, pH, PCO_2, lactate, and ventilation measured at different exercise levels in a patient from each of the three groups and a normal subject. The three solid lines, in order of decreasing heaviness, represent case C16 in Group III, case C12 in Group II, and case C4 in Group I. The broken line represents a normal patient. The intervals on the abscissa in each diagram are as in the lowest one. (Ventilation could not be measured in case C16).

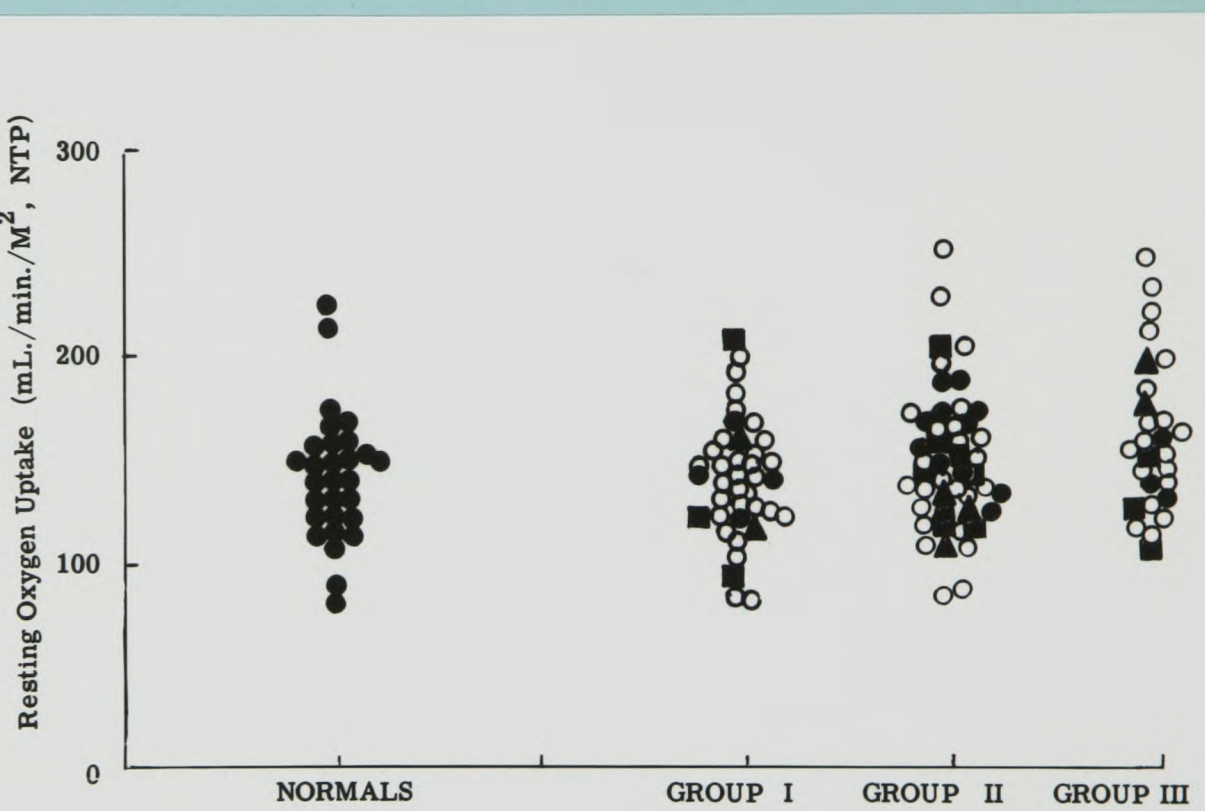


Fig. 6j The resting oxygen uptake per sqare metre of body surface area at cardiac catheterisation in normal subjects and in three groups of patients with cyanotic congenital heart disease. Symbols as in Fig. 6g.

The normal ventilatory response of the Fallot group to sub-critical exercise is accompanied by biochemical changes which, oxygen saturation apart, are similar to those in non-cyanosed patients and normal subjects at the same exercise levels. Above the critical level it appears that there are disturbances in the other humoral factors and the level of oxygen tension is not by itself a potent determinant of relative hyperventilation. In Fig. 6i the level of exercise is related to the ventilation and to the measured variables during stepwise increases in exercise in representative cases from each group and one normal subject for comparison. While ventilation is normal up to a certain point, relative hyperventilation begins at lower levels in the patients, according to the severity of the disease as judged by the arterial oxygen saturation at rest.

Oxygen Consumption and Carbon Dioxide Output

(a) At rest Most authors (Holling and Zak, 1950; Burchell et al, 1950; Ernsting and Shephard, 1951; Davison et al, 1953) have found the basal oxygen consumption to be normal in patients with cyanotic congenital heart disease. Likewise we have seen no abnormality of the oxygen consumption either at cardiac catheterisation or before bicycle or step tests. Fig. 6j illustrates the findings in 114 patients and 29 normal subjects drawn from our laboratory records; it is seen that there is no significant difference between the groups.

(b) On exercise Taking as the basis for comparison the figures of Åstrand (1960), we have found no abnormality of the oxygen uptake for a given work load in our patients. Doubtless at higher

exercise levels a limit would be imposed by the restriction of pulmonary blood flow, but other factors cause a cessation of exercise before this point is approached. These findings appear to provide further testimony to the fact that adaptive mechanisms are highly effective in preserving the oxygen economy in such cases.

The CO_2 output was measured in only a few patients, but in them it was found that at rest and at sub-critical exercise levels the respiratory quotient lay within the normal range. On effort it rises above unity in the patients in whom the arterial PCO_2 drops, but we have no figures in cases where the latter rises. Our data indicate therefore that the resting oxygen consumption is normal in these patients, and that it increases normally with effort at least up to the critical level of exercise.

Heart Rate

This is higher for a given amount of exercise than in normal subjects (our data), but there are wide individual differences. The heart rate cannot be used as an index of exercise limitation or of physical working capacity. Thus in the most severely disabled patient (case C16) the rate rose no higher than 135 at the point of maximum effort and dyspnoea. This aspect of the circulatory adjustment to exercise is discussed by Kjellberg et al. (1959).

DISCUSSION

In normal subjects during exercise the ventilation and oxygen uptake increase in linear fashion with the load at lower levels of effort. After a certain point, ventilation increases disproportionately, and at this point there is evidence of lactate accumulation and metabolic acidosis (Dejours, 1959; Cotes, 1963).

Severe effort hyperventilation leads to a fall in PCO_2 to levels that may be well below those of the resting state. The tendency towards alkalaemia, which is the consequence of the release of CO_2, only partially compensates for the acidaemia associated with lactate production, and the arterial pH falls. There are no significant changes in PCO_2 of arterial blood of normal subjects on effort (Asmussen and Nielsen, 1958; Mitchell, Sproule and Chapman, 1958).

Whether or not ventilation is a factor limiting exercise in normal subjects, dyspnoea is usually accompanied by considerable relative hyperventilation, though of course there are wide individual variations in the exercise level needed to produce this, depending on sex, age, body habitus and state of training.

In normal subjects at the lower levels of exercise, of the order of those to which we have subjected our cyanosed patients, there are biochemical changes of only relatively small degree. The arterial lactate increases to only about 2 mM./1, and the pH and the PCO_2 remain close to their resting values (Dejours, 1959 and our unpublished data). It is against these relatively minor changes that the response of the cyanosed patients must be judged.

In patients who are acyanotic at rest but are cyanosed on effort the metabolic changes with exercise, oxygen saturation apart, are not far removed from normal; the lactate rises to levels a little higher than in normals at the same exercise load, but the increase is not as great as that which we have seen in normal subjects at exercise levels sufficient to produce relative hyperventilation. The 'acyanotic' patient has a pulmonary blood flow sufficient to lower the arterial PCO_2 on effort, and hypoxaemia and slight metabolic acidosis appear to be the main humoral disturbances; he can continue exercising without distress in the presence of relative hyperventilation. Thus case C3, who was almost totally disabled before pulmonary valvotomy and infundibular resection, had a good pulmonary blood flow after operation (Table XVII). The metabolic changes with effort were small. The main humoral disturbance was hypoxaemia. In cases C1 and C2, particularly the latter, lactic acidaemia was greater and hypoxaemia relatively mild. It may be significant that they were amongst the older patients, and were unique in this series in that they suffered from angina pectoris.

Where the pulmonary blood flow is adequate, therefore, hyperventilation leads to a fall in arterial PCO_2 to levels below the resting ones. The severely cyanosed patients, on the other hand, show a different pattern of response. On account of the considerably restricted pulmonary blood flow, hyperventilation is ineffectual in clearing the body of carbon dioxide. The changes in lactate are on the whole smaller than those in the acyanotic group for a given degree of disability, and the oxygen saturation is lower. It is of considerable significance

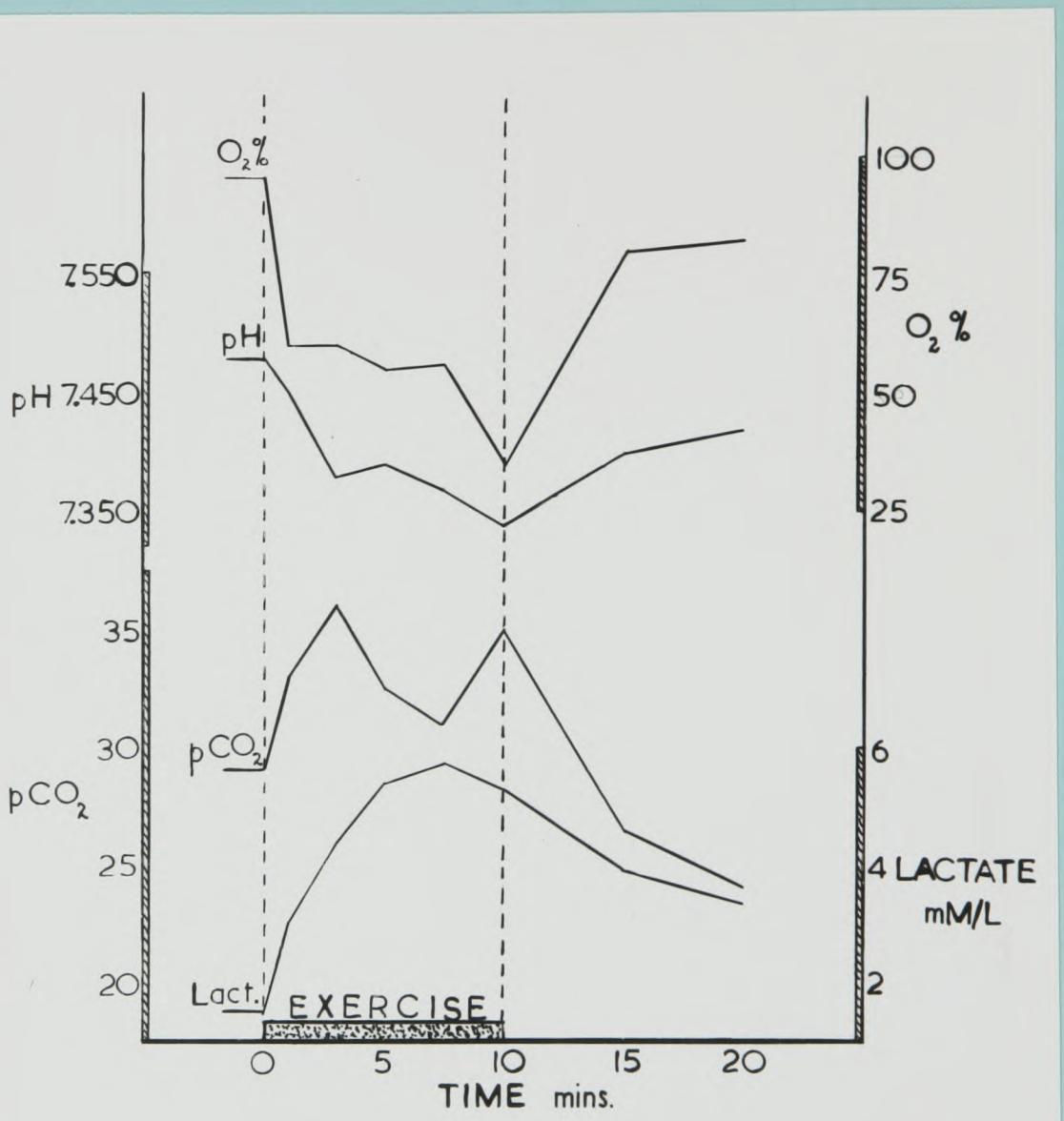


Fig. 6k The effect of exercise on the arterial oxygen saturation, pH, PCO_2, and lactate, in case C13 (see text).

that the arterial PCO_2 rises, and that the pH indicates that there is an acidaemia which is more hypercapnic than metabolic. These facts are fundamental to the understanding of the disability of the cyanosed patients.

The changes in arterial PCO_2 are also of importance in the intermediate group. We have been able to study somewhat more closely the minute-by-minute changes in a few such patients. As shown in Fig. 6k (case C13), in the first minute of exercise the arterial oxygen fell and the PCO_2 rose as the ventilation increased to its steady-state level. The arterial pH fell at this stage partly due to the rise in CO_2 and partly to the increase of lactate. By the third minute the oxygen had reached a steady level, the PCO_2 was at its first peak, and the pH was falling in response to the rising lactate. In the fifth minute the oxygen was at the same level, but the PCO_2 now fell in response to the hyperventilation. At this stage the ventilation was 31.5 l/min. and the oxygen uptake 1.15 l/min. The situation did not then alter materially until at the tenth minute he became dyspnoeic rather suddenly. The oxygen saturation at this time fell again, the PCO_2 rose once more and the pH fell, the lactate now being unchanged or a little lower than its peak value. It is likely that such changes accompany the sudden access of dyspnoea that is often seen at about this stage of steady exercise.

Thus, of the three classical humoral stimuli to respiration, hypoxia, hypercapnia and acidaemia, only the latter is present during severe exercise in normal subjects, whereas all three operate in the more disabled cyanosed cases even on mild effort.

Nielsen (1936) and Nielsen and Smith (1952) showed clearly in normal subjects the interrelation of hypoxia and hypercapnia in the determination of ventilation. At normal alveolar oxygen levels the effect of increasing PCO_2 is apparent above a level of 36 mm. When the alveolar PO_2 is 47 mm, there is little response from increasing PCO_2 until its level reaches 33 mm, after which a further increase of 5 mm. in PCO_2 leads to a trebling of the ventilation. At a PO_2 of 37 mm. the threshold lies at a PCO_2 of about 31 mm. Thereafter an increase of as little as 2 mm. increases the ventilation by 30 l/min. (Nielsen and Smith, 1952).

As Asmussen (1963) points out, the increased response to CO_2 under conditions of hypoxia was discussed by Miesche-Rüsch in 1885, and formulated more precisely by Lindhard, in 1911.

Nielsen (1936) also investigated the influence of acidaemia on ventilation. The lowering of the CO_2 threshold following acidaemia caused by ingestion of ammonium chloride was shown clearly. Whether CO_2 and acidaemia are separate and cumulative stimuli to respiration is beyond the scope of this paper to discuss, but this concept forms the basis of the multiple-factor theory of Gray (1946) and the later mathematical refinements of the ventilatory equation (e.g. that of Cunningham (1963) and Lloyd (1963)).

Of especial interest was case C17. This patient with severe Fallot's tetralogy treated by a Blalock anastomosis had a resting arterial oxygen saturation of 76 per cent dropping to 20 per cent with exercise on the bicycle. Despite this gross fall, he was content to carry on at a level of 400 kg. m./min, was not dyspnoeic, and was stopped on

account of his gross cyanosis. This case illustrates well the measure of adaptation to hypoxaemia, and confirms the view that other factors than this are the special ones related to severe dyspnoea; the arterial PCO_2 did not rise above its resting level, and the pH dropped only a little by virtue of mild lactic acidaemia.

The general adaptations to hypoxaemia are too well known to require emphasis. On the enzymatic and metabolic levels, adaptation to chronic hypoxia has been shown to exist in animals. Tappan et al. (1957) found that guinea-pigs under those conditions have increased glycolysis and adenosine triphosphatase capacities, and accumulate higher levels of high-energy phosphates. Myoglobin stores, desoxyribonucleic acid, and succinoxidase activity are significantly higher. Hurtado (1963) states that natives of the Andes carry out muscular activity with less production of lactate than sea-level man. Such adaptive mechanisms may be operative in patients with chronic hypoxaemia and the lactate-pyruvate metabolism be correspondingly altered. On the other hand the normal oxygen uptake and the low lactate production of these cases suggests that there is little or no deficiency of oxygen supply to the tissues.

In 1958 Wood pointed out that in the Eisenmenger syndrome the patient with a patent ductus arteriosus was significantly less disabled than his fellow with a communication at atrial or ventricular level, and gave it as his opinion that this might be due to the fact that the head and neck were supplied with highly oxygenated blood from the left ventricle, the deoxygenated blood entering the aorta through the ductus distal to the origin of the carotid vessels. This observation gains in

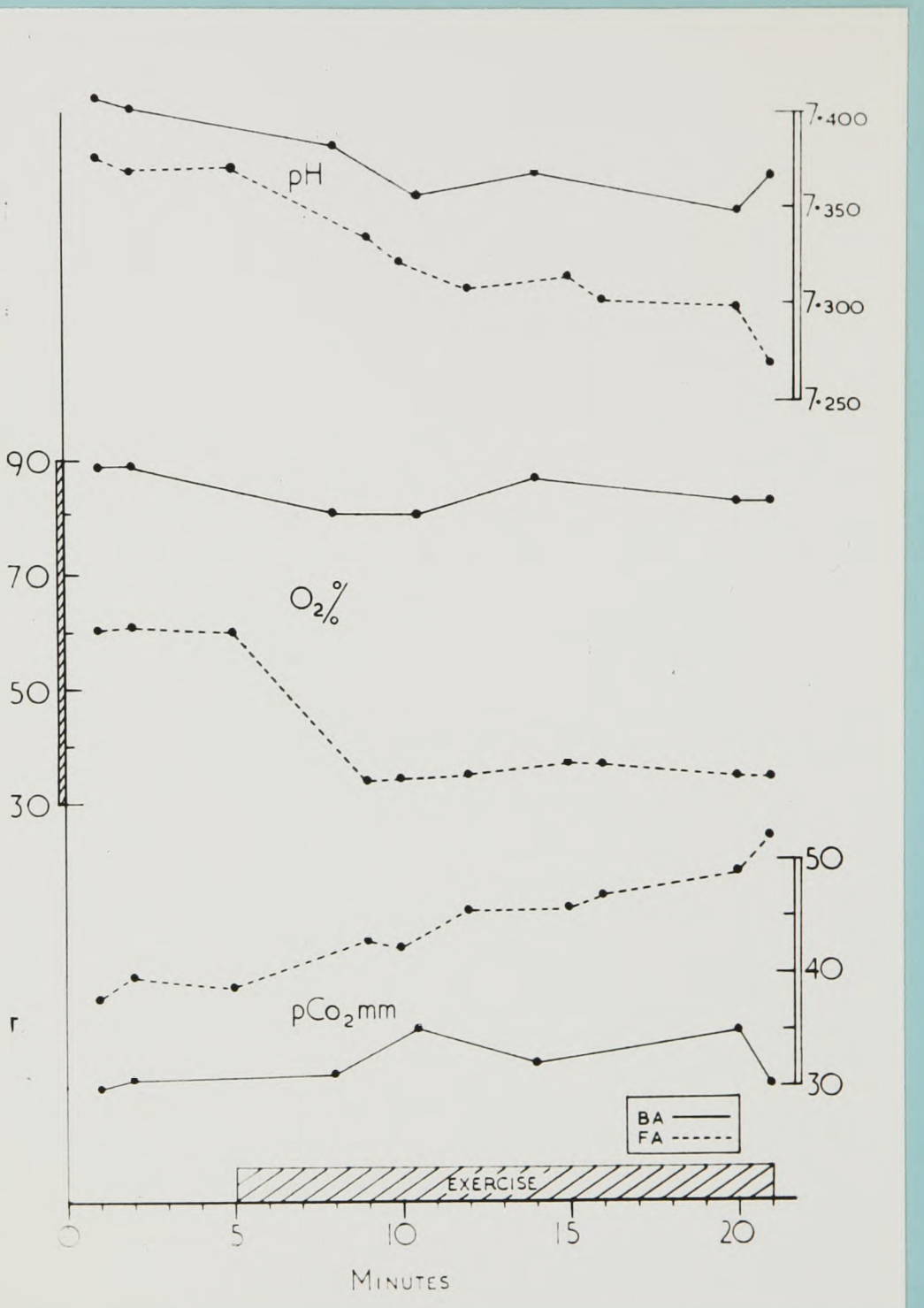


Fig. 61 Differential hypercapnia.

Changes in arterial blood of case H.H. aged 20, on exercise. In the right brachial artery the oxygen saturation remained high, the PCO_2 low, and the pH high; in the femoral artery there was gross hypoxaemia in association with hypercapnia and acidaemia (Case 2 of Table XX).

significance when it is realised that the oxygenated blood, being essentially pulmonary venous in origin, is low in CO_2 content. Not only is there differential cyanosis in the patient with the 'Eisenmenger ductus', but more significantly to the patient's symptomatology must there be 'differential hypercapnia'.

Since the above was published the existence of this differential hypercapnia has been clearly demonstrated in two patients, both with patent ductus arteriosus. Samples were withdrawn from the right brachial artery and the descending aorta on exercise. The first patient had a dominant left-to-right shunt and only a small right-to-left shunt, yet showed a differential of 5.5 mm. Hg. in PCO_2. The second had a large right-to-left shunt and developed a differential hypercapnia of 22 mm. Hg. The findings are given in Table XX, and illustrated in Fig. 61.

TABLE XX

Case	Age	Diagnosis		O_2 % BA	O_2 % FA	PCO_2 BA	PCO_2 FA	pH BA	pH FA
1		PDA	Rest	96.5	97.0	36.5	38.0	7.420	7.415
			Exercise	95.0	88.5	32.5	38.0	7.395	7.360
2		PDA	Rest	88.5	61.6	31.0	39.0	7.405	7.375
			Exercise	83.6	34.5	30.5	52.5	7.370	7.270

Miescher-Rüsch in 1885 concluded from his studies that only dissolved carbon dioxide, and not oxygen, was the humoral stimulus to ventilation, though hypoxia could alter the excitability of the respiratory centre.

As quoted by Asmussen (1963), he finished his discussion with the sentence, "So carbon dioxide spreads its protecting wings over the oxygen needs of the body." This appears to be particularly appropriate to the patient with morbus caeruleus.

While dyspnoea is a symptom, its objective expression is hyperventilation. Any stimulus to ventilation is, in the appropriate circumstances, a stimulus towards dyspnoea. It is likely that the chemical changes occurring in these cyanosed patients, acting in the milieu of hypoxaemia, are the special ones related to the severe dyspnoea which they suffer.

SUMMARY

A characteristic chest deformity is observed in children who have hyperkinetic pulmonary hypertension. The postulate that this is caused by abnormality of lung function, particularly a reduction in lung compliance, has been examined by performing lung function studies in infants and in older subjects with septal defects. The presence together of high flow and high pressure in the pulmonary circuit appears to be associated with a lowered compliance, and the relationship between abnormalities of pulmonary vascular dynamics and lung mechanics has been discussed.

The clinical and haemodynamic associations of disability have been assessed in atrial septal defect and, in order better to understand the disability of patients with left-to-right shunts, studies have been performed of the effects of exercise on the pulmonary haemodynamics in such patients. In a number of cases, especially in atrial septal defect with hyperkinetic pulmonary hypertension, exercise leads to an increase in both pulmonary flow and pressure. A significant inverse relationship exists between the product of pulmonary flow and pressure on the one hand, and lung compliance on the other, and the increment of this product with exercise is seen to be significantly related in atrial septal defect to the level of the resting pressure. An increase in lung compliance has been noted following closure of atrial septal defects, and it is suggested that this is a significant factor in the symptomatic improvement which follows such surgery.

Exercise studies have also been performed in patients with septal defects and central cyanosis, and the role of the blood gases in the

determination of hyperventilation and dyspnoea has been examined. Exercise in the more severe cases leads not only to hypoxaemia, but also to hypercapnia and consequent acidaemia, and the three classical humoral stimulants to ventilation are seen then to be operating together. As a corollary of this, the presence of differential hypercapnia as well as differential cyanosis in the 'Eisenmenger ductus' has been demonstrated, and would explain the relatively slight disability of these patients.

APPENDIX

TABLE II

Haemodynamic Data in 44 cases of V.S.D.

Case No.	P.A.P. mm.Hg.	P.F / S.F.	P.I. lit./min./ sq.m.	T.P.R. dynes-secs-cm^{-5} - m^2	Chest deformity
V 1	55/30	2.5	9.3	370	Severe
2	100/50	4.5	?	?	"
3	90/55	1.6	8.0	700	"
4	35/20	2.4	13.2	150	"
5	80/50	3.0	12.8	400	"
6	90/45	2.3	8.3	600	"
7	95/55	2.0	7.5	800	"
8	90/50	2.0	7.4	680	"
9	85/45	1.3	5.5	850	"
10	100/50	1.7	8.3	650	"
11	90/50	2.0	8.5	600	"
Avge.	83/45	2.3	8.9	580	
12	80/45	2.8	14.8	300	Moderate
13	90/45	3.1	9.0	550	"
14	80/30	1.5	4.0	950	"
15	55/20	1.6	10.0	250	"
16	80/30	5.0	16.5	225	"
17	115/55	4.0	14.0	425	"
18	80/50	1.7	6.6	725	"
19	70/40	1.6	7.5	550	"
20	95/50	1.6	9.6	550	"
21	90/55	2.0	15.4	350	"
22	95/60	?	?	?	"
Avge.	85/44	2.5	10.7	485	

Haemodynamic Data in 44 cases of V.S.D.

Case No.	P.A.P. mm.Hg.	P.F./ S.F.	P.I. lit./min./ sq. m.	T.P.R. dynes-secs-cm^{-5} - m^2	Chest deformity
V 23	30/15	3.0	25.0	50	Absent
24	80/25	4.4	15.0	225	"
25	15/8	1.8	5.6	150	"
26	15/6	1.5	?	?	"
27	18/5	2.1	7.5	100	"
28	20/10	8.0	23.5	50	"
29	17/5	2.7	12.2	60	"
30	65/30	2.5	7.5	450	"
31	25/15	1.2	6.3	250	"
32	40/15	2.6	7.2	200	"
33	35/5	1.6	6.5	200	"
34	25/10	1.3	5.0	250	"
35	20/10	1.1	3.6	300	"
36	55/20	4.0	10.1	250	"
37	55/30	8.0	35.0	100	"
38	25/15	1.4	6.7	225	"
39	65/50	3.0	7.7	575	"
40	70/40	1.3	6.5	600	"
41	55/25	3.2	10.7	250	"
42	25/10	4.5	20.6	60	"
43	85/45	3.3	10.0	450	"
44	50/20	1.4	4.0	600	"
Avge.	43/22	2.8	11.5	220	

Eisenmenger Complex

V 45	110/65	1.9	5.1	1250	Absent
46	100/40	0.9	3.1	1400	"
47	130/60	0.8	3.9	1890	"
48	125/55	0.3	1.7	4150	"
49	85/45	1.3	5.5	830	Moderate
50	90/60	0.8	3.3	1700	Absent
Avge.	107/54	1.0	3.8	1870	

TABLE III LUNG COMPLIANCE IN INFANTS AND YOUNG CHILDREN

1. NORMALS

No.	Initials	Age (months)	Compliance (ml./cm. H_2O)	F. R. C. (ml.)	Compliance/ F. R. C.
N 1	DF	4	9.5	111	0.085
2	AS	9	12.0	223	0.054
3	GS	6	7.6	180	0.042
4	DH	7	10.7	104	0.103
5	MR	11	10.4	262	0.040
6	AB	3	7.9	150	0.053
7	BS	2	4.6	78	0.059
8	GT	6	12.2	193	0.063
9	HA	6	15.0	195	0.077
10	JG	7	10.7	152	0.071
11	TM	6	8.5	164	0.050
12	DJ	8	9.4	214	0.044
				Mean =	0.062 S. D. ± 0.019

2. RESPIRATORY INFECTIONS

R 1	DS	5	4.5	153	0.029
2	MD	13	7.3	264	0.027
3	RG	8	4.2	135	0.031
4	SV	14	6.4	262	0.024
5	AG	17	11.1	318	0.035
6	HM	8	1.9	136	0.014
7	HM	8	3.2	153	0.020
8	RS	4	1.3	150	0.008
9	NS	12	4.4	243	0.019
10	VG	2	2.2	62	0.035
11	PH	13	10.0	261	0.038
12	CB	8	5.1	136	0.037
				Mean =	0.026 S. D. ± 0.010

TABLE III (continued)

3. V.S.D. NO P.H.T. NO RESPIRATORY INFECTION

No.	Initials	Age (months)	Compliance (ml./cm.H_2O)	F.R.C. (ml.)	Comp./ F.R.C.	PF/SF	P.A.P.
V 1	LS	3	4.4	79	0.056	2.0	39/16
2	SH	24	25.1	380	0.066	2.2	35/10
3	AW	34	19.0	460	0.041	1.3	30/17
4	YA	36	19.9	447	0.045	2.0	25/10
5	GB	8	18.7	172	0.092	1.5	21/6
6	AB	13	11.5	233	0.049	-	-
7	LH	12	10.5	230	0.045	-	-
8	CH	13	11.2	193	0.058	-	-
9	FH	13	12.6	247	0.052	-	-
10	VJ	16	25.7	295	0.087	-	-
11	AG	30	11.0	265	0.042	2.0	25/15
12	PG	9	7.7	172	0.045	2.0	30/18
13	AE	30	5.0	135	0.037	3.0	-
14	JS +	25	22.5	450	0.050	2.1	20/10
				Mean = 0.055	S.D. ± 0.016		

4. V.S.D. P.H.T. NO RESPIRATORY INFECTION

V15	LC	10	5.3	214	0.025	3.0	55/20
16	JW	4	3.2	104	0.031	2.5	60/30
17	PM	36	14.2	421	0.034	4.0	65/20
18	DP	4	2.6	125	0.021	?	70/20
19	RP	38	7.5	420	0.018	3.0	50/20
20	MO	3	4.4	105	0.042	2.0	85/45
21	BC ≠	4	3.9	126	0.031	2.4	50/20
				Mean = 0.029	S.D. ± 0.008		

5. V.S.D. WITH RESPIRATORY INFECTION

V18	DP	4	1.4	125	0.011	?	70/20
22	VA	19	5.8	380	0.016	-	-
23	LW	10	1.4	172	0.008	-	-
24	SC	18	7.5	380	0.019	-	-
				Mean = 0.014	S.D. ± 0.005		

+ ASD ≠ PDA

TABLE IV

THE EFFECT OF POSTURE ON LUNG COMPLIANCE

	No.	Initials	Compliance (ml./cm.H_2O)		
			Supine	Left	Right
NORMALS	N 1	DF	10.2	5.7	9.8
	3	GS	7.6	7.5	6.6
RESPIRATORY INFECTIONS	R 2	MD	7.3	6.7	5.6
	6	HM	1.9	1.9	1.9
	7	HM	3.6	3.4	2.8
V. S. D. NO P. H. T.	V 1	LS	4.4	3.0	3.8
	6	AB	11.7	10.3	8.8
V. S. D. P. H. T.	V 21	BC	3.9	3.3	3.8
V. S. D. P. H. T. RESPIRATORY INFECTION	V 18	DP	3.3	3.4	3.4
		Mean =	6.4	5.0	5.2

LUNG COMPLIANCE IN PATIENTS WITH SEPTAL DEFECTS

I A.S.D. without pulmonary hypertension.

Case No. and Initials		Age	Dyspnoea Grade	P.A.P. (mm.) S/D	P.I. (L/min./sq.m.)	S.I.	Compliance ($L/cm.H_2O$)	F.R.C. (L) Meas.	F.R.C. (L) Pred.	C/F.R.C. Meas.	C/F.R.C. Pred.	P x F*
101	LB	38	II	25/10	22.6	2.9	0.082	-	2.5	-	0.033	376
102	JW	23	0	16/5	8.3	3.6	0.350	5.9	3.3	0.059	0.106	91
103	JC	12	0	13/5	23.3	5.6	0.101	1.6	1.9	0.060	0.053	245
104	AB	9	0	15/5	7.8	3.4	0.051	1.3	1.5	0.040	0.035	82
105	RP	36	0	25/15	11.0	4.0	0.224	-	2.9	-	0.065	240
106	DW	10	0	20/10	10.3	3.1	0.070	-	1.1	-	0.063	150
107	KC	12	0	20/5	12.0	3.4	0.093	-	1.7	-	0.060	140
108	MR	9	0	20/10	Ratio	3.8	0.056	1.4	1.6	0.040	0.035	-
109	AW	14	0	15/5	10.3	3.3	0.060	-	1.6	-	0.037	91
110	PC	14	0	35/10	11.4	2.8	0.089	-	2.0	-	0.045	218
113	FW	42	I	30/10	5.4	2.8	0.221	2.6	2.1	0.085	0.104	106
114	LC	23	0	20/10	8.0	3.4	0.146	3.2	2.8	0.046	0.053	144
115	RS	12	0	-	-	-	0.069	1.5	1.5	0.045	0.045	-
116	JN	19	I	15/5	10.0	3.1	0.157	2.9	2.3	0.054	0.068	100
117	WM	29	0	20/5	10.5	2.4	0.080	2.2	3.3	0.036	0.025	121
118	PH	32	I	20/10	7.3	2.7	0.086	-	2.4	-	0.036	110
120	SR	29	0	35/10	14.7	4.0	0.140	-	2.5	-	0.056	324
124	MB	20	0	23/5	13.8	4.7	0.209	3.6	2.7	0.058	0.077	193
125	JH	35	I	36/14	12.8	3.2	0.112	3.7	2.6	0.030	0.043	294
Mean		22		22/8	11.5	3.4	0.126	2.7	2.2	0.050	0.055	173
							±0.071	±1.0	±0.3	±0.015	±0.018	±78

II A.S.D. with pulmonary hypertension.

Case No. and Initials		Age	Dyspnoea Grade	P.A.P. (mm.) S/D	P.I. (L/min./sq.m)	S.I.	Compliance ($L/cm.H_2O$)	F.R.C. (L) Meas.	F.R.C. (L) Pred.	C/F.R.C. Meas.	C/F.R.C. Pred.	P x F
135	MW	52	II	85/20	4.6	2.6	0.040	2.2	2.1	0.018	0.019	254
136	KJ	47	II	45/15	8.4	2.2	0.090	-	2.3	-	0.039	252
138	RR	52	II	75/40	9.4	2.3	0.178	-	2.3	-	0.077	535
140	ET	58	II	55/25	7.4	2.1	0.155	-	2.7	-	0.058	296
143	EP	49	II	80/40	6.0	1.5	0.109	-	2.6	-	0.043	360
144	NW	59	I	45/25	6.7	3.0	0.119	-	2.8	-	0.043	234
145	RM	24	I	60/25	22.2	2.5	0.190	-	3.2	-	0.059	930
146	DB	31	I	70/30	15.5	4.5	0.140	3.8	2.4	0.036	0.058	775
147	LI	54	II	50/28	3.4	1.5	0.213	-	3.4	-	0.062	119
149	LE	59	I	40/15	7.8	2.5	0.073	-	2.6	-	0.028	234
150	SB	52	I	40/15	3.7	1.7	0.232	5.1	4.2	0.045	0.055	81
Mean		49		59/25	8.6	2.4	0.140 ±0.059	3.7 ±1.4	2.8 ±0.6	0.033 ±0.014	0.048 ±0.036	339 ±267

III V.S.D. without pulmonary hypertension

Case No. and Initials		Age	Dyspnoea Grade	P.A.P. (mm) S/D	P.I. (L/min./sq.m)	S.I.	Compliance ($L/cm.H_2O$)	F.R.C. (L) Meas.	Pred.	C/F.R.C. Meas.	Pred.	P x F
V 46	SR	15	0	13/5	3.0	2.1	0.230	4.0	2.4	0.053	0.094	27
47	SR	12	0	15/7	6.0	4.0	0.250	2.8	1.8	0.093	0.139	66
48	BC	12	I	18/4	4.0	3.6	0.160	1.9	2.3	0.086	0.069	47
49	MB	14	0	15/5	6.5	5.3	0.092	2.4	2.1	0.037	0.043	65
50	EJ	14	I	20/10	11.3	3.6	0.095	2.4	2.2	0.040	0.043	170
51	BP	13	I	20/5	9.3	4.3	0.100	1.8	2.4	0.056	0.042	112
52	RI	16	0	15/5	6.9	2.9	0.200	3.1	3.1	0.066	0.066	69
53	RP	9	0	25/5	9.3	3.8	0.090	1.9	1.5	0.049	0.060	149
54	LU	6	0	15/10	5.1	2.0	0.070	0.9	1.0	0.080	0.070	61
55	SG	6	I	35/20	11.1	4.0	0.050	1.3	1.0	0.040	0.048	300
56	GB	56	I	27/12	11.0	4.1	0.150	2.4	2.5	0.062	0.060	266
57	PF	18	0	20/10	10.1	5.1	0.140	2.9	2.5	0.048	0.056	151
58	PH	14	I	43/14	10.0	5.5	0.120	-	1.8	-	0.070	280
59	MG	23	0	35/15	6.3	3.2	0.120	-	4.3	-	0.029	145
60	CT	16	0	32/15	13.6	4.4	0.160	-	1.9	-	0.083	312
61	JT	29	I	20/12	4.2	2.6	0.340	-	3.1	-	0.112	68
62	SM	41	I	38/20	5.0	3.3	0.220	-	2.8	-	0.078	160
63	TE	32	I	25/15	-	-	0.203	-	3.5	-	0.057	-
Mean		19		29/11	7.8	3.7	0.155 ±0.072	2.3 ±0.8	2.3 ±0.8	0.059 ±0.017	0.067 ±0.026	144 ±93

IV V.S.D. with pulmonary hypertension.

Case No. and Initials		Age	Dyspnoea Grade	P.A.P. (mm.) S/D	P.I. (L/min./sq.m)	S.I.	Compliance (L/cm.H_2O)	F.R.C. (L) Meas.	F.R.C. (L) Pred.	C/F.R.C. Meas.	C/F.R.C. Pred.	P x F
V 65	AC	19	I - II	80/50	12.9	3.4	0.070	3.6	3.3	0.028	0.021	838
66	PW	7	II	90/60	10.0	5.6	0.030	1.3	0.9	0.024	0.033	750
67	PD	7	II	65/30	11.4	4.3	0.023	0.9	1.0	0.026	0.023	580
68	WH	14	I - II	50/25	7.9	3.7	0.064	1.4	1.8	0.046	0.035	304
69	MT	18	I - II	100/50	9.7	3.9	0.038	1.9	2.7	0.020	0.041	750
70	SE	6	I	65/35	6.2	-	0.058	1.3	0.9	0.043	0.061	315
71	NG	6	I	75/30	16.0	6.2	0.034	1.0	1.0	0.034	0.034	844
72	NC	17	I	100/25	7.3	2.5	0.190	-	2.8	-	0.068	453
74	TB	29	I - II	45/10	30.0	3.7	0.090	-	2.8	-	0.032	750
75	MD	14	II	85/45	-	-	0.053	-	1.8	-	0.029	-
78	SC	14	II	60/40	8.0	4.1	0.084	-	1.8	-	0.048	300
79	EC	40	II	60/35	3.9	2.6	0.093	-	2.4	-	0.037	105
80	PE	22	I	100/55	10.7	2.1	0.063	-	2.4	-	0.029	825
81	BH	19	I	115/50	10.0	3.6	0.120	-	3.2	-	0.038	830
83	CB	47	I - II	50/30	7.1	4.0	0.148	-	3.4	-	0.044	284
84	NF	14	I	50/5	23.0	4.1	0.064	-	1.7	-	0.028	800
85	JB	15	I	105/60	5.2	2.4	0.083	-	2.9	-	0.029	232
88	JH	62	III	130/40	3.8	2.1	0.122	-	4.2	-	0.029	304
Mean		21		80/39	10.8	3.6	0.080 ±0.042	1.6 +0.91	2.3 ±0.92	0.031 ±0.010	0.037 ±0.012	545 ±260

V Eisenmenger

Case and Initials	No.	Age	Dyspnoea Grade	P.A.P. (mm) S/D	P.I. (L/min./sq.m)	S.I.	Compliance (L/cm.H_2O)	F.R.C. Meas.	F.R.C. Pred.	C/F.R.C. Meas.	C/F.R.C. Pred.	P x F
1	GC	36	A.S.D. II	75/25	5.5	4.3	0.110	2.2	2.5	0.050	0.044	160
2	MR	19	P.D.A. I	120/75	4.9	2.4	0.214	3.1	3.7	0.069	0.058	490
3	HH	18	P.D.A. I	150/80	1.1	2.9	0.148	-	2.1	-	0.071	126
4	AC	23	V.S.D. III	120/60	1.9	3.3	0.103	-	2.7	-	0.038	171
5	TC	25	V.S.D. II	110/50	2.7	2.1	0.190	-	3.8	-	0.050	216
6	SB	36	V.S.D. I	105/60	5.1	3.0	0.120	3.1	3.7	0.038	0.032	400
9	MT	38	A.S.D. III	150/60	2.5	3.2	0.270	-	2.6	-	0.104	260
10	EW	9	P.D.A. I	115/65	6.6	4.5	0.051	-	0.8	-	0.064	594
11	DJ	19	V.S.D. II	125/80	4.5	2.8	0.147	-	2.3	-	0.064	346
15	AW	18	V.S.D. II	90/40	4.6	2.7	0.137	-	2.4	-	0.057	300
16	AB	43	A.S.D. II	95/40	2.7	1.9	0.175	3.9	3.7	0.045	0.047	150
Mean		26		114/58	3.8	3.0	0.151 ±0.058	3.1 ±0.7	2.7 ±1.7	0.050 ±0.014	0.048 ±0.019	292 ±148

* P x F is the product of the mean pulmonary arterial pressure (mm. Hg) and the pulmonary index (L/min./sq.m.)

TABLE VII

FORCED VITAL CAPACITY, FORCED EXPIRATORY RESISTANCE AND PEAK FLOW.

Group		F.V.C. %predicted	F.E.R. %	P.F. L/min.
I	Mean	93	77	420
	S.D.	25 (19)	17 (16)	106 (14)
	Range	56 - 150	39 - 96	250 - 620
II	Mean	92	75	360
	S.D.	20 (15)	10 (14)	124 (13)
	Range	54 - 125	60 - 85	180 - 425
III	Mean	93	85	430
	S.D.	21 (18)	9 (7)	137 (7)
	Range	56 - 130	75 - 92	280 - 650
IV	Mean	82	81	350
	S.D.	17 (20)	10 (15)	114 (12)
	Range	55 - 112	68 - 95	140 - 490
V	Mean	102	80	460
	S.D.	14 (13)	10 (14)	136 (10)
	Range	75 - 120	61 - 93	250 - 630

Note: The number of patients in each group is shown in brackets. This table and Fig. 2n include later cases whose details are nor given in Table VIII.
For designation of groups see Table VIII.

TABLE VIII

FORCED VITAL CAPACITY: FORCED EXPIRATORY RESISTANCE AND PEAK FLOW

Case No.	Initials and age	Disability grade	P.A.P.	P.I.	S.I.	F.V.C. % pred.	F.E.R.	Peak flow
GROUP I : A.S.D. without P.H.T.								
A 101	L.B. 38	II	25/10	22.6	2.9	56	72	250
102	J.W. 23	0	16/4	8.3	3.6	95	93	620
103	J.C. 12	0	13/5	23.3	5.6	72	83	275
104	A.B. 9	0	15/4	7.8	3.4	74	77	-
108	M.R. 9	0	22/10	Ratio	3.8	100	-	-
111	K.I. 41	I	18/4	9.8	2.6	69	63	340
112	D.R. 26	0	25/5	7.2	2.8	59	57	-
113	F.W. 42	I	30/8	5.4	2.8	75	39	370
114	L.C. 23	0	25/10	8.0	3.4	95	-	-
115	R.S. 12	0	-	-	-	90	-	-
116	J. N. 19	I	15/4	10.0	3.1	87	-	-
117	W.M. 29	0	18/5	10.5	2.4	82	-	-
118	P.H. 32	I	20/10	7.3	2.7	115	96	440
119	J. G. 16	0	28/10	6.2	3.5	150	83	440
120	S.R. 29	0	35/10	14.7	4.0	119	80	400
121	J. S. 25	0	27/8	15.0	4.3	120	83	460
					Mean	93	77	401
					S.D.	25	17	104
GROUP II : A.S.D. with P.H.T.								
A 135	M.W. 52	II	84/22	4.6	2.7	54	-	-
137	D.K. 38	II	75/40	7.2	4.2	80	61	-
138	R.R. 52	II	75/38	9.4	2.3	89	71	300
139	D.B. 49	II	45/15	4.8	2.3	80	60	220
140	G.T. 58	II	55/25	7.8	2.1	96	60	180
141	F.H. 52	II	40/15	5.4	3.1	122	83	405
142	F.M. 42	II	42/13	6.4	2.0	100	65	240
143	E.P. 49	II	80/40	6.0	1.5	97	79	425
144	N.W. 59	I	50/25	6.7	3.0	76	82	315
145	R.M. 24	I	65/25	22.2	2.5	71	80	420
					Mean	86	71	310
					S.D.	18	10	96

FORCED VITAL CAPACITY: FORCED EXPIRATORY RESISTANCE AND PEAK FLOW (Continued)

Case No.	Initials and age	Disability grade	P.A.P.	P.I.	S.I.	F.V.C. % pred.	F.E.R.	Peak flow
GROUP III : V.S.D. without P.H.T.								
V 46	S.R. 15	0	13/5	3.0	2.1	113	-	-
47	S.R. 12	0	15/7	6.0	4.0	96	-	-
48	B.C. 14	0	18/4	4.3	3.6	48	-	-
49	M.B. 14	0	15/5	6.5	5.3	79	-	-
50	E.J. 14	I	20/10	11.3	3.6	93	-	-
51	B.P. 13	I	18/5	9.3	4.3	99	-	-
52	R.I. 16	0	15/5	6.9	2.9	87	-	-
53	R.P. 9	0	24/7	9.3	3.8	100	-	-
54	L.U. 6	0	15/8	5.1	2.0	60	-	-
55	S.G. 6	I	35/18	14.8	6.1	95	-	-
56	G.B. 56	I	27/12	11.1	4.0	73	75	-
57	P.F. 18	0	20/10	10.1	5.1	102	-	-
58	P.H. 14	I		10.0	5.5	77	92	280
59	M.G. 23	0	35/15	6.3	3.2	114	81	440
60	C.T. 15	I	32/15	13.6	4.4	122	84	380
61	E.P. 23	I	23/8	7.3	4.5	130	88	-
					Mean	93	83	340
					S.D.	21	6	79
GROUP IV : V.S.D. with HYPERKINETIC PULMONARY HYPERTENSION								
V 65	A.C. 19	I-II	80/50	12.9	3.4	100	68	-
66	P.W. 7	I-II	90/60	10.0	5.5	63	-	-
67	P.D. 7	I	67/32	11.4	4.3	55	-	-
68	W.H. 13	II	50/25	7.9	3.7	82	89	-
69	M.T. 17	II	100/50	9.7	3.9	54	92	-
70	S.E. 6	I	65/35	6.2	-	88	-	-
71	N.G. 6	I	75/30	16.0	6.3	87	-	-
72	N.C. 17	I	100/25	7.3	2.5	105	84	470
73	D.H. 16	I	45/15	5.6	2.7	100	-	-
74	T.B. 29	I-II	45/8	30.0	3.7	108	93	420
75	M.D. 14	II	105/60	-	-	93	85	180

FORCED VITAL CAPACITY: FORCED EXPIRATORY RESISTANCE AND PEAK FLOW (Continued)

Case No.	Initials and age	Disability grade	P.A.P.	P.I.	S.I.	F.V.C. % pred.	F.E.R.	Peak flow
GROUP IV: (continued)								
V 78	S.C. 14	I	60/40	5.6	2.9	70	89	320
79	E.C. 40	II	60/35	3.9	2.6	75	63	140
80	P.E. 21	I	100/55	10.7	2.1	63	91	390
81	B.H. 19	I - II	115/50	10.0	3.6	88	84	460
83	J.W. 30	I	80/30	4.0	2.0	82	74	280
84	C.B. 47	II	50/30	7.1	4.0	84	69	490
85	J.B. 15	I	105/60	5.2	2.4	90	95	260
86	J.H. 62	III	130/40	3.8	2.1	78	75	250
					Mean	82	81	340
					S.D.	17	10	113
GROUP V: EISENMENGER								
E 2	M.R. 19	I	120/75	4.9	2.4	103	-	-
3	H.H. 18	II	150/80	1.1	2.9	97	84	420
4	A.C. 23	III	120/60	1.9	3.3	85	83	320
5	T.C. 25	II	110/50	2.7	2.1	110	83	508
6	S.B. 36	I	105/60	Ratio	1.7	104	61	-
9	MDT 38	II - III	150/60	2.7	3.1	107	73	-
10	E.W. 9	I	115/65	6.6	4.5	75	84	-
11	D.J. 19	II	125/50	4.5	2.8	120	93	420
12	W.G. 35	I	80/30	1.4	2.4	118	72	610
13	J.L. 26	II	-	-	-	106	90	560
15	A.W. 18	I	90/40	4.6	2.7	82	79	300
					Mean	101	80	466
					S.D.	14	10	106

TABLE IX DETAILS OF 100 DENVER PATIENTS STUDIED

(B = before surgery; A = after surgery)

Case No.	Initial and age	Sex	PI		SI		PAP		Symptoms		TPR	
			B	A	B	A	B	A	B	A	B	A
AD 1	GH 26	F	8.9	-	2.3	-	100/32	-	III	0	530	-
2	CC 6	F	13.0	6.4	3.0	6.4	27/16	19/9	0	0	123	250
3	AC 5	M	40.0	4.8	6.8	4.8	20/7	20/15	I	0	20	300
4	ME 19	F	7.1	2.9	3.3	2.9	24/12	20/3	I	0	185	285
5	WG 6	M	16.4	3.8	4.2	3.8	30/10	30/15	I	0	100	450
6	DG 4	F	-	-	-	-	-	15/9	0	0		
7	VL 33	F	6.7	+	2.7	-	65/23	-	II	-	-	-
8	RG 8	M	13.0	-	4.0	-	50/36	-	0	0	252	-
9	CG 5	F	5.3	-	3.3	-	44/?	-	I	0	-	-
10	RC 5	F	11.3	5.2	5.0	5.2	30/11	38/17	I	0	136	400
11	JG 8	M	15.2	-	6.6	-	40/?	44/13	0	0	120	-
12	AM 14	M	10.0	3.1	2.9	3.6	38/19	30/12	I	0	240	460
13	NC 29	F	14.5	5.4	3.0	4.0	30/14	30/13	II	0	105	202
14	DW 20	M	-	27.0	-	4.4	47/17	40/17	II	0	-	74
15	CP 34	F	10.5	3.1	3.1	3.1	20/13	22/10	I	0	130	362
16	DD 14	F	18.6	3.9	2.6	2.6	43/25	18/10	II	III‡	80	80
17	JU 5	M	-	-	-	-	37/?	-	0	0	-	-
18	SK 4	M	14.2	4.8	4.1	4.3	35/18	29/15	0	0	23	295
19	GC 4	M	8.1	5.3	3.7	4.6	35/14	39/14	0	0	207	333
20	EA 27	F	13.1	4.2	2.9	3.5	82/48	38/18	I	0	360	500
21	TG 32	F	7.3	3.4	2.2	3.4	39/12	28/10	II	0	230	377
22	FH 31	M	10.6	-	2.9	-	87/40	-	III	-	425	-
23	JT 28	F	20.0	3.8	2.6	3.8	92/?##	23/8	III	0	240	276
24	HH 33	F	24.8	-	3.8	-	39/15	-	II	-	83	-
25	JJ 20	F	-	3.6	-	3.6	-	22/10	0	0	-	312
26	HB 10	F	-	5.2	-	5.2	-	27/10	III	0	-	247
27	TK 5	F	14.0	-	5.1	-	30/13	-	0	0	107	-
28	AA 4	F	19.0	-	-	-	29/10	-	I	0	70	-
29	WS 24	F	21.4	5.0	2.9	5.0	33/13	20/10	I	0	75	240
30	MG 21	F	-	-	-	-	-	-	-	-	-	-
31	BH 14	F	-	4.8	-	4.8	24/3	24/13	II	0	217	27
32	EG 42	F	-	-	-	-	-	-	II	0	-	-
33	RB 13	M	-	4.5	2.9	3.7	38/12	32/19	I	0	160	402
34	SR 13	F	10.1	5.4	3.7	5.4	30/13	20/15	0	0	150	202
35	GG 43	F	5.5	4.5	3.3	4.5	69/30	28/15	III	0	638	385

DETAILS OF 100 DENVER PATIENTS STUDIED

(continued)

Case No.	Initial and age	Sex	PI		SI		PAP		Symptoms		TPR	
			B	A	B	A	B	A	B	A	B	A
AD 36	MM 24	F	-	-	-	-	24/5	-	II	0	-	-
37	MAR 35	F	5.1	-	4.1	-	70/13	-	III	-	1080	-
38	DY 45	F	-	-	-	-	31/10	-	I	0	-	-
39	EH 13	M	-	3.4	-	3.4	26/10	27/12	II	0	-	474
40	CR 30	M	9.2	-	3.0	-	27/7	-	II	0	121	-
41	JJ 6	F	10.0	-	3.4	-	52/17	-	0	-	210	-
42	BR 15	F	7.4	2.9	2.7	2.9	40/13	25/10	0	0	235	412
43	RW 13	M	6.0	-	4.6	-	100/50	-	I	-	1000	-
44	RM 12	M	7.9	2.4	4.1	2.4	35/25	19/12	0	0	313	480
45	GM 28	M	12.3	-	2.3	-	35/15	-	0	0	188	-
46	FM 9	M	10.7	3.2	3.7	3.2	45/20	48/17	0	0	240	530
47	RD 16	F	6.0	-	3.2	-	95/45	35/10	I	0	757	-
48	MD 10	F	7.0	3.1	2.6	3.1	35/15	30/12	I	0	283	420
49	DH 25	F	8.8	-	4.5	-	27/12	-	I	0	155	-
50	DJ 10	F	21.2	3.0	3.9	3.0	24/12	23/10	I	0	70	402
51	DR 35	M	10.2	-	4.2	-	35/20	-	I	I	204	-
52	JL 21	F	21.0	4.1	6.7	4.1	47/17	37/13	I	0	120	420
53	MB 7	M	22.0	5.5	4.4	5.5	32/12	22/8	0	0	80	220
54	PM 37	F	13.8	-	3.6	-	50/15		I	0	170	-
55	ES 1	M	8.1	4.9	3.2	4.9	55/?	36/10	-	-	-	-
56	NL 5	F	7.2	3.4	4.6	3.4	38/20	25/13	II	0	283	400
57	ES 25	F	21.0	-	4.3	-	27/8	-	I	0	70	-
58	RB 5	M	16.1	3.9	4.9	3.9	36/12	21/13	0	0	130	340
59	AH 18	F	8.9	3.3	2.9	2.3	41/11	25/10	II	0	189	346
60	JM 23	M	8.0	3.3	3.1	2.6	42/16	25/11	0	0	290	380
61	CH 37	M	7.5	-	1.5	-	27/12	-	II		215	-
62	CP 10	F	-	-	-	-	-	-	0	0	-	-
63	RC 20	M	7.1	-	2.1	-	33/10	-	0	0	196	-
64	LS 7	M	12.8	-	5.2	-	22/10	-	I	0	101	-
65	VG 28	F	7.5	-	3.5	-	47/6	-	0	0	273	-
66	VH 13	F	11.5	-	3.1	-	28/10	-	0	0	120	-
67	DV 21	F	13.7	-	1.6	-	40/15	-	II	0	136	-
68	CM 7	F	-	-	-	-	-	-	0	0	-	-
69	ET 27	F	+	-	4.1	-	-	-	I	0	-	-
70	SM 6	M	20.1	-	6.1	-	41/15	-	I	0	98	-

DETAILS OF 100 DENVER PATIENTS STUDIED

(continued)

Case No.	Initials and age	Sex	PI		SI		PAP		Symptoms		TPR	
			B	A	B	A	B	A	B	A	B	A
AD 71	RB 18	M	19.5	16.8	-	2.7	69/34	45/20	II	I	189	113
72	YR 26	F	-	-	-	-	-	-	III	0	-	-
73	BH 12	F	5.0	-	2.4	-	14/8	-	0	0	163	-
74	BB 3	F	10.7	-	4.0	-	38/21	-	II	0	201	-
75	GW 20	F	-	-	-	-	-	-	0	0	-	-
76	RC 21	M	12.1	-	2.9	-	34/18	-	0	0	-	-
77	SR 6	M	6.3	-	4.3	-	34/13	-	0	0	252	-
78	RC 30	M	7.0	-	2.0	-	76/30	-	I	0	512	-
79	JS 10	F	12.0	3.7	-	-	37/13	-	II	0	141	-
80	ER 19	F	-	-	-	-	-	-	0	0	-	-
81	MM	F	5.7	-	2.3	-	58/20	-	I	0	464	-
82	BU 24	F	-	-	-	-	-	-	0	0	-	-
83	JC 9	F	6.6	-	3.9	-	32/14	-	0	0	214	-
84	CL 32	F	7.9	-	3.1	-	24/13	-	I	0	208	-
85	MH 32	F	3.6	-	2.3	-	110/48	105/50	I	II	1530	1600
86	RC 11	F	-	-	-	-	-	-	0	0	-	-
87	JS 12	M	6.2	-	2.7	-	24/11	-	0	0	198	-
88	JD 37	M	14.0	-	3.9	-	35/12	-	I	0	104	-
89	PV 33	F	-	-	-	-	34/14	-	III	0	-	-
90	RC 45	F	-	-	-	-	51/29	-	II	II	-	-
91	BG 25	F	5.6	-	3.4	-	24/9	-	II	0	185	-
92	MJF 9	F	9.9	-	3.7	-	21/8	-	0	0	101	-
93	PE 26	F	7.3	-	2.1	-	26/10	-	0	0	170	-
94	PS 13	F	10.9	-	3.2	-	20/10	-	0	0	98	-
95	MM 30	F	-	-	-	-	60/20	-	III	-	-	-
96	PL 25	F	-	-	-	-	27/5	-	0	0	-	-
97	CM 5	F	-	-	-	-	-	-	0	0	-	-
98	FR 39	F	-	-	-	-	30/7	-	III	-	-	-
99	BR 3	F	-	-	-	-	-	-	0	0	-	-
100	FV 8	F	-	-	-	-	-	-	0	0	-	-

Case No.	Sex Age	Diagn.	B_2S.A. m	$\dot{V}_{O_2}$ ml/min. S.T.P.D.	Heart Rate	FLOWS L/min. Qs	Qp	Qe	SHUNTS L/min. Left to Right	Right to Left	Fick	Qp - Qe / Qp Dye Curves	PRESSURES (mm. Hg.) P.C.V. m	P.A. s.d.m.	R.V. s.d.	Systemic s.d.m.
AN 1	M 14	A.S.D.	1.65	R 240	100	9.2	14.0	9.2	4.8	0	34	33	12	25/12/17	25/7	125/80/95
				E 520	130	14.3	17.2	14.3	2.9	0	17	35	-	35/20/25	35/7	160/80/105
AN 2	F 38	A.S.D.	1.60	R 200	132	4.2	9.9	4.2	5.7	0	58	-	11	26/16/20	26/5	-
				E 370	132	-	13.5	-	-	0	-	-	11	28/15/20	-	-
AN 3	F 30	A.S.D.	1.70	R 170	70	3.8	10.0	3.8	6.2	0	62	68	5	33/10/17	36/10	125/65/82
				E 420	90	6.2	15.0	6.2	8.8	0	59	84	-	-	39/6	135/72/90
AN 4	F 16	A.S.D.	1.50	R 160	80	5.5	14.5	5.5	9.0	0	62	66	6	25/6/11	28/6	-
				E 470	115	10.3	12.2	10.3	1.9	0	16	47	-	20/8/10	20/0	-
AN 5	F 24	A.S.D.	1.50	R 190	80	4.0	13.6	4.0	9.6	0	70	77	7	20/6/13	45/6	90/55/60
				E 450	120	8.6	20.3	8.6	11.7	0	58	74	-	25/10/15	50/6	130/80/100
AN 6	F 28	A.S.D.	1.60	R 250	68	6.4	23.6	6.4	17.2	0	73	81	10	34/12/20	32/6	125/75/90
				E 390	94	6.1	23.2	6.1	17.1	0	74	115	-	33/20/25	33/8	125/75/80
AN 7	F 34	A.S.D.	1.60	R 140	75	5.1	20.4	5.1	15.3	0	75	78	12	36/14/23	39/5	118/68/85
				E 330	90	-	27.4	-	-	0	-	92	-	40/17/26	-	-
AH 38M	52	A.S.D.	2.10	R 190	50	3.6	8.0	3.6	4.4	0	55	40	6	40/15/22	40/10	100/55/75
				E 790	85	-	15.0	-	-	0	-	35	-	50/15/28	-	100/55/75
AH 39F	59	A.S.D. (A.F.)	1.90	R 270	94	5.8	12.8	5.8	7.0	0	55	54	-	45/25/35	40/10	125/80/100
				E 410	104	6.3	13.0	6.3	6.7	0	52	65	-	-	50/10	125/80/100
AH 40F	59	A.S.D.	1.50	R 180	70	3.8	10.9	3.8	7.1	0	65	67	5	40/15/26	40/10	95/55/65
				E 450	95	6.0	18.8	6.0	12.8	0	68	90	-	50/15/28	-	-
AH 41M	54	A.S.D. (A.F.)	1.90	R 180	75	2.7	6.4	2.7	3.7	0	58	79	12	50/28/35	50/14	135/80/100
				E 760	100	-	16.9	-	-	0	-	38	-	75/25/40	-	150/80/100
AH 42M	48	A.S.D.	1.80	R 200	90	5.0	9.8	5.0	4.8	0	46	74	6	90/35/50	90/4	150/100/12
				E 870	110	12.4	18.9	12.4	6.5	0	34	-	-	100/45/55	-	-

TABLE XII

AH 43F	A.S.D. 1.35	R 210	90	6.0	21.0	6.0	15.0	0	72	-	7	72/28/43	75/10	130/70/90
31		E 600	140	8.9	23.0	8.0	15.0	0.9	65	-	10	105/43/100	-	170/85/112
AH 44F	A.S.D. 1.60	R 200	68	4.1	9.9	3.2	6.7	0.9	68	-	-	72/15/20	74/0	99/70/84
39		E 370	126	-	16.8	-	-	0	-	-	-	75/24/39	-	114/85/99
AH 45F	A.S.D. 1.70	R 180	70	2.6	11.8	2.6	9.2	0	78	78	20	80/40/50	80/15	110/60/80
49	+ M.S. (A.F.)	E 400	130	5.7	22.0	5.7	16.3	0	74	80	-	100/45/50	100/15	140/65/90
AE 61M	A.S.D. 1.90	R 180	72	4.5	2.7	2.4	0.3	2.1	11	-	-	80/30/45	80/3	80/45/60
35	Eisen.	E 680	110	9.4	7.9	6.3	1.7	3.1	22	-	-	110/40/65	-	110/55/75
AS 82M	A.S.D. 1.90	R 280	84	6.5	25.4	6.5	19.0	0	75	70	12	30/14/17	40/10	138/85/90
22	+ P.S.	E 590	106	-	24.3	-	-	0	-	75	-	48/15/28	85/10	165/90/105
AS 83F	A.S.D. 0.90	R 130	100	2.9	6.8	2.0	3.9	0	57	-	9	29/12/18	70/8	96/52/74
9	+ P.S.	E 230	120	-	7.7	-	-	0	-	-	-	33/12/18	80/10	90/60/75
VN 1 M	V.S.D. 1.60	R 250	68	6.0	9.0	6.0	3.0	0	33	40	11	23/13/16	36/10	105/70/85
14		E 800	100	10.2	13.8	10.2	3.6	0	26	54	-	28/19/22	41/8	120/72/85
VN 2 M	V.S.D. 1.50	R 180	72	4.9	5.6	4.9	0.7	0	12	17	6	21/10/16	26/6	150/90/105
16		E 780	107	14.0	16.0	14.0	2.0	0	12	14	-	28/10/18	28/0	165/100/11
VN 3 M	V.S.D. 1.80	R 240	92	5.7	9.6	5.7	3.9	0	40	45	11	25/12/17	30/8	160/100/11
37		E 620	88	8.9	12.9	8.9	4.0	0	31	25	-	28/18/22	34/8	160/90/110
VN 4 F	V.S.D. 1.50	R 170	80	5.7	11.5	5.7	5.8	0	50	53	9	28/10/14	32/4	100/72/82
15		E 610	120	10.5	13.0	10.5	2.5	0	19	59	-	48/25/31	-	-
VN 5 M	V.S.D. 1.40	R 230	72	6.2	19.0	6.2	12.8	0	67.5	30	13	32/15/24	52/7	140/80/100
15		E 440	-	7.5	-	7.5	-	0	-	23	-	-	-	160/95/112
VH 31M	V.S.D. 1.80	R 280	84	6.6	15.4	6.6	8.8	0	57	46	9	45/20/32	55/2	105/65/85
26		E 670	115	11.2	17.9	11.2	6.7	0	37	22	-	65/40/52	-	125/80/95
VH 32M	V.S.D. 1.50	R 200	60	3.8	11.3	3.8	7.5	0	66	68	9	100/25/60	100/10	130/70/95
17		E 530	130	5.3	18.0	5.3	12.7	0	70	64	-	135/50/90	-	145/85/105
VH 33M	V.S.D. 1.60	R 230	72	5.6	15.6	5.6	10.0	0	64	50	17	115/50/65	115/7	115/62/80
18		E 470	94	7.0	8.2	5.1	2.1	0.9	26	26	-	150/60/80	150/8	150/75/90
VE 62F	V.S.D. 1.60	R 210	72	4.6	7.3	4.2	3.1	0.4	42	48	5	125/50/80	125/8	125/75/90
19	Eisen.	E 550	100	10.0	11.0	7.5	3.5	2.5	32	22	-	160/75/105	160/8	165/75/105

VE 63M	V.S.D.	1.70	R 220	68	3.6	4.5	3.1	1.4	0.5	31	28	7	95/50/65	95/4	95/60/75
25	Eisen.		E 630	94	12.1	5.9	5.7	0.2	6.4	35	-	-	125/65/85	125/6	125/80/95
VS 81M	V.S.D.	1.90	R 250	68	6.0	11.9	6.0	5.9	0	50	39	15	35/15/25	60/8	115/70/90
23	+ P.S.		E 560	100	8.2	21.0	8.2	12.8	0	61	51	-	40/14/28	60/9	150/90/105
VS 82M	V.S.D.	1.70	R 250	75	6.2	9.1	6.2	2.9	0	32	15	6	18/6/11	100/8	130/60/80
19	+ P.S.		E 660	108	11.5	13.1	10.1	3.0	1.4	23	37	-	20/5/9	110/5	130/70/85
PN 1 M	P.D.A.	1.20	R 160	88	4.0	5.1	4.0	1.1	0	22	12	-	28/15/20	32/5	105/65/80
10			E 450	115	7.0	-	7.0	-	0	-	28	-	-	32/5	-
PH 30F	P.D.A.	1.30	R 180	85	2.7	13.9	2.7	11.2	0	80	95	17	100/55/70	100/7	165/65/95
21			E 320	105	3.6	9.0	3.6	5.4	0	60	58	15	105/60/78	100/7	-
PE 64F	P.D.A.	1.50	R 200	75	5.3	3.3	2.9	0.4	2.4	12	-	6	110/63/82	110/5	103/57/85
27	Eisen.		E 460	107	-	4.2	-	-	-	-	-	6	143/74/110	-	137/71/110
PE 65F	P.D.A.	1.60	R 160	80	4.3	6.5	3.7	2.8	0.4	43	-	8	110/70/85	110/8	110/70/85
34	Eisen.		E 610	125	9.1	-	7.7	-	1.4	-	-	-	150/80/110	-	-

Case No.	Sex	Age Years	B.S.A. (m^2)	Hb. (G/100ml)	Diagnosis	Clinical disability Grade	$\dot{V}O_2$ ml/min(STPD) Rest	Exerc.	$\dot{V}$ L/min(BTPS) Rest	Exerc.	V.E. Rest	Exerc.	Resp. Rate Rest	Exerc.
AN 1	M	14	1.65	13.7	A.S.D.	0	240	520	5.5	16.0	2.3	3.1	12	18
AN 2	F	38	1.60	13.3	A.S.D.	1	200	370	10.8	12.3	5.3	3.1	28	28
AN 3	F	30	1.70	14.4	A.S.D.	2	170	420	5.5	12.6	3.2	3.0	20	23
AN 4	F	16	1.50	11.5	A.S.D.	0	160	470	4.1	10.0	2.6	2.1	14	16
AN 5	F	24	1.50	14.8	A.S.D.	0	190	450	6.0	13.7	3.2	3.1	20	30
AN 6	F	28	1.60	11.6	A.S.D.	0	250	390	6.0	10.0	2.4	2.6	16	18
AN 7	F	34	1.60	12.9	A.S.D.	1	140	330	6.9	17.8	4.9	5.4	21	25
AN 8	F	51	1.80	14.0	A.S.D.	1	230	-	9.6	-	4.2	-	22	-
AH 38	M	52	2.10	15.3	A.S.D., P.H.T.	2	190	790	6.8	21.2	3.6	2.7	15	20
AH 39	F	59	1.90	12.8	A.S.D., P.H.T. A.F.	1	270	410	7.1	11.9	2.6	2.9	17	24
AH 40	F	59	1.50	13.3	A.S.D., P.H.T.	1	180	450	5.6	13.4	3.1	3.0	19	21
AH 41	M	54	1.90	16.7	A.S.D., P.H.T. A.F.	2	180	760	4.3	17.7	2.4	2.3	13	15
AH 42	M	48	1.80	16.4	A.S.D., P.H.T.	2	200	870	8.8	25.6	4.4	3.0	18	24
AH 43	F	31	1.35	10.6	A.S.D., P.H.T.	2	220	600	7.3	14.9	3.3	2.5	25	26
AH 44	F	39	1.60	13.1	A.S.D., P.F.T.	2-3	200	370	6.6	12.9	3.3	3.5	15	26
AH 45	F	49	1.70	15.9	A.S.D., P.H.T. M.S., A.F.	2	180	400	4.4	15.9	2.5	3.9	20	28
AS 82	M	22	1.90	13.9	A.S.D., P.S.	0	280	590	7.5	19.5	2.7	3.3	17	20
AS 83	F	9	0.90	12.6	A.S.D., P.S.	1	130	230	4.4	9.9	3.4	4.2	20	30
VN 1	M	14	1.60	14.0	V.S.D.	1	250	800	6.5	21.3	2.6	2.7	14	17
VN 2	M	16	1.50	13.6	V.S.D.	0	180	780	5.0	11.0	2.8	1.5	15	23

TABLE XIII

VN 3	M	37	1.80	14.7	V.S.D.	0	240	620	5.3	16.9	2.2	2.7	16	22
VN 4	F	15	1.50	12.8	V.S.D.	0	170	610	4.8	18.2	2.8	3.0	19	26
VN 5	M	15	1.40	11.8	V.S.D.	0	230	440	6.9	12.5	3.0	2.9	25	32
VH 31	M	26	1.80	15.0	V.S.D., P.H.T.	0	280	670	6.6	17.2	2.4	2.6	15	26
VH 32	M	17	1.50	15.3	V.S.D., P.H.T.	1	200	530	5.3	13.9	2.6	2.6	16	21
VH 33	M	18	1.60	15.8	V.S.D., P.H.T.	1	230	470	6.7	14.5	2.9	3.1	18	22
VH 34	M	62	1.80	17.2	V.S.D., P.H.T. A.F.	3	220	-	8.4	-	3.8	-	15	-
VE 62	F	19	1.60	12.3	V.S.D., P.H.T.	2	210	550	7.0	15.5	3.3	2.8	14	20
VS 81	M	23	1.90	15.8	V.S.D., P.S.	0	250	560	6.6	12.0	2.6	2.1	15	20
VS 82	M	19	1.70	15.6	V.S.D., P.S.	1	250	660	7.0	17.6	2.8	2.7	15	22
VS 83	M	29	1.80	15.1	V.S.D., P.S.	1	210	-	6.2	-	3.0	-	14	-
PN 1	M	10	1.20	11.7	P.D.A.	0	160	450	4.1	12.5	2.6	2.8	15	17
PH 30	F	21	1.30	13.4	P.D.A., P.H.T.	1	180	320	6.6	14.3	3.7	4.5	30	36
PE 65	F	34	1.60	15.1	P.D.A., P.H.T.	1	160	610	5.5	18.9	3.4	3.1	18	21

Case No.		ARTERIAL BLOOD S_{O_2}	pH	pCO_2 mm.Hg.	Bicarb. m.Eq/L.	Lact. mM/L.	Pyr. mM/L.	PULMONARY ARTERIAL BLOOD S_{O_2}	pH	pCO_2 mm.Hg.	Bicarb. m.Eq/L.
AN 1	R	97.8	7.420	33.0	21.5	1.23	0.11	88.5	7.405	35.0	21.5
	E	-	-	-	-	-	-	-	-	-	-
		97.1	7.410	35.0	22.0	1.76	0.12	80.8	7.380	38.0	22.0
AN 4	R	95.0	-	-	-	-	-	87.6	7.360	45.0	23.0
	E	-	-	-	-	-	-	69.5	7.340	58.0	23.0
		94.9	-	-	-	-	-	71.0	7.350	56.0	24.5
AN 5	R	95.1	7.415	42.0	25.0	0.85	0.07	90.0	7.400	42.0	24.5
	E	-	-	-	-	1.11	0.08	-	-	-	-
		94.8	7.395	41.0	24.0	1.26	0.08	83.6	7.375	45.0	24.0
AN 6	R	96.0	7.405	32.5	22.0	0.65	0.07	89.0	7.405	34.5	22.5
	E	97.0	7.425	33.0	23.0	0.72	0.07	85.0	7.415	32.0	21.5
		97.1	7.410	36.5	23.0	0.78	0.10	87,5	7.410	37.0	23.0
AH 38	R	93.4	7.350	36.0	20.0	0.91	0.06	81.9	7.345	39.0	20.0
	E	92.9	7.350	36.0	20.0	1.24	0.07	71.0	7.330	40.0	19.5
		89.1	7.350	34.0	19.5	1.30	0.09	63.7	7.330	40.0	19.5
AH 39	R	96.0	7.425	48.0	28.5	0.52	0.07	86.4	7.415	49.0	26.5
	E	-	7.430	40.0	25.5	0.72	0.10	76.5	7.425	46.0	27.0
		94.5	7.430	41.0	26.0	0.98	0.09	79.6	7.415	52.0	27.0
AH 40	R	94.6	7.360	-	-	1.04	0.13	87.5	-	-	-
	E	92.2	7.355	-	-	1.76	-	78.0	-	-	-
		94.6	-	-	-	2.80	-	80.7	-	-	-
AH 41	R	95.9	7.380	39.5	22.5	0.72	0.11	83.2	7.365	44.0	23.5
	E	92.1	7.375	39.5	22.5	1.30	0.12	70.7	7.365	46.0	22.0
		92.1	7.330	41.0	22.5	1.89	0.14	73.0	7.345	48.0	22.0

TABLE XIV

AH 42	R	91.6	7.390	35.0	22.4	1.04	0.08	82.5	7.370	38.0	21.0
	E	93.7	7.400	31.0	21.0	2.20	0.12	71.4	7.370	38.0	20.5
		90.0	7.370	34.5	20.5	2.14	0.13	71.7	7.365	38.5	20.5
AH 43	R	92.6	7.415	35.0	23.0	0.78	0.06	86.5	-	-	-
	E	89.8	7.370	37.5	21.0	2.14	0.12	75.6	-	-	-
		88.1	7.345	37.5	20.0	2.90	0.16	76.7	-	-	-
AH 45	R	93.7	7.390	38.0	23.0	0.98	0.09	87.0	7.380	40.0	22.5
	E	-	-	-	-	-	-	-	-	-	-
		95.1	7.390	37.5	23.0	1.89	0.10	87.0	7.345	40.5	21.0
VN 2	R	98.4	7.400	40.0	24.0	-	-	78.0	7.395	40.0	24.0
	E	-	-	-	-	-	-	-	-	-	-
		95.6	-	-	-	-	-	68.3	7.370	40.0	22.5
VN 3	R	94.3	-	-	-	-	-	81.0	7.370	52.0	26.0
	E	-	-	-	-	-	-	68.1	7.350	53.0	25.0
		92.9	-	-	-	-	-	68.5	7.345	58.5	25.0
VN 5	R	98.0	7.410	32.5	21.5	0.70	0.09	90.2	7.370	38.5	22.0
	E	-	-	-	-	-	-	-	-	-	-
		97.2	7.440	30.0	22.5	1.30	0.12	-	-	-	-
VH 31	R	98.5	7.350	48.0	24.0	0.96	0.10	86.9	7.310	51.5	22.6
	E	-	-	-	-	1.43	0.11	-	-	-	-
		95.7	7.345	47.5	23.0	1.78	0.13	78.8	7.310	56.5	22.4
VH 32	R	98.6	7.370	44.0	23.8	0.86	0.09	90.0	7.335	50.0	23.3
	E	-	-	-	-	0.94	0.10	-	-	-	-
		97.5	7.385	36.5	22.0	1.22	0.09	83.2	7.345	52.5	23.8
VH 33	R	94.5	7.385	34.0	20.5	-	0.12	88.4	7.380	36.0	21.0
	E	-	7.380	38.5	22.0	-	0.12	68.4	7.335	46.0	22.0
		92.2	7.380	35.5	21.5	-	0.17	68.5	7.340	39.0	19.5

VE 62	R	91.8	7.425	33.0	23.0	0.97	0.07	77.6	7.400	36.0	22.0
	E	82.9	7.415	34.5	23.0	2.08	0.11	68.5	7.370	39.5	21.0
		85.0	7.410	33.0	22.0	1.57	0.12	63.5	7.375	38.5	21.0
VS 81	R	97.9	7.330	44.2	24.0	0.59	0.06	88.3	-	-	-
	E	-	-	-	-	0.84	0.07	-	-	-	-
		97.9	7.370	39.0	23.4	0.88	0.08	85.0	7.330	44.0	23.5
VS 82	R	96.0	7.440	42.0	27.0	0.68	0.11	82.8	-	-	-
	E	-	-	-	-	-	-	-	-	-	-
		92.0	7.455	37.0	26.0	1.50	0.12	71.7	-	-	-
PN 1	R	97.4	7.285	42.5	19.0	0.65	0.09	78.4	7.270	48.0	20.0
	E	-	-	-	-	1.20	0.11	-	-	-	-
		97.2	7.315	38.0	21.0	1.04	0.12	-	-	-	-
PH 30	R	95.5	-	-	-	0.91	0.06	90.2	-	-	-
	E	-	-	-	-	-	-	78.6	-	-	-
		95.0	-	-	-	1.50	0.09	75.8	-	-	-
PE 65	R	93.5	7.415	38.0	24.0	0.53	0.07	-	-	-	-
	E	90.0	7.370	40.5	22.0	1.89	0.11	-	-	-	-
		89.9	7.360	38.0	20.0	2.54	0.12	-	-	-	-

Case No.		Ex. Load Kpm/min.	$\dot{V}_{O_2}$ ml/min. S.T.P.D.	Heart Rate	$\dot{V}$ L/min. B.T.P.S.	ARTERIAL BLOOD $S_{a}O_2$	pH	pCO_2 mm.Hg.	Bicarb. m.Eq/L.	Lact. mM/L.	Pyr. mM/L.
VS 83	Rest	0	306	84	8.5	97.0	7.455	40.0	27.0	0.98	0.01
	Ex.	200	780	112	15.0	-	7.440	42.0	27.0	2.01	0.12
						96.5	7.445	41.0	26.5	1.95	0.13
		400	1050	120	21.5	-	7.440	39.0	25.5	2.15	0.14
						98.5	7.435	36.0	24.5	2.47	0.15
		600	1300	144	29.0	-	7.425	34.0	24.5	3.64	0.14
						97.0	7.395	40.0	23.5	5.20	0.19
		800	1700	164	34.0	97.2	7.415	38.0	24.0	6.90	0.19
						97.0	7.410	36.0	23.0	7.55	0.19
	Recov. (5')		-	108	-	97.0	7.400	36.0	22.0	6.20	0.26
	(10')		-	104	-	-	7.455	34.0	24.5	5.65	0.25
AS 82	Rest	0	-	86	9.3	97.0	7.420	36.2	23.0	0.65	0.09
	Ex.	200	-	108	19.5	-	-	-	-	-	-
						97.0	7.415	34.0	22.0	1.43	0.12
		400	-	115	28.2	-	7.410	35.5	22.0	1.69	0.13
						96.5	7.415	34.0	22.0	2.02	0.14
		600	-	126	35.8	-	7.420	34.0	22.5	1.56	0.14
						96.5	7.420	33.5	22.0	2.08	0.14
		800	-	160	49.4	-	7.420	35.0	22.0	2.34	0.16
						96.5	7.410	30.0	20.0	2.86	0.18
		1000	-	175	-	96.5	7.360	26.5	17.0	8.13	0.26
						-	-	-	-	-	-
	Recov. (5')		-	130	13.9	-	-	-	-	5.07	-
	(15')		-	107	-	-	7.420	34.0	22.0	1.36	-

TABLE XV

AH 41	Rest	0	310	76	7.9	95.8	7.495	35.0	27.5	1.10	0.11
	Ex.	200	750	100	15.4	97.4	7.465	33.0	25.0	2.20	0.13
						96.4	7.445	36.0	25.0	2.46	0.16
		400	1205	124	22.0	97.5	7.435	35.5	24.0	2.46	0.18
						97.4	7.425	37.0	24.0	3.64	0.19
		600	1510	144	33.0	96.0	7.375	39.5	22.5	3.70	0.22
						96.0	7.405	31.0	21.0	5.45	0.22
	Recov (5')		-	88	8.9	-	7.450	30.0	22.5	-	-
VH 33	Rest	0	347	76	6.6	98.7	7.435	37.0	24.5	-	0.08
	Ex.	200	710	126	18.1	95.9	7.435	37.0	24.5	-	0.11
						95.9	7.430	31.0	22.5	-	0.12
		400	1055	144	21.0	94.8	7.425	37.0	24.0	-	0.14
						88.4	7.385	35.5	21.5	-	0.14
		600	1390	180	32.0	79.6	7.395	33.5	21.0	-	0.15
						77.3	7.375	32.0	19.5	-	-
AN 8	Rest	0	250	88	10.0	96.0	7.530	28.0	24.5	1.11	0.06
	Ex.	200	755	110	19.0	-	7.540	27.0	24.0	1.82	-
						94.0	7.470	32.0	23.0	1.63	-
		400	1050	140	24.8	-	-	-	-	-	-
						95.0	7.450	33.0	23.0	2.08	0.08
		600	-	156	36.0	-	-	-	-	-	-
						96.0	7.430	34.0	22.0	2.80	0.14
	Recov. (5')		-	100	-	96.0	7.475	27.0	21.5	-	-

PH 30	Rest	0	200	96	4.0	-	7.420	34.0	22.5	0.65	0.07
	Ex.	200	560	104	13.4	-	-	-	-	-	-
						-	7.450	32.5	23.0	1.04	0.08
		400	1025	140	21.0	-	7.400	34.5	22.0	2.21	0.11
						-	7.410	33.0	22.0	2.03	0.13
		600	-	160	-	-	7.430	32.5	22.5	2.37	0.12
AH 45	Rest	0	256	80	6.1	98.0	7.485	30.5	23.0	1.36	0.06
	Ex.	200	660	156	19.6	-	7.500	27.5	22.0	1.75	0.09
						97.6	7.450	24.5	19.0	6.37	0.13
		400	-	180	34.2	-	7.445	23.5	19.5	5.46	0.16
						98.0	7.500	19.5	18.0	7.54	0.17
	Recov. (5')		-	112	6.3	-	7.420	26.0	18.5	5.85	-
	(15')		-	96	4.9	-	7.440	26.0	19.5	4.55	-
AH 39	Rest	0	265	80	12.2	94.0	7.525	34.5	28.5	0.85	0.07
	Ex.	200	750	128	22.8	-	7.500	34.0	27.5	1.69	0.01
						96.2	7.500	36.0	28.0	1.95	0.12
		400	1150	156	30.8	-	7.495	33.0	26.0	2.86	0.12
						92.0	7.485	34.0	26.0	3.38	0.13
	Recov. (5')	-	-	100	15.1	-	7.485	32.0	25.0	2.47	0.15
	(10')	-	-	100	11.0	96.0	7.520	30.0	26.0	1.95	0.13
VH 34	Rest	0	254	88	13.6	94.9	7.430	35.0	24.0	1.06	0.08
	Ex.	200	550	124	30.6	96.7	7.420	33.0	23.0	1.23	0.08
						95.0	7.415	35.0	23.0	1.50	0.10

AN 5	Rest	0	224	104	8.2	98.0	7.455	40.0	27.0	0.78	0.08
	Ex.	200	955	150	29.0	98.0	7.465	33.5	25.5	2.28	0.13
						98.0	7.495	33.5	27.0	1.69	0.12
	Recov. (10')		-	-	-	98.0	7.475	37.0	27.0	1.04	0.10
	(20')		-	-	-	96.5	7.490	35.0	27.0	0.98	0.09

TABLE XVII

Case		O_2 uptake (l/min.) STPD	Vent. (l/min.) BTPS	Heart rate	Pressures (mm. Hg.) P.A.	Pressures (mm. Hg.) B.A.	Oxygen % P.A.	Oxygen % B.A.	Oxygen % Mixed venous	Flow (l./min.) Pulm.	Flow (l./min.) Syst.	Flow (l./min.) Effec.	Shunt (l./min.) L-R	Shunt (l./min.) R-L	Arterial blood pH	Arterial blood Pco_2 (mm)	Arterial blood Standard bicarb. (mEq/l.)	Arterial blood Lactate (mM/l.)	Arterial blood Pyruvate (mM/l.)
C 3	R	0.246	7.0	75	18/6	130/60	82.8	95.8	76.5	10.2	6.9	6.9	3.3	0	7.440	42.0	27.0	0.68	0.12
	E	0.657	17.6	108	20/5	130/70	71.7	92.0	66.6	14.6	14.0	12.2	2.4	1.8	7.455	37.0	26.0	1.50	0.12
C 4	R	0.264	8.8	75	17/7	125/75	74.7	88.2	78.2	6.0	10.5	6.0	0	4.5	7.430	33.0	22.0	0.98	0.11
	E	0.620	19.8	115	17/5	130/70	61.9	81.9	61.9	7.6	13.2	7.6	0	5.6	7.420	33.0	22.0	1.56	0.09
C 7	R	0.180	8.2	72	80/30	80/45	64.5	80.9	60.7	2.7	4.5	2.4	0.3	2.1	4.420	33.0	21.0	1.17	-
	E	0.675	24.8	110	110/55	110/55	57.0	75.5	43.5	7.9	9.4	6.3	1.7	3.1	7.410	32.0	20.5	1.63	0.12
C 8	R	0.160	6.2	65	15/5	110/60	65.8	90.2	65.5	2.4	3.1	2.4	0	0.7	7.430	38.0	24.5	0.91	0.10
	E	0.355	11.5	80	17/7	-	52.4	82.1	53.0	3.8	5.8	3.8	0	2.0	7.420	35.0	23.5	1.56	0.13
C 9	R	0.100	4.5	65	15/5	100/60	70.2	88.0	62.0	1.7	2.0	1.3	0.4	0.7	7.410	33.0	21.5	0.78	1.00
	E	0.245	13.8	96	15/5	110/70	50.1	76.2	50.1	2.3	4.0	2.3	0	1.7	7.420	30.5	21.0	1.37	1.00
C 14	R	0.216	7.4	68	95/50	95/60	74.7	89.5	64.8	4.5	3.6	3.1	1.4	0.5	7.365	47.0	24.0	0.59	0.07
	E	0.630	30.8	94	125/65	125/80	50.2	70.0	48.4	5.9	12.1	5.7	0.2	6.4	7.380	41.0	23.0	1.30	-
C 18	R	0.194	6.6	80	120/60	120/70	66.5	65.0	47.6	2.9	4.6	1.7	1.1	2.9	-	-	-	-	-
	E	-	-	136	-	135/70	-	45.1	-	-	-	-	-	-	-	-	-	-	-
C 20	R	0.190	7.2	79	18/12	130/80	66.0	75.3	66.1	2.2	6.3	2.2	0	4.1	7.300	34.0	21.0	1.24	0.11
	E	0.464	15.8	100	20/10	160/80	51.2	68.0	53.2	3.6	9.9	3.6	0	6.3	7.355	35.0	19.0	3.00	0.19

TABLE XVIII DATA OBTAINED DURING STEP AND BICYCLE EXERCISE GROUP I

Case No.	State	Work (kg.m./min.)	Duration (min.)	Vent. (L/min.) BTPS	O_2 uptake (L/min.) STPD	Heart rate	Dyspnoea grade	Arterial blood							
								O_2 %	pH	PO_2 (mm.) (calculated)	PCO_2 (mm.)	Standard bicarb. (mEq./l)	Lactate (mM/l.)	Pyruvate (mM/l.)	L/P
1	Rest			9.25		84	0	97	7.440	96	33.0	23.5	1.04	0.12	8.6
	Ex. steps	400	4	34.0		120	II	63	7.410	32	35.0	22.0	2.73	0.15	18.2
			7			130	III	60	7.405	31	34.0	21.0	3.44	0.15	23.0
	Recovery		5	24.0				79	7.420	43	29.0	20.5	3.00	0.18	16.7
			10					88	7.445	55	31.0	22.5	1.82	0.11	16.5
2	Rest			7.6			0	96	7.452	84	36.0	25.0	0.83	0.10	8.3
	Ex. steps	400	3	28.0			I	87	7.405		38.0	23.5	3.51	0.12	29.2
			10				II	80	7.395	45	33.0	21.0	4.75	0.18	26.4
3	Rest			7.6		92	0	93	7.455	67	34.0	25.0	0.91	0.10	9.1
	Ex. cycle	300	3	21.4	1.07	110	I	86	7.455	50	36.0	25.0	1.24	0.12	10.3
			7			120	I	85	7.460	49	30.0	23.0	1.30	0.14	9.3
			17			120	I	81	7.465	45	36.0	26.0	0.91	0.12	7.6
	cycle	500	3	45.0	1.34	160	II	73	7.460	37	30.0	24.0	1.36	0.12	11.3
4	Rest			6.5		82	0	94	7.420	72	27.0	19.0	1.04	0.10	10.4
	Ex. walking	200	10	18.2	0.58	100	0	78	7.420	42	28.0	20.0	1.17	0.09	13.0
	cycle	300	4	25.6	0.83	120	I	69	7.410	36	31.0	20.5	2.53	0.10	25.3
			10			126	I	56	7.420	28	31.0	21.0	2.73	0.17	16.0
	cycle	400	4	40.2	1.160	160	II	50	7.395	26	33.0	20.5	3.18	0.17	18.7
			10			164	II	47	7.375	26	23.0	18.5	4.42	0.19	23.3
	Recovery		10			104		86	7.400	54	28.0	18.5	-	-	-

(continued) . .

TABLE XVIII (continued) GROUP I

Case No.	State	Work (kg.m./min.)	Duration (min.)	Vent. (L/min.) BTPS	O_2 uptake (L/min.) STPD	Heart rate	Dyspnoea grade	Arterial blood							
								O_2	pH	PO_2 (mm.) (calculated)	PCO_2 (mm.)	Standard bicarb. (mEq./l)	Lactate (mM/l.)	Pyruvate (mM/l.)	L/P
5	Rest			4.3	0.11	76	0	95	7.480	74	33.5	25.7	0.55	0.07	7.9
	Ex. cycle	200	4	11.3	0.38	135	I	89	7.445	56	33.2	24.5	1.69	0.09	18.8
			10			140	I	83	7.450	51	30.5	23.0	2.08	0.12	17.3
	cycle	400	4	25.8	1.03	160	II	80	7.410	45	32.2	22.0	3.90	0.13	30.0
			10			160	II	81	7.395	46	30.5	20.5	3.84	0.17	22.6
	Recovery		5	8.2		100		94	7.395	73	32.5	21.0	2.99	0.18	16.6
			10	5.0					7.425		28.0	21.0	2.40	0.17	14.1
6	Rest			6.0		84	0	94	7.505	65	28.0	23.0	0.72	0.08	9.0
	Ex. walking	200	6	13.5	0.58	96	0	93	7.495	64	29.0	23.0	0.85	0.07	12.1
	cycle	300	3	19.7	0.87	120	I	88	7.435	55	30.0	20.5	1.82	0.15	12.1
			9			132	I	69	7.390	37	36.0	20.5	2.40	0.15	16.0
			12			130	I	68	7.440	34	33.0	21.4	2.40	0.16	15.0
	cycle	400	4			150	II	51	7.410	26	36.0	21.4	2.34	0.16	14.6
	Recovery		5			84	0	72	7.435	37	33.0	20.5	2.15	0.22	9.8
7	Rest			10.2	0.36	80	0	97	7.485	91	27.0	22.0	1.82	0.13	14.0
	Ex. cycle	400	4	38.0	1.24	120	I	81	7.454	44	29.0	21.0	2.67	–	-
			10			136	II	70	7.390	37	32.0	19.0	3.64	0.18	20.2
	cycle	600	3			160	II	66	7.400	34	31.0	19.0	4.29	–	-
	Recovery		5			96	0	97	7.420	98	26.0	19.0	3.38	–	-
			10			98	0	98	7.510	99	22.0	22.0	1.82	–	-

(continued) ...

TABLE XVIII (continued)

GROUP II

Case No.	State	Work (kg.m/min.)	Duration (min.)	Vent. (L/min.) BTPS	O_2 uptake (L/min.) STPD	Heart rate	Dyspnoea grade	Arterial blood							
								O_2	pH	PO_2 (mm.) (calculated)	PCO_2 (mm.)	Standard bicarb. (mEq./l)	Lactate (mM/l.)	Pyruvate (mM/l.)	L/P
10	Rest					78	0	86	7.425	52	29.5	21.0	0.78	0.09	8.7
	Ex. cycle	300	4			108	II	70	7.395	37	35.8	21.0	2.34	0.14	16.7
			10			120	III	40	7.375	21	38.5	19.5	2.73	0.13	21.0
	Recovery		6				I	85	7.395	52	35.0	21.0	2.15	0.15	14.3
			10				I						1.69	0.13	13.0
11	Rest					84	0	87	7.440	53	28.0	22.4	0.88	0.07	12.6
	Ex. steps	300	5			125	II	55	7.375	30	31.0	20.5	3.58	0.16	22.4
12	Rest			10.1	0.29	68	0	90	7..440	59	30.0	21.5	1.04	0.11	9.5
	Ex. walking	200	10	16.9	0.53	96	I	83	7.410	49	30.0	20.0	1.24	0.10	12.4
	cycle	200	4	24.7	0.62	108	I	82	7.415	48	30.0	20.0	1.43	0.10	14.3
			10				I	82	7.400	48	29.0	19.5	1.79	0.13	13.8
	cycle	300	4	34.1	1.08	120	II	78	7.405	43	32.5	20.0	1.95	0.16	12.2
			7			120	II	73	7.390	39	32.0	19.5	2.15	0.13	16.5
			10			120	II	51	7.370	27	36.0	19.0	3.06	0.16	19.1
	Recovery		5	13.4		96	0	79	7.390	44	29.0	18.5	2.60	0.17	15.3
			10	10.0		72	0	68	7.400	36	31.0	19.0	-	-	-
13	Rest			6.5	0.21	70	0	90	7.480	57	29.0	24.5	1.45	0.16	9.0
	Ex. cycle	400	1			120	I	59	7.454	31	33.0	22.5	3.00	0.17	17.6
			3			136	II	62	7.375	32	36.0	20.0	4.42	-	-
			5	31.5	1.15	140	II	55	7.390	29	32.5	19.5	5.33	0.19	28.0
			7			154	II	57	7.365	30	31.5	18.5	5.72	0.23	24.9
			10			156	III	33	7.340	20	35.0	17.0	5.33	0.24	22.2
	Recovery		5	9.6		114	0	79	7.400	44	26.5	19.5	3.90	0.27	14.5
			10	7.0		120	0	83	7.435	49	24.0	20.0	3.38	0.22	15.4

(continued) ...

TABLE XVIII (continued)

GROUP II

Case No.	State	Work (kg.m/min.)	Duration (min)	Vent. (L/min.) BTPS	O_2 uptake (L/min.) STPD	Heart rate	Dyspnoea grade	Arterial blood							
								O_2	pH	PO_2 (mm.) (calculated)	PCO_2 (mm.)	Standard bicarb. (mEq./l)	Lactate (mM/l.)	Pyruvate (mM/l.)	L/
14	Rest			8.0		100	0	86	7.455	51	34.7	24.5	1.37	0.12	11.
	Ex. cycle	400	4	53.4	1.19	150	II	48	7.370	26	43.3	2.15	5.26	0.17	31.
			7				II	45	7.315	27	44.0	20.0	8.06	0.18	44.
			10				III	46	7.295	28	46.5	20.3	-	-	-
	Recovery		2				I	72	7.325	41	33.5	17.5	-	-	-
15	Rest			6.9	0.19	64	0	84	7.435	49	32.5	22.0	1.09	0.08	13.
	Ex. walking	200	5	22.0	0.59	90	I	68	7.440	30	33.0	22.0	1.07	0.10	10.
	steps	300	3	40.0	1.06	140	II-III	43	7.380	24	35.5	19.0	3.38	0.10	33.
	Recovery		5	11.0				79	7.380	45	30.5	18.5	-	-	-
			10	9.8				79	7.400	44	30.0	19.5	1.82	0.15	12.
			15	7.9				82	7.415	47	30.0	20.5	-	-	-

(continued) . . .

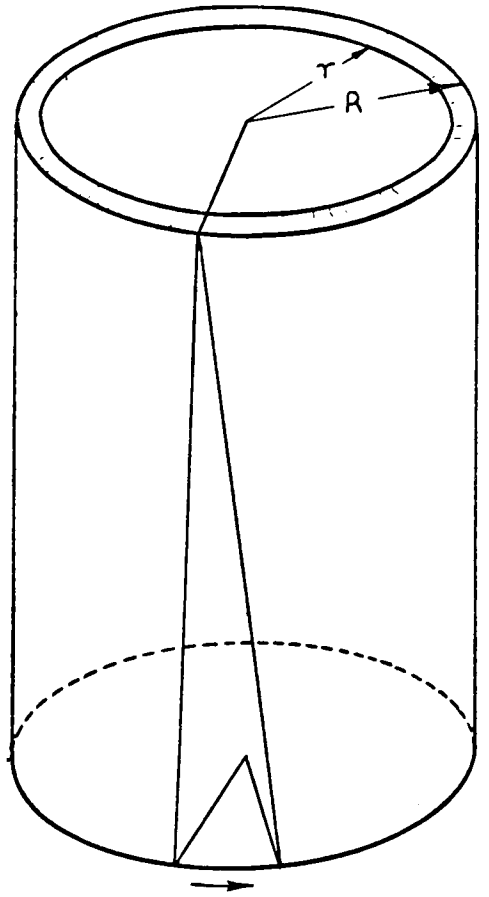
TABLE XVIII (continued)

GROUP III

Case No.	State	Work (kg. m/min.)	Duration (min.)	Vent. (L/min.) BTPS	O_2 uptake (L/min.) STPD	Heart rate	Dyspnoea grade	Arterial blood O_2	pH	PO_2 (mm.) (calculated)	PCO_2 (mm.)	Standard bicarb. (mEq./l)	Lactate (mM/l.)	Pyruvate (mM/l.)	L/P
16	Rest					96	0	58	7.362	31	42.0	21.0	1.04	0.09	11.6
	Ex. cycle	200	4			135	II	31	7.350	19	46.0	20.0	2.79	0.11	25.4
			6			132	III	25	7.275	18	53.0	17.5	3.51	0.12	29.2
	Recovery		2			120	II	18	7.272	14	55.5	17.0	-	-	-
			5			106	II	27	7.245	19	46.5	16.0	3.12	0.16	19.5
			10			120	II	36	7.310	22	46.0	17.5	2.73	0.14	19.5
			24			120	I - II	21	7.315	15	49.5	18.5	3.20	-	-
17	Rest			6.1	0.192	84	0	76	7.400	41	38.0	22.0	0.60	0.07	8.6
	Ex. walking	200	4	18.7	0.584	100		59	7.405	31	37.0	22.0	0.52	0.07	7.4
			10	14.4		100		50	7.380	26	35.0	19.0	0.91	0.07	13.0
	cycle	200	4				I	50	7.370	26	38.5	20.0	1.04	0.07	14.9
			7	21.0				45	7.390	24	36.0	20.0	2.01	0.11	18.3
			10	19.1	0.576			45	7.385	24	36.5	20.0	1.50	1.10	15.0
	cycle	300	1					30	7.360	18	39.0	19.0	2.99	0.11	27.2
			4	16.2	0.813			48	7.370	26	36.0	19.5	3.25	0.16	20.3
			10	17.3			I	48	7.345	26	39.0	19.0	3.51	0.18	19.5
	cycle	400	2					40	7.380	22	36.0	19.5	2.73	-	-
			4	24.3		130	I - II	20	7.360	14	38.0	18.0	3.12	-	-
	Recovery		5	7.8		96		71	7.380	37	33.0	19.5	2.15	-	-
			10	4.5		88		74	7.420	39	35.0	22.0	1.11	-	-
18	Rest					100	0	75	7.430	39	33.0	22.0	-	-	-
	Ex. walking	300	2			160	III - IV	34	7.241	23	54.0	20.0	-	-	-
19	Rest					110	0	54	7.375	29	30.5	20.0	1.89	0.15	12.6
	Ex. steps	200	4			140	II	46	7.330	26	34.0	19.0	3.09	0.12	25.8
			6			130	III	32	7.300	19	49.0	18.0	2.93	0.11	26.6

A MECHANICAL ANALOGY LINKING THE ERECTILE PROPERTIES OF THE PULMONARY VASCULATURE WITH THE MECHANICAL FORCES ACTING ON TUBES IN TORSION.

If the smaller radicles of the pulmonary vascular tree were contributing to the mechanical properties of the lungs by virtue of their own erectile properties and consequent resistance to distortion, an approximate analogy which serves to assess roughly the magnitude of this contribution would be a hollow spring. The ramifying branches of the vascular tree alter their shape not so much by extension as by straightening, in which case, as in a spring, the relevant motion is that of torsion and not extension. The appropriate modulus to consider is therefore the bulk modulus (n) and not Young's modulus (when a spring is stretched, its molecules move in torsion relative to each other and not in extension).



The torsional properties of a hollow tube are expressed by the formula

$$C = \frac{n}{21}(R_1^4 - r_1^4) \quad \text{(1)}$$

where r and R are inner and outer radii, l is the length, n the bulk modulus, and C the couple required to twist the lower end of the cylinder through one radian.

For unit length, $C = K\, n(R_1^4 - r_1^4)$ (2)

If the wall of the cylinder is under tension, the latter may be expressed (Laplace) by $P = \frac{kT}{r_2}$ where P is the distending pressure, T the tension in the wall and r_2 the radius. Thus

$T = Pr_2/k$ _____ (3)

For a substance like muscle, the modulus of rigidity is clearly some direct function of the tension in it, i.e. $n = f(T) = f(P r_2/k)$.

Assuming the simplest relationship $n = K'.P.r_2$ _____ (4)

$\therefore$ From (2) $C = K'.P.r_2 (R_1^4 - r_1^4)$

Assuming $r_2 = \frac{R_1 + r_1}{2}$

$$C = K''P.\ (R_1 + r_1)\ (R_1^4 - r_1^4)$$

or $$C = K''P.\ (R_1^5 - R_1^4 r_1 + r_1 R_1^4 - r_1^5)$$ _____ (5)

This can now be applied to the small vessels in typical situations of varying flow and pressure.

(1) A.S.D. Lumen is large and wall thin: say $R_1 = 4$, $r_1 = 3$

Pressure is low, say 15 mm.

Then $C = K''.\ 15\ (1024 - 4.81 + 3.256 - 243)$

$= K''.\ 18525$

(2) V.S.D. with hyperkinetic pulmonary hypertension.

Lumen is large and wall thick, say $R_1 = 5$, $r_1 = 3$

Pressure is high, say 40 mm.

$C = K''.\ 40\ (3125 - 5.81 + 3.625 - 243)$

$= K''.\ 174,080$

(3) Eisenmenger

Lumen is small and wall variably thick, say $R_1 = 3$, $r_1 = 1$

Pressure is high, say 40 mm.

$C = K''.\ 40\ (243 - 3.1 + 1.81 - 1)$

$= K''.\ 12800$

The mechanical forces required to produce a given degree of distortion in situation (2) are thus far greater than in situations (1) and (3). The vessels concerned are not specified, but could be the small muscular arteries and muscularised arteries as well as the capillaries which invest the alveolus. This raises the question of the compliance of the alveolus, which could thus be a function not only of surface tension forces and elastic tissue but also of the vasculature associated with it.

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