PHYSIOLOGICAL RESPONSES TO ARTIFICIAL VENTILATION

by

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To

A.B. and E.L.B.

whose sacrifices made it

possible.

CONTENTS

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PROLOGUE

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The investigations described in this thesis originated from a desire to resolve the conflicting views held on the importance of the inspiratory flow waveform during intermittent positive pressure ventilation (I.P.P.V.). There is a large number of ventilators available with widely varying prices and a particular ventilator is often bought in the belief that its inspiratory flow waveform is the "best". A great deal of public money is involved and there is little good evidence on which to base a choice. To carry out these investigations, it has been necessary to design and construct a ventilator which can provide a number of predictable and repeatable inspiratory flow waveforms during I.P.P.V. This part of the thesis has taken the author outside medicine into engineering, where much has been learnt during the design and construction of the ventilator to be described and also during the design and construction of a second ventilator which is not described.

Through reading the literature on the physiology of artificial ventilation, the author became interested in the history of all forms of this life-saving procedure and at the same time aware that no exhaustive account of this facet of the history of medicine existed. This led to consultation with the Department of the History of Medicine in Oxford and to the chapter on the development of artificial ventilation.

The author has also studied some theoretical aspects of changes in inspiratory flow waveform by means of an electrical lung model, a mathematical analysis and a hybrid computer program. Observations have been

made in patients and dogs to record some of the effects of changes in inspiratory flow waveform in I.P.P.V. The bulk of the experimental work in this thesis concerned dogs with healthy lungs because the physiology of I.P.P.V. cannot ethically be studied in the human. On the other hand, the effects of different inspiratory waveforms and different inspiratory to expiratory time relationships can be expected to be much more important in the patient who has either a disturbed cardiovascular system or has lung disease. It is hoped that this thesis will indicate meaningful observations which may be made in ill patients and which may lead to a reduction in mortality and morbidity.

CHAPTER

1

ARTIFICIAL RESPIRATION, THE HISTORY OF AN IDEA.

The following historical section is presented in an historical format with notes to the text. The notes together with the full bibliography for this section are placed at the end of the chapter. The whole chapter is almost exactly as published in the October 1971 issue of the journal, History of Medicine.

CHAPTER

1

ARTIFICIAL RESPIRATION, THE HISTORY OF AN IDEA.

"Thou takest away their breath, they die, and return to their dust."

Psalms 104, 29.

INTRODUCTION

The simple automatic act of breathing is essential to life, but may be interrupted in a variety of ways. Cessation of this act of breathing is not necessarily fatal if there is some means available to produce artificial respiration, but if this assistance is lacking death will always supervene. This article proposes to sketch the history of the various means of artificial respiration and to discuss the effects of its development upon the progress of physiology, medicine, surgery and resuscitation.

PRE-PHYSIOLOGY

The oldest references to artificial respiration are in Egyptian Mythology where by one account Isis resurrected Osiris with the breath of life.[1.] Other early references occur in the Bible in Genesis 2, 7 and Kings I, 17, 21, both of doubtful physiological significance. However, another Biblical reference is strongly quoted as evidence of artificial respiration.

> "And he went up, and lay upon the child, and put his mouth upon his mouth, and his eyes upon his eyes, and his hands upon his hands: and he stretched himself upon the child; and the flesh of the child waxed warm.
>
> Then he returned, and walked in the house to and

> fro; and went up and stretched himself upon him: and the child sneezed seven times, and the child opened his eyes."
>
> Kings II, 4, 34-35.

This reference is the best of the three but again the exact meaning is doubtful. It does appear that this could be a description of mouth to mouth respiration, even though the reason for recovery may well have been rewarming of the patient.

Despite these references the medical and lay populace do not seem to have used any form of artificial respiration for the dying or recently dead. Not only did they not use it for resuscitation, but its absence hindered their physiological study of the thoracic cavity and its organs. Without artificial respiration thoracotomy inevitably led to the collapse of one or both lungs, which usually resulted in the death of the animal in a short time and always to very severe interference with the physiological mechanisms. Galen was well aware of this problem and wrote of it on several occasions in his Anatomical Procedures,[2] most graphically

> "For with this perforation (pleural membrane) the whole process of respiration is destroyed. while if it be not perforated you cannot see within the thorax at all, except by excising a rib and leaving the pleura unharmed."[3]
>
> "For this operation it is best to use a large pig, for then the membrane lining the ribs is strong."[4]

This method is of course a very poor one for visualising the thoracic contents, as the pleural membrane is opalescent when it is thick enough not to be torn during dissection from the rib cage. Galen also describes in detail his method for exposing the heart of an animal for examination of its action, without perforation of the pleural membrane.[5] A related approach via median sternotomy is today made by cardiac surgeons so that

the pleural cavities are not disturbed and post-operative complications reduced in incidence and degree. Galen was obviously a very capable surgeon to be able to dissect his living animals to display the heart directly, or the thoracic contents through the pleural membrane, as these animals were not anaesthetised and even if well restrained would be hyperventilating with pain and fear. He was also prepared to use his surgical skill in the case of the slave Maryllus whose lower sternum he resected for a perichrondral infection, to expose the pulsating heart to the world.[6.] This is an operation which is unlikely to be undertaken lightly today, and that the slave lived can only be justification for the highest praise.

Galen, himself a great experimentalist, must have been very close indeed to discovering the usefulness of artificial respiration, because in one of his experiments he used bellows to inflate the lungs of a dead animal.[7.] It is interesting to speculate what might have happened if the procedure described had resuscitated an animal recently killed by the effect of an open pneumothorax.

The next reference to artificial respiration, once again of almost folk-tale origin, also concerns mouth-to-mouth artificial respiration. In 1472 Bagellardus issued this advice to midwives:-

> "If she find it (the newborn) warm, not black, she should blow into its mouth, if it has no respiration." 8.

Marvellous advice only to be ruined by the succeeding phrase "or into its anus"! So it may be assumed that Bagellardus did not recognise the real significance of his advice.

PHYSIOLOGY

Almost a century later Vesalius was describing in a matter-of-fact way his technique for keeping an experimental animal alive to examine its thoracic contents.

> "But that life may in a manner of speaking be restored to the animal, an opening must be attempted in the trunk of the trachea, into which a tube of reed or cane should be put; you will then blow into this, so that the lung may rise again and the animal take in air. Indeed, with a slight breath in the case of this living animal the lung will swell to the full extent of the thoracic cavity, and the heart become strong and exhibit a wondrous variety of motions. So, with the lung inflated once and a second time, you examine the motion of the heart by sight and touch as much as you wish."[9].

and later,

> "With this observed, the lung should again be inflated, and with this device, than which I have learned nothing more pleasing to me in Anatomy, great knowledge of the differences in the beats should be acquired. For when the lung, long flaccid, has collapsed, the beat of heart and arteries appears wavy, creepy, twisting, but when the lung is inflated, it becomes strong again and swift and displays wondrous variations."[10].

and again,

> "And as I do this (the anatomical dissection) and take care that the lung is inflated at intervals, the motion of heart and arteries does not stop."[11].

It is not clear from the above excerpts whether Vesalius was copying a technique or whether he had invented it. The suggestion "than which I have learned nothing more pleasing to me in Anatomy (quo mihi gratius in Anatome nullum comperi)" seems to indicate that it was shown to Vesalius, but a careful search has not revealed a source from which Vesalius might have copied the technique. It is not mentioned by Mondino di Luzzi,[12]. nor does it appear to be known to the great experimentalist Leonardo

da Vinci who though not a physician had a powerful friend in Marco Antonio della Torre, Professor of Anatomy at Padua and Pavia. Leonardo did however, repeat the Galen experiment and concluded that,

> "To me it seems impossible that any air can penetrate into the heart through the trachea, because he who inflates it, does not expire any part of air from any part of this."[13].

He also tried to ascertain the mechanism of speech.

> "The extension and restriction of the trachea together with its dilatation and attraction are the cause of the varying of the voice of the animals from high to deep and from deep to high; as to which 2nd action, the shortening of this trachea, not being sufficient at the rising of the voice, it dilates itself somewhat towards the upper part, which receives no degree of sound (and) comes to raise the voice of this remnant of the shortened pipe. But on this we shall make an experiment in anatomizing the animals, giving air into their lungs and pressing them, narrowing and dilating the 'fistola', the generator of their voice."[14].

Like Galen, Leonardo was close to the fundamental discovery of artificial respiration.

It would appear that if Vesalius did obtain his technique from anyone it would have been early in the 16th Century. There is a suggestion by Fodéré[15]. (unsubstantiated) that Paracelsus in 1530 tried bellows "with moderation and gentleness" on a dead subject without success. Pagel has stated that he does not know of this reference in Paracelsus' texts,[16] but Vesalius may well have been the person who chanced upon the technique. He knew Galenic texts intimately and may well have carried out Galen's inflation experiment on a recently dead animal with surprising results.[17] If he did invent the technique himself, its description must surely be the most modest for such dramatic revival. He may perhaps have feared the wrath of the Church.

From this time onwards the Vesalian technique may be assumed to have remained well known in Padua. Colombo mentions it,[18.] giving greater detail on the tracheotomy procedure, and Harvey very casually mentions it in 'De motu locali animalium':-

> "a cock's head off, the arteries being ligatured and artificial ventilation being given."[19.]

No doubt the anatomy demonstrations regularly made use of this method to display the actions of thoracic organs. Harvey also mentions that he repeated the Galen experiment of testing for air passage to the heart.[20.]

Another casual reference to artificial respiration occurs in Highmore's 'Corporis humani disquisitio anatomica' in 1651.[21.] However only 13 years later and 50 miles away in London Croune was demonstrating to the Royal Society his revival of strangled chickens.[22.] Hooke, who was present at this demonstration, later makes a great show of reviving an open-chested dog.

> "In prosecution of some inquiries into the nature of respiration in several animals, a dog was dissected, and by means of a pair of bellows, and a certain pipe thrust into the wind-pipe of the dog, the heart continued beating for a very long while after all the thorax and belly had been opened; nay, after the diaphragm had been in great part cut away, and the pericardium removed from the heart. And from several trials made, it seemed very probable, that this motion might have been continued as long, almost, as there was any blood left within the vessels of the dog: for the motion of the heart seemed very little changed, after above an hour's time, from the first displaying the thorax; though we found, that upon removing the bellows, the lungs would presently grow flaccid, and the heart begin to have convulsive motions: but upon renewing the motion of the bellows, the heart recovered its former motion, and the convulsions ceased."[23.]

Then on October 10th 1667[24.] Hooke first performed his experiment, which was later reported in the Phil. Trans.[25.] from the demonstration on 24th October,[26.] of keeping a

dog alive without any respiratory movements by passing a constant flow of air into the animal. This experiment was very important as it convincingly proved that the heart's movements and those of respiration were independent. This had not previously been generally believed.[27.] At the end of this communication to the Phil.Trans. Hooke showed that he had a very good grasp of the possibility of extra-corporeal respiration,

> "I shall shortly further try, whether the suffering the Blood to circulate through a vessel, so as it may be openly exposed to the fresh Air, will not suffice for the life of an animal."[25.]

Hooke lived however before the isolation of oxygen and methods for providing a thin uncoagulated blood film, and his attempts were unsuccessful. 200 years were to elapse before further experimentation was attempted, and 250 before success was achieved with this particular branch of artificial respiration.

Richard Lower, who was Hooke's associate in the dog experiment of October 10th but not credited in the Phil.Trans., also used artificial respiration on a dog to prove that the blood changed colour in the lungs and that this was dependent upon respiration or at least the passage of fresh air into the lungs.[28.] This evidence established that the blood changed colour in the lungs whereas previously it had been generally believed that the change occurred in the left heart, though this was at times debated.

Thus it can be seen that even after artificial respiration had been well described by Vesalius a further 120 years passed before the gross physiology of the thorax was fully understood. It was indeed a great restriction to the development of physiology that Galen did not chance upon the technique of artificial respiration.

RESUSCITATION

The idea of artificial respiration became widely accepted during this age of intense physiological experimentation which coincided with the foundation of the Royal Society in 1660 (Charter in 1662). Physiology seems never to have forgotten the technique again. However, in the associated fields of medicine, surgery and resuscitation many years had to pass before acceptance of the idea.

During the 18th Century drowning became a major public and medical issue, and in the latter half of the Century several Societies were founded to promote the recovery of persons apparently drowned.[29.]

(a) Intermittent Positive Pressure Ventilation.

However, well before these, in 1740, the Academie des Sciences (Paris) had issued its 'Avis' which advised strongly that mouth-to-mouth respiration was the best method for recovering apparently drowned persons.[30.]

The first authentic case of human recovery by artificial respiration would seem to be the report by Tossach in 1744 concerning the resuscitatinn of a suffocated miner using the mouth-to-mouth technique.

> "I must submit to better Judges to determine whether the Experiment I design to relate was the Mean of saving the Man's Life on whom it was tried; it is at least very simple, and absolutely safe, and therefore can at least be no Harm, if there is not an Advantage in acquainting the Publick of it."[31.]

Tossach was a cautious as well as a clever innovator. Jackson[32.] also gives a very accurate description of mouth-to-mouth resuscitation, though not from personal experience. It was not long before the effectiveness of bellows was substituted as the motive force. Buchan clearly describes such recommended measures:-

> "To renew the breathing a strong person may blow his own breath into the patient's mouth with all the force he can, holding his nostrils at the same time. When it can be perceived by the rising of the chest or belly that the lungs are filled with air, the persons ought to desist from blowing, and should press the breast and belly so as to expel the air again; and this operation may be repeated for some time, alternately inflating and depressing the lungs so as to imitate natural respiration. If the lungs cannot be inflated in this manner, it may be attempted by blowing through one of the nostrils and at the same time keeping the other close. Dr. Monro for this purpose recommends a wooden pipe fitted at one end for filling the nostril, and at the other end for being blown into by a person's mouth, or for receiving the pipe of a pair of bellows, to be employed for the same purpose, if necessary. When air cannot be forced into the chest by the mouth or nose, it may be necessary to make an opening in to the wind-pipe for this purpose." 33.

This is almost a modern resuscitation manual. However, it was not long before Fothergill, probably the greatest worker of this resuscitation era, was pointing out the advantages of mouth-to-mouth over bellows,

> "(1) as the bellows may not be at hand;
>
> (2) as the lungs of one man may bear, without injury, as great a force as those of another can exert, which by the bellows cannot always be determined;
>
> (3) the warmth and moisture of the breath would be more likely to promote the circulation than the chilling air forced out of a pair of bellows." 34.

The discovery of carbon dioxide by Black in 1754[35.] and of oxygen by Priestly,[36.] Lavoisier[37.] and Scheel,[39.] caused mouth-to-mouth respiration to be outmoded[39.] by intermittent positive pressure ventilation, first with bellows and then with pistons.[40.] These pistons in some cases included a withdrawal phase to assist expiration - a technique used in modern times to assist venous return to the heart rather than to assist expiration, but a technique also with some attendant dangers. John Hunter in his writing on this subject showed his typically

practical approach with two suggestions:-

> "Perhaps the dephlogisticated air, described by Dr. Priestly may prove more efficacious than common air. It is easily procured, and may be preserved in bottles or bladders." 41.

and,

> "If during this operation the larynx be gently pressed against the oesophagus and spine, it will prevent the stomach and intestines being too much distended by the air." 41.

This manoeuvre is in modern anaesthesia known as Sellick's manoeuvre after its modern proposer,[42] some 200 years after Hunter's suggestion. The suggestion hints at the complication of gastric inflation which is a possible hazard of these techniques, but it was not long before endotracheal intubation was being used for access to the lungs. Tracheotomy also was advised in some cases[43] and occasionally bronchotomy,[44] but because of their poor reputation in other conditions they lapsed in preference to endotracheal intubation, which was performed by blind techniques or by touch during this period. Tracheotomy presented the additional difficulty of air leak upwards through the larynx. This difficulty was overcome in the endotracheal technique by wedging the tube in the glottis. The advent of cuffed tubes to seal the trachea did not occur for another 100 years.[45]

Early in the 19th Century doubts were raised concerning the safety of positive pressure ventilation noteably by Brodie,[46] Villermé[47] and Vicq d'Azyr.[48] Positive evidence was provided by Leroy in 1828[49] when he reported the results of experiments on animals which had been drowned and resuscitation attempted by artificial ventilation with bellows. The resultant emphysema was blamed on the bellows and it was not until 1888 that Paltauf[50] demonstrated pulmonary emphysema to be a

result of drowning per se, and Champneys[51] that the lungs of dead infants withstood 20-80 mmHg. pressure before rupturing. Even so, in the 20th Century there were still complaints of the dangers.[52] There was obvious division of opinion on these matters because, although the Royal Humane Society abandoned bellows and positive pressure resuscitation from their official resuscitation scheme, the Edinburgh Almanack for 1834 quotes,

> "v. In order to restore breathing, introduce the pipe of a common bellows (where the apparatus of the Society is not at hand) into one nostril, carefully closing the other one and the mouth: at the same time drawing downwards and pushing gently backwards the upper part of the wind-pipe, to allow a more free admission of air; blow the bellows gently, in order to inflate the lungs, till the breast be a little raised; the mouth and nostrils should then be set free, and a moderate pressure made with the hand upon the chest. Repeat this process till life appears."[53]

(b) Tank Respirators.

Also at about this time Dalziel[54] had invented the first tank respirator which operated by exposing the outside of the thorax to a subatmospheric pressure thus allowing the more positive pressure of the atmosphere to cause inspiration. This particular technique of artificial ventilation did not become popular though Lewins wrote enthusiastically of it.[55] As the effects on the lungs are little different from normal positive pressure ventilation it is likely that it suffered with bellows, pistons and mouth-to-mouth as a result of Leroy's article and the appraisal of the article by Magendie and Duméril.[56] This criticism of positive pressure techniques was one of the reasons for the enthusiasm which greeted the manual techniques discussed below. The tank respirator was reintroduced by Hauke,[57] and also by Woillez.[58]

"Zur Notize!

At the session of the Ac. de Méd. of 20th June 1876 (Gaz. des Hop. 72) M. Woillez read a paper on an apparatus called 'Spirophore' resuscitating asphyxiated persons. Concerning the structure and method of application, this apparatus by Woillez is however nothing else but a copy of my 'Pneumatic Tub'. Woillez does not give any hint to the fact that I first suggested this method and carried out experiments with it. Two years ago I published an article on the 'Pneumatic Cuirass' in which I described the first experiments with ill children; the inventor of the 'Spirophore' is quite silent about this."[59].

In 1880 Waldenburg introduced the first cuirass respirator.[60] This is a respirator working on the same principle as the tank respirators but covering only the thorax and not enclosing the body as the tank respirators do. Doe in 1889 described Braun's tank respirator for newborn babies.[61]. Following this spate of activity interest disappeared in this form of treatment until Stewart and Rogoff[62]. in 1918 and later Drinker and McKhann[63]. produced their versions for use in the treatment of anterior poliomyelitis. Modifications flourished over the next 10 years and a Medical Research Council Report in 1939 deals fully with the various types produced.[64]. At this time, just before the Second World War Lord Nuffield offered to send one of these models (the Both)[65]. anywhere in the British Commonwealth.

In this context, mention must be made of Thunberg's 'Barospirator'[66]. used in the treatment of poliomyelitis by Petrén and Sjovall.[67]. Also about this time, in 1938, a blistering article[68]. appeared in the Bulletin de l'Academie de Médicine claiming Woillez as the originator of the tank respirator, but as has been pointed out Woillez was antedated by 40 years. Tank respirators, although successful in terms of ventilating the patient, proved very unwieldy for nursing procedures and rapidly lost favour when better alternatives became available.

(c) Manual Methods of Artificial Respiration.

It is now necessary to return to the first half of the 19th Century and continue examination of the methods of resuscitation after drowning which still caused much public concern. Leroy himself had suggested a many-tailed bandage which was alternately tightened and loosened, but there had been a manual method of artificial respiration described by De Haen in 1783[69.] and the Royal Humane Society Report of 1812 mentions manual methods.[70.] Dalrymple produced a different bandage from Leroy for the Royal Humane Society,[71.] suction cups were produced for attachment to the chest,[72.] and Van Hasselt described a method for lifting the rib cage by pushing fingers beneath the thoracic margin.[73.] The greatest impetus to manual methods was however given in 1855-56 by Marshall Hall,[74.] and this new method was followed quickly by Silvester's.[75.] For the remainder of the Century fierce controversy, well described by Karpovitch[76.], raged as to the best method. There were numerous attempts to adjudicate between the methods, the most notable being by Djelitzin in 1893[77.] and the monumental inquiry in England headed by Schaffer.[78.] This latter inquiry added yet another method to those available and found in favour of this new method, later to be known as Schaffer's method. Some of the experiments employed to test these various techniques were themselves rather heroic. In one,[79.] a medical student volunteered to be deeply anaesthetised to apnoea, a very dangerous procedure at any time, and allowed the various methods of artificial respiration to be tried for their relative effectiveness! Schaffer's method tended to hold sway until 1932 when Holger Nielsen described the method which was to supplant all other manual methods,[80.] but not all opinion was in favour of manual methods.

> "but it seems to me to be clear from every consideration that the mouth-to-mouth or nose method gives the

patient the best chance, for, to recapitulate:-

(1) The quantity of tidal air is greater than by any indirect method, and, therefore, the stimulation of the mechanisms of circulation and respiration, the elimination of the poison, and the oxygenation of the blood are all as great as possible.

(2) The impurities, if present at all, are negligible.

(3) The method can be applied without a moment's loss of time."[81].

This advice given in 1906 by Woods is still appropriate today. He was not however to prevail so soon, and even as recently as 1951 a comprehensive investigation of methods of artificial respiration by the National Research Council gave its imprimatur to Holger Nielsen's method without even considering mouth-to-mouth respiration.[82]. Only since 1958 has the work of Safar and others returned mouth-to-mouth respiration to popularity as the method of choice in emergency resuscitation.[83].

SURGERY

At the end of the 19th Century, experimental and therapeutic surgery of the thoracic cage and organs was being obstructed by the same problem which had frustrated the early physiologists; the chest could not be opened without the patient dying.

> "Hundreds of thousands of people are succumbing to tuberculosis, because as yet no one has been able to operate inside the thorax."[84].

(a) Intermittent Positive Pressure Ventilation.

The answer was not only centuries old, but also all around as it was in "constant use"[85]. in the physiological laboratory. It was being used in 1887 in cases of poisoning by Fell,[86]. and it was in fact a modification of Fell's positive pressure technique which was advised for use in surgery by Parham.[87]. Parham, incidentally, gives a very comprehensive table of all the previous successful intra-

thoracic operations on humans starting with Richerand in 1818. Tuffier and Hallion's technique[88.] (1906) was similar to that advised by Parham but used an expiratory resistance to keep the lung partially inflated for surgery upon it, and this technique is virtually the same as that used today.

On the other hand, the influential and persuasive surgeon Sauerbruch describes a subatmospheric operating theatre from which only the patient's head was excluded.[89.] The subatmospheric pressure supported the patient's lungs and enabled him to breathe spontaneously during his operation. Sauerbruch persisted with this technique for many years even when the positive pressure method had become generally established. With the acceptance of the positive pressure method there arose automatic mechanical devices to produce an intermittent flow. Some of the more important early models being those of Matas,[90.] Janeway,[91.] Dräger,[92.] Giertz,[93.] while the first truly automatic positive pressure ventilator was described by Bowditch in 1879-80 for use in physiology,

> "The most perfect method of keeping an animal alive by artificial ventilation is doubtless by means of bellows driven by a steam, gas or water motor. Where power of this sort is not to be had the object can be accomplished by breaking up the steady stream of air supplied by a water-bellows, or tromp, into a succession of impulses following each other at a rate corresponding to the normal respiratory movements of the animal." 94.

Parallel with this interest in positive pressure ventilation came the invention of direct laryngoscopy by Kirstein in 1895[95.] and the greater use of cuffed endotracheal tubes to prevent the leakage of gas. Thus the technique first described by Vesalius finally entered the everyday practice of surgery - an example of failure of communication that would have befitted the Dark Ages.

(b) Apnoeic Respiration.

In the early years of this Century the famous experiment of Hooke and Lower[27.] was restudied in various physiological laboratories apparently without knowledge of the prior effort nor of one another. Nagel[96.] in 1900 curarised pidgeons and passed air retrogressively into the opened humerus (into which the lung extends) and this air eventually escaped via the trachea. This work was followed by others who all insufflated air into the tracheas of various animals.[97 & 98.] This latter method was later introduced as a technique for humans in 1951,[99.] and is currently used in anaesthesia for certain operations. Techniques, relying only upon insufflation, cannot be used for long term artificial respiration because of the build up of body carbon dioxide.[97.] They also require oxygen as the delivery gas for any longer than a few minutes if hypoxia is to be avoided.[100.]

(c) Extracorporeal Respiration.

Hooke's suggestion for extracorporeal respiration was revived by Legallois in 1812[101.] and later experimentally by Brown-Séquard and others[102.] in the latter part of the 19th Century, but without success as an anticoagulant was not discovered until 1916.[103.] In 1929 in Russia perfusion was successfully carried out on dogs and isolated dogs' heads;[104.] however the work remained unknown and Gibbon[105.] worked out his own system from 1937 onwards culminating in the first human use in 1953 for an intra-cardiac operation.[106.]

> "Credit should also be given to others like Björk and Crafoord[107.] who, in 1948, introduced the now widely used rotating disc oxygenator, to Clark and Gollan[108.] who developed the first modern bubble oxygenator and to the technical virtuosity of Lillehei and his colleagues[109.] who in turn successfully used perfusion from reservoirs of oxygenated blood, cross circulation, dog lung oxygenators and finally introduced the

disposable plastic bubble oxygenator."[110.]

Current investigation in this field is on membranes for oxygen transference which do not require haemodilution nor cause erythrocyte damage, in the hope that extracorporeal respiration for days or weeks will be possible.[111.]

MEDICINE

Tank respirators had been commonly used to treat patients with anterior poliomyelitis since the 1920s and I.P.P.V. had been used intermittently in the treatment of respiratory depression since 1887, yet it was not until the disastrous epidemic of poliomyelitis in 1951 that the technique of positive pressure ventilation was fully exploited in general medicine. Lassen[112.] and Ibsen[113.] employed teams of medical students pumping bags filled with oxygen and nitrous oxide, and later air, to sustain life in patients affected with bulbar and respiratory paralysis. Soon a plethora of automatic machines became available to replace the students. Two of these ventilators are still in wide use throughout the world (Engström[114.] and Radcliffe[115.]). The new technique swept Europe and parts of the rest of the world, but the United States of America remained resistant to this advance and persisted in the use of the tank respirators until the mid-1960s. The use of positive pressure ventilation is now firmly established in medicine, and is the raison d'etre for the vast majority of intensive care units, now one of the most rapidly expanding areas of medical specialisation. However, once again their use could have benefitted medicine much earlier. Brodie[116.] in a letter to the French physiologist Flourens in 1811 suggested the use of curare with artificial respiration by bellows to treat tetanus. In 1858[117.] a patient with tetanus was first treated with curare without artificial respiration and died - no doubt as much due to respiratory

paralysis as to tetanic spasm. Brodie also foreshadowed medical treatment when,

> "It occurred to me that in an animal under the influence of this or of any other poison that acts in a similar manner, by continuing the artificial respiration for a sufficient length of time after natural respiration had ceased, the brain might recover from the impression, which the poison had produced, and the animal might be restored to life."[118.]

This advice was applied by Fell[86.] who used this technique in the treatment of patients suffering from opium poisoning. Still the idea had not been fully accepted because it was not until after the Copenhagen poliomyelitis epidemic that severe drug overdosage was regularly treated by artificial respiration.[119.]

CONCLUSION

Today more and more automatic respirators are appearing, each said to be better than the others and almost all antedated in principle by 150 years. There is however a new field of previously uninvented devices based on the Coanda effect[120.] and the associated field of fluidics.[121.] These are compact devices, with no moving parts, both attributes which are clinically useful. The physiological effects of artificial ventilation itself have been investigated, notably over the last 20 years,[122.] with recent emphasis given to the details of alterations in the type of ventilation itself.[123.] To investigate further these physiological effects, artificial ventilators have been developed which are able to vary the rate of breathing, the inspiratory to expiratory time ratio, the inspiratory flow pattern, the inspiratory pressure pattern and the tidal volume,[124.] and very recently one which alters only one of these variables at a time.[125.]

Thus the development of artificial ventilation is

continuing, as it expands to fill an increasing medical need. Its history has been beset with problems of repudiation, forgetfulness, plagarism and even misrepresentation, which have all had their effects upon its acceptance and development as a major technique in medicine. It is hoped that the lessons learnt will not be forgotten again.

NOTES

1. Jayne W.A. (1925) The Healing Gods of Ancient Civilisations. Yale University Press:New Haven p,65. However this myth is particularly complex and on checking Jayne's reference on this point I was not able to locate his interpretation of the myth. The following translations by Budge E.A.W. do throw some light on the interpretation,

   "She (Isis) made light with her feathers, she made air to come into being with her wings, and she uttered cries of lamentation at the bier of her brother. She stirred up from his state of inactivity him whose heart was still." Hymn to Osiris B.C. 1500. The Gods of the Egyptians II (1904) Methuen:London p.150.

   "to breathe the breath of Isis." Pyramid Text-Unås. The Gods of the Egyptians II p.204.

   "When Isis wished to revivify Osiris she gathered together his flesh, and bound up his hands, and embraced him." Pyramid Text - Pepi II 868. Osiris and the Egyptian Resurrection I (1909) Warner:London p.86.

2. Galen on Anatomical Procedures A.D. 177. Translated by C. Singer 1956. Wellcome Historical Museum: London pp195,196, 206-207, 207.

3. Ibid., p.195.

4. Ibid., p.206.

5. Ibid., pp.190-192.

6. Ibid., p.192.

7. Galen (A.D.175) De usu partium corporis humani. lib. VII cap.IV Translated by M.T. May (1968) Cornell University Press:New York p.339.

   "You can clearly see this for yourself even after the animal is dead, if you blow air through the rough artery into the whole lung and then empty it out again by pressure."

8. Bagellardus P. (1472) Libellus de egritudinibus infantium. Barval. p.3 unnumbered.

   "si reperiret ipsu calidu no nigru debet inflare in os eius ipso no habete respiratione aut in anu eius."

9. Vesalius A. (1543) De humani corporis fabrica. Lib.VII Cap.XIX - De vivorum sectione nonnulla. Oporinus:Basel. p.658 (should be 662 but error in first edition).

10. Ibid., p.658-659 (really 662-663).

11. Ibid., p.658 (really 663).

12. Personal communication from Dr. G. Whitteridge.

Mondino de'Luzzi (Mundinus) (1478) Anothomia. A. de Carchano:Pavia.

13. Leonardo da Vinci (1513) Quaderni d'Anatomica II fol.1, recto or p.2. Eds. Vangensten O.C.L., Fonahn A. & Hopstock H. (1912) J. Dybwad:Christiania.

14. Leonardo da Vinci (c.1507-1509) Quaderni d'Anatomic IV fol.10, verso or p.18. Eds. Vangensten O.C.L., Fonahn A. & Hopstock H. (1914) J. Dybwad:Christiania. The Leonardo dates from K. Clark (1968) The drawings of Leonardo da Vinci in the collection of Her Majesty the Queen at Windsor Castle. 2nd Ed. Phaidon:London Vol.III p.30 and 45.

15. Fodéré F.E. (1819) Dictionaire des Sciences Médicales 34, 413. Also Harrison W. (1916) Detroit Med.J.16, 270. A brief historical review of the employment of a bellows as a means of inducing artificial respiration during the three hundred years which elapsed between A.D. 1530 and 1830. Harrison most probably obtained his reference from Fodéré though he gives no references.

16. Pagel W. personal communication.

17. Haller A. von. Elementa physiologiae corporis humani. Tome III Respiratio - Vox (1766) F. Grasset:Lausanne p.247 credits Vesalius with being the first to carry out "Hooke's Experiment."25.

18. Colombo R. (1559) De re anatomica. Lib.XIIII De viva sectione p.261. N. Beuilacquae:Venetiis.

19. Harvey W. (1627). De motu locali animalium (Trans. C. Whitteridge 1968 Royal College of Physicians:Cambridge pp.103-105).

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21. Highmore N. (1651) Corporis humani disquisitio anatomica. Lib.II,Pars III, Cap.III De usu & motu pulmonum. Comitis S. Broun:Hague pp.189-190.

22. Croune W. (1664) Birch T. The history of the Royal Society of London for improving of natural knowledge. (1756) A. Millar:London Vol.1 p.433.

23. Hooke R. (1664) Birch T. Vol.1 p.486.

24. "The experiment of opening the thorax of a dog was made by Dr. Lower and Mr. Hooke, which succeeded well, as it had done formerly, according to the account already registered of it.[23]. Sir George Ent reflecting upon this experiment, said, that it showed what was not the use of respiration, but not what it was: that the lungs not beating at all, but only kept extended with fresh air blown in by bellows, showed, that the lungs did not serve to promote by their agitation the motion of the blood. Mr. Hooke considered, that the dog being continually supplied with fresh air was kept alive, but was ready to die, if either he was left unsupplied, or his lungs only kept full with the same air; and thence conceived, that the true use of respiration was to discharge the fumes of the blood." Birch T. Vol.II p.198.

25. Hooke R. (1667) Phil.Trans. R. Soc. Lond. 2, 539. An account of an experiment made by Mr. Hook , of preserving animals alive by blowing through their lungs with bellows.

The origin of this idea for artificial respiration which suddenly appeared to burst forth amongst the Royal Society is unreported. However, Ralph Bathurst in his doctoral thesis (Praelectiones tres de respiratione. 1654. Printed in "The life and literary remains of Ralph Bathurst M.D. Dean of Wells, and President of Trinity College in Oxford" by Thomas Warton. R. & J. Dodsley:London 1761 p.127.) shows that he had read critically Highmore's book[21]. and thus would know of the technique. Also he was friendly with Harvey when the latter was at Oxford, and the subject may well have been mentioned between them. The connection may have been through Bathurst's membership of the Royal Society, but perhaps more likely through his intimacy with Thomas Willis who had Richard Lower as his apprentice. However the technique should have been known to the educated well-read physicians of the time. An interesting aside is that Borelli who compiled his great work during this era mentions only the experiments of Croune[22]. ("Croon") and has no mention of Vesalius or his followers (Borelli G.A. 1681 De motu animalium. A. Bernabo:Roma. Pars Altera p.216).

26. Birch T. Vol.II p.201.

27. "Towards the latter end of this Experiment a piece of the Lungs was cut quite off; where 'twas observable, that the Blood did freely circulate, and pass thorow the Lungs,not only when the Lungs were kept thus constantly extended, but also when they were suffer'd to subside and lye still. Which seem to be Arguments, that as the bare Motion of the Lungs without fresh Air contributes nothing to the life of the Animal, he being found to survive as well, when they were not mov'd, as when they were; so it was not the subsiding or movelesness of the Lungs, that was the immediate cause of Death, or the stopping the Circulation of the Blood through the Lungs, but the want of a sufficient supply of fresh Air." Phil.Trans. R. Soc. Lond. 2, 539.

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CHAPTER

2

THE PROBLEM

CHAPTER 2

THE PROBLEM

Intermittent positive pressure ventilation (I.P.P.V.) has been used in humans with increasing frequency since 1952 (Lassen 1953; Ibsen 1954), and during this time numerous mechanical ventilators have been developed. These ventilators produce different inspiratory flow patterns and have different inspiratory to expiratory time ratios (I:E ratios). Certain inspiratory flow patterns and I:E ratios are thought to be better than others, and studies using commercial ventilators have been performed which purport to support this impression (Engström and Norlander 1962; Norlander 1964; Robinson 1967; Herzog and Norlander 1968; Lyager 1968). The evidence in these papers is inconclusive or conflicting.

There have, however, been a number of studies of the effects on general body physiology of altering the I:E ratio and the flow pattern of inspiration. Early studies were those of Cournand and his colleagues (Cournand et al. 1948; Werkö 1947) who investigated the effects of varying inspiratory flow patterns during intermittent positive pressure breathing (I.P.P.B.) and found that their type III inspiratory pressure curve (Fig.2:1) had the least disturbing action on cardiac output. The effects of subatmospheric pressures during expiration in patients requiring artificial ventilation who had unstable circulatory responses were also studied at about this time (Maloney et al. 1953). This work strongly suggested that in such patients a subatmospheric pressure in expiration was highly desirable to maintain

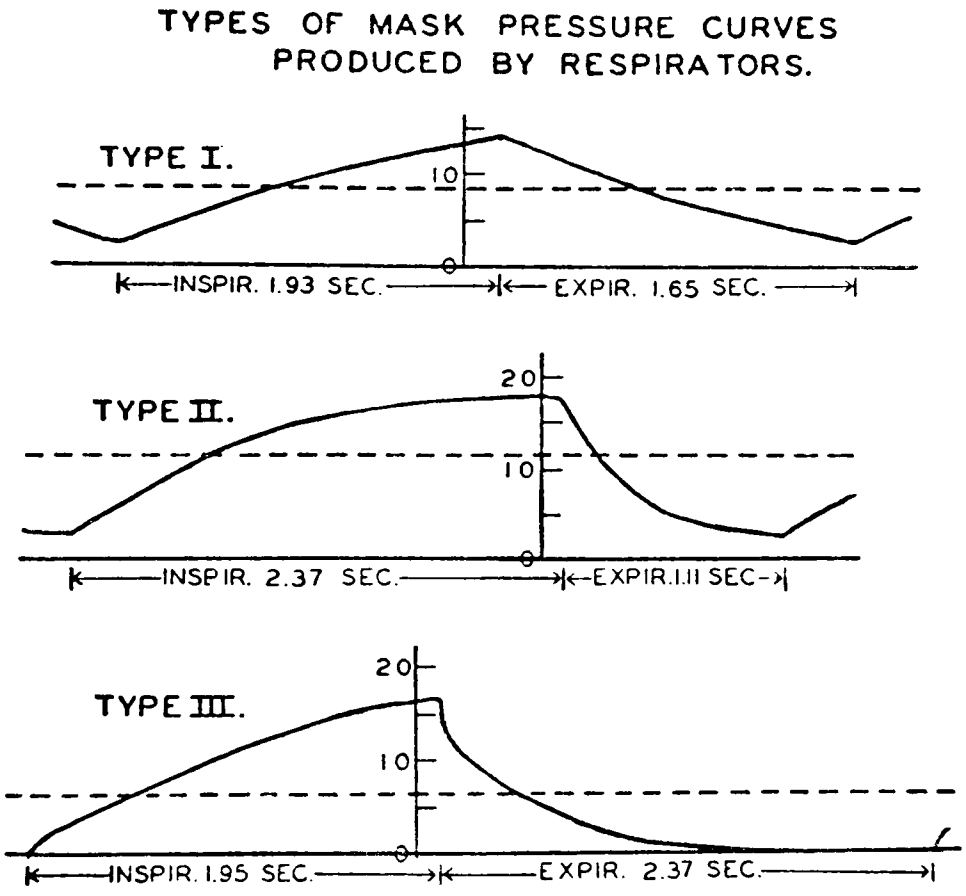


Fig. 2:1 The three "different" waveforms employed by Cournand et al. (1948), showing that the main difference is in inspiratory to expiratory ratio (from Cournand et al. 1948).

cardiac output, and such a refinement was included in the design of many commercial ventilators.

These early studies were followed by the work of Watson (1961) who built a variable waveform pressure generator (Watson et al. 1962) and used this ventilator to study the effects of varying I:E ratios and inspiratory flow patterns. Watson (1962a) found that the physiological dead space to tidal volume (V_D/V_T) ratio increased on shortening the inspiratory time. This finding was confirmed by Bergman (1963) in dogs, and by Fairley and Blenkarn (1966) and Bergman (1967) in humans. In a series of experiments in the years 1968-1969 Lumley and her group did not, however, find this increase, though the same group (Sykes and Lumley 1969; Finlay et al. 1970) later confirmed that V_D/V_T ratio increased with shortening of inspiration. Watson (1962b) also found that compliance decreased with shortening of the inspiratory time and this was confirmed using an indirect method by Sykes and Lumley (1969) but not by Finlay et al. (1970).

In a similar series of experiments Bergman (1963) using air to ventilate dogs found that the alveolar to arterial oxygen partial pressure (A-a P_{O_2}) gradient increased with shortening of the inspiratory time, but this finding has not been observed when more than 30% O_2 has been used in the inspired gas (Fairley and Blenkarn 1966; Bergman 1967; Sykes and Lumley 1969). The effect of I:E ratio upon venous admixture ($\dot{Q}_s/\dot{Q}$) and arterial to alveolar carbon dioxide partial pressure (a-A P_{CO_2}) gradient have been investigated only by Finlay et al. (1970) and their results were equivocal with a suggestion that shortening of inspiration led to an increase in $\dot{Q}_s/\dot{Q}$ and in a-A P_{CO_2} gradient. The effects of changing I:E ratios on cardiac output have also been studied by Finlay et al. (1970) with results

suggesting that there is no effect.

Another aspect of the physiology of artificial ventilation which Watson (1962a and b) studied was the effect of alteration of the inspiratory flow pattern at different I:E ratios. His studies showed that inspiratory flow pattern had no effect on V_D/V_T ratio and compliance for any given duration of inspiration. These findings have been confirmed by Bergman (1963 and 1967) and Adams et al. (1970) who both studied other variables, such as cardiac output, $\dot{Q}_s/\dot{Q}$, A-a P_{O_2} gradient as well as V_D/V_T and compliance.

On close examination of the methods used in these investigations several deficiencies became obvious. Watson (1961) used a ventilator which was a pressure generator the performance of which would be modified by the subject's respiratory mechanics. In addition he measured arterial carbon dioxide partial pressure (P_{a,CO_2}) indirectly by a "rebreathing" method (Campbell and Howell 1960). Bergman (1963 and 1967) also used ventilators which were pressure generators to produce changes in flow pattern. The methods used, in fact changed only the initial flow velocity and not the profile of the flow pattern. Fairley and Blenkarn (1966) only studied the effects of increasing flow velocity, and in calculating $\dot{Q}_s/\dot{Q}$ assumed a constant arterio-venous oxygen content difference. Sykes' group did not use pneumotachography to monitor the flow pattern delivered and consequently had to use indirect methods for the determination of "no flow" conditions to measure dynamic compliance. None of these investigators used an experimental design which tested for interactions between I:E ratio and inspiratory flow pattern in their combined effect on the patho-physiology of I.P.P.V.

Recently a different alteration to the inspiratory flow pattern has been examined by Knelson et al., (1969 and 1970) and Lyager (1970). These authors suggest that a pause at the end of inspiration, with no gas flow occurring, improves certain physiological variables. With the techniques used by these authors the I:E ratio is always changed, and in some of the studies described by Lyager (1970) the shape of the gas flow pattern in inspiration is also altered. Such studies, therefore, are not examining only the effects of a pause at the end of inspiration.

It was against this background of controversy, of some unconfirmed findings, and of many unanswered questions that the present study was undertaken. It was decided to investigate only the effects of changes in the inspiratory flow pattern and I:E ratios, as the work of Auchincloss and Gilbert (1967), Prys-Roberts (1968), Morgan et al., (1969) and Sykes et al., (1970) suggests that a subatmospheric pressure in expiration is virtually never necessary if patients are sufficiently hydrated.

Theoretical aspects of the study of inspiratory flow pattern and I:E ratio have been reported but are either insufficiently searching (Otis et al., 1956; Campbell and Brown 1963) or make fundamental errors (Wald et al., 1968; Jain and Guha 1970). Further discussion concerning this aspect will occur in the appropriate section.

CHAPTER

3(a)

VARIABLE WAVEFORM GENERATOR

CHAPTER 3(a)

VARIABLE WAVEFORM VENTILATOR

There have been a number of studies of the physiological effects of different tracheal pressure wave patterns in patients requiring artificial ventilation with intermittent positive pressure ventilation (I.P.P.V.) (Werkö, 1947; Cournand et al., 1948; Maloney et al., 1953; Watson, 1962(a) and (b); Bergman, 1963 and 1967; Grenvik, 1966; Auchinloss and Gilbert, 1967; Robinson, 1967; Herzog and Norlander, 1968; Adams et al., 1970). These studies have in some instances used specially designed ventilators which could vary the pressure wave pattern. (Clutton-Brock, 1957; Watson et al., 1962; Adams, 1970.)

The tracheal pressure waveform that is produced by I.P.P.V. is only partially controlled by the ventilator itself, as the final waveform is dependent very largely upon the patient's respiratory mechanics. Also in any given situation the pressure waveform alters in shape as it is observed at different points in the airway downstream from the ventilator, and these changes in turn may vary at different flow rates. However, the tracheal flow pattern does not suffer these variations as at any given instant the flow will be the same at any two points from the ventilator output to the bifucation of the trachea assuming no leaks, except for very minimal changes due to gas compression and heating. Flow measurement is, therefore, a better measure of the pattern of ventilation than pressure measurement. This is especially so if the ventilator can be made powerful enough to be a flow generator (Mapleson, 1962) and so independent of patient characteristics.

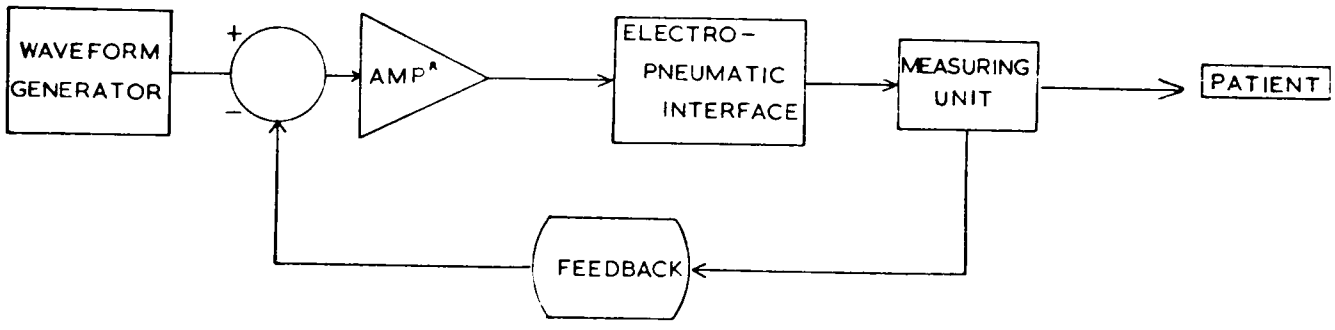


Fig. 3(a):1 Block diagram of ventilator design.

A ventilator has been designed which produces a flow waveform variable over a wide range, and a block diagram of the design is shown in Fig. 3(a):1. The ventilator consists of a variable electronic signal generator controlling an electropneumatic interface through an amplifier. The pneumatic output is passed to the patient. A feedback circuit may be necessary if the changing load produced by the patient materially affects the output of the electropneumatic interface. Each part of the ventilator will be described with its performance where appropriate,

WAVEFORM GENERATOR

The waveform generator (Fig. 3(a):2) which was designed and built for this purpose (Childs and Sitch, 1969) is capable of producing a widely variable electrical signal which may be displayed as a waveform. The selected signal is constructed by placing pins in a matrix board with twenty horizontal and fifty vertical steps. The "on" time of the generator has a total range of 0.05-4.99 seconds in steps of 0.01 sec. During the "on" time the horizontal steps are scanned at equal time intervals of 1/20 of the "on" time. The "off" time is similarly controlled from 0.05-5.00 sec. During the "on" time the vertical position of the selector pins determines the output voltage and so wave shapes may be built up.

Electronically the waveform generator consists of a solid-state twenty step counting ring the counting rate of which is controlled by the "on" and "off" time oscillators. The matrix board consists of a fifty step voltage divider, and as the counting circuit passes each column the voltage selected by the pin position is passed to a sample-and-hold and integrating circuit, which produces a fairly smooth signal output. A photograph of the electrical output of the waveform generator dictated

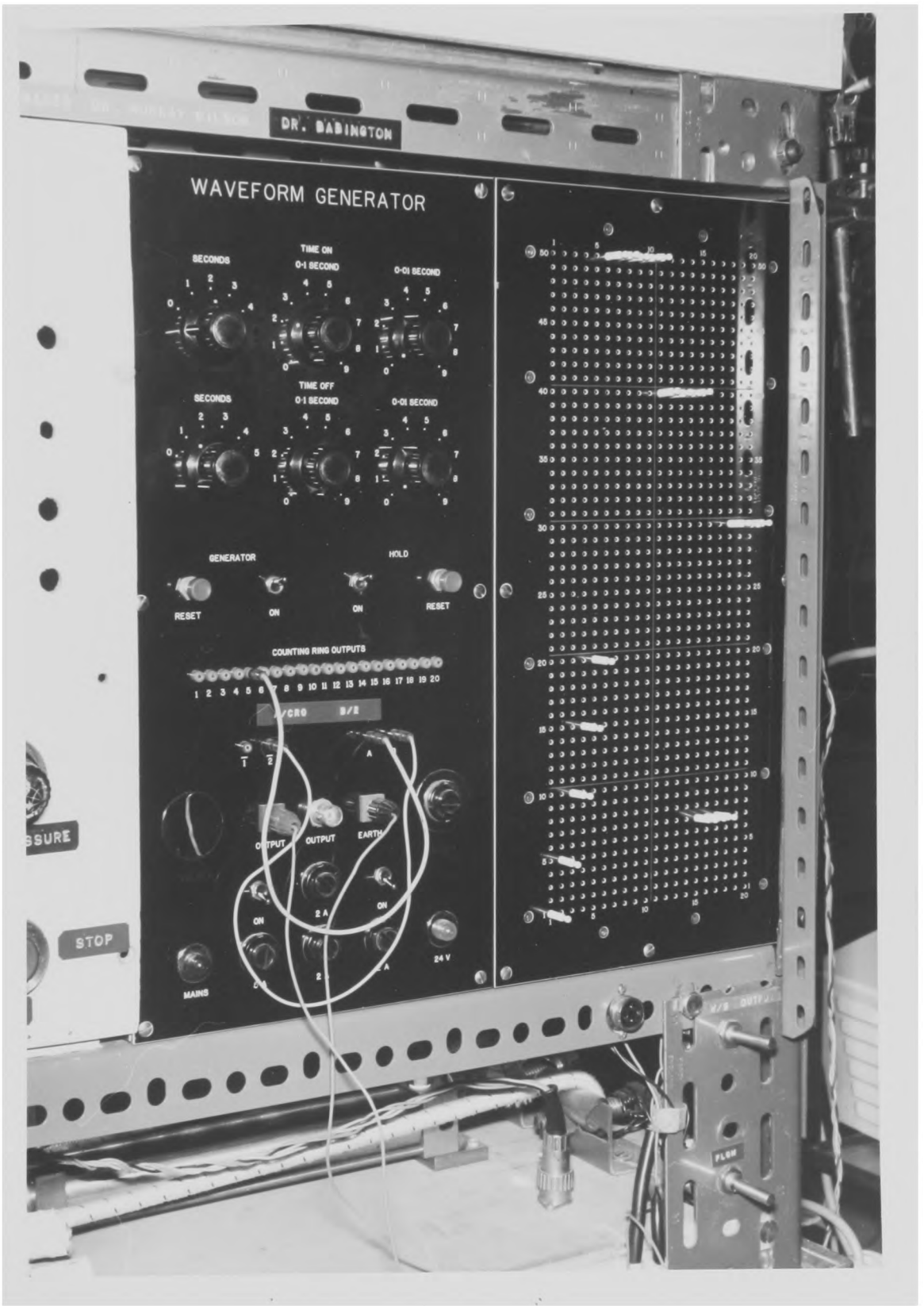


Fig. 3(a):2 Electronic waveform signal generator.

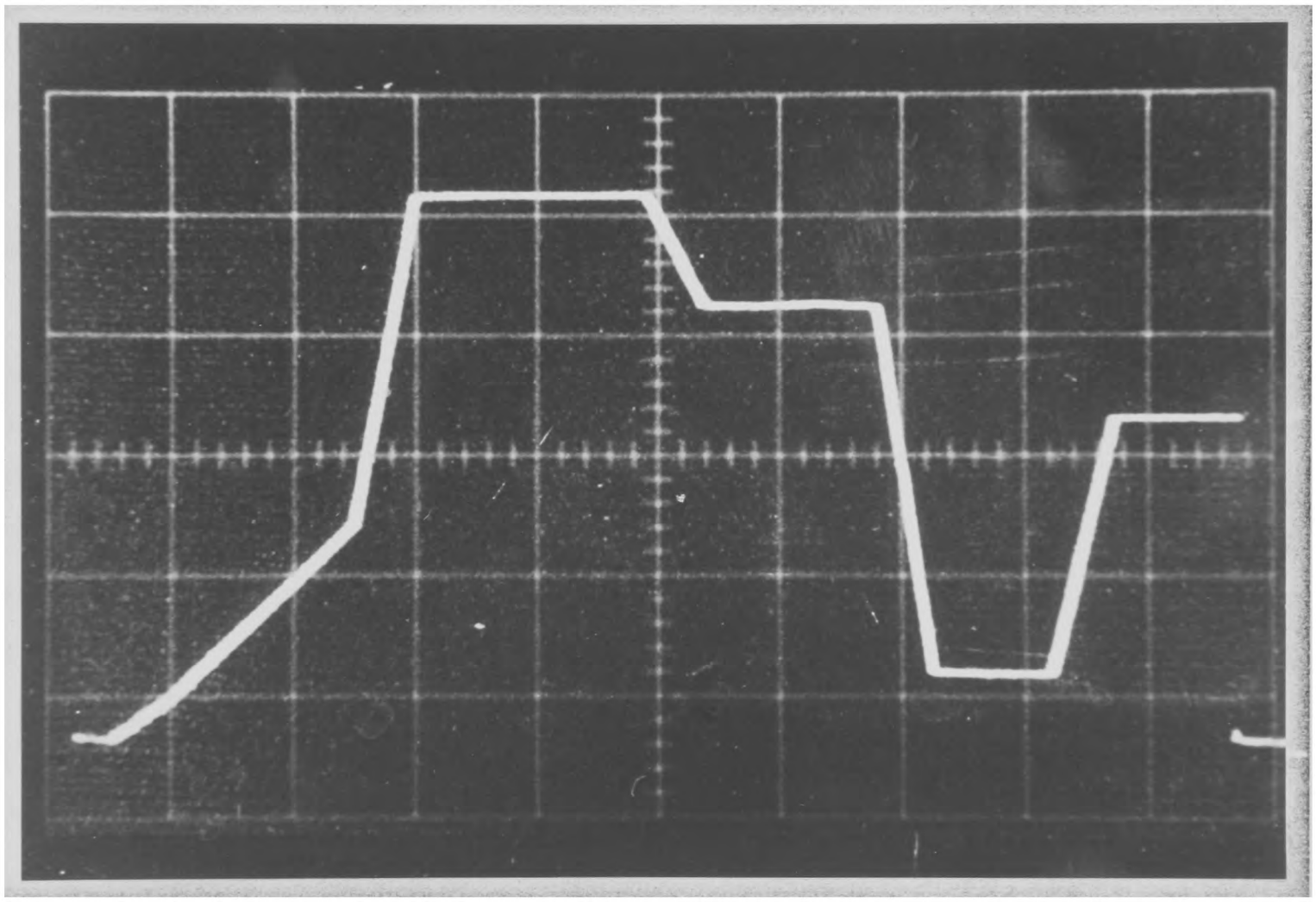


Fig. 3(a):3 Oscillographic display of the electrical signal from the pin settings of Fig.3(a):2.

by the pin settings in Fig. 3(a):2 is shown in Fig. 3(a):3.

The waveform generator also has the capacity for synchronous control of the solenoids in the patient inspiratory/expiratory valve. The synchronous control is arranged to prevent spill from the inspiratory to expiratory limbs and so allow accurate measurements of gas volumes. It is also possible to stop the counting ring at any predetermined point in the time cycle (either inspiratory or expiratory) with both solenoid valves closed to allow measurement of airways resistance (Neergaard and Wirz, 1927). The signal from the generator is variable up to 5 volts, and a power supply of 12 volts and two of 24 volts are built in to the generator to supply feedback and power amplifiers, and the solenoids for the patient valve.

ELECTROPNEUMATIC INTERFACE

When the signal generator has produced an electrical signal of a chosen form the signal must be converted into a gas flow. This is achieved by an electropneumatic converter (Westinghouse, Brake and Signal Co. Ltd.) (Fig. 3(a):4) which converts the electrical signal in the first instance into a pressure which is proportional to the electrical input. If this pressure is applied to a suitable restriction the gas flow from the restriction will closely follow the shape dictated by the signal generator.

Fig. 3(a):5 shows a schematic outline of the internal function of the converter. There are two chokes, or restrictions, a fixed one at A and a variable one formed by the ball-bearing F on its seat D. Movement of the ball towards the seat renders the choke A relatively less effective and the pressure rises in tube B. This causes the relay valve C to become unbalanced and so to open and permit a flow to the outlet J. This flow will continue

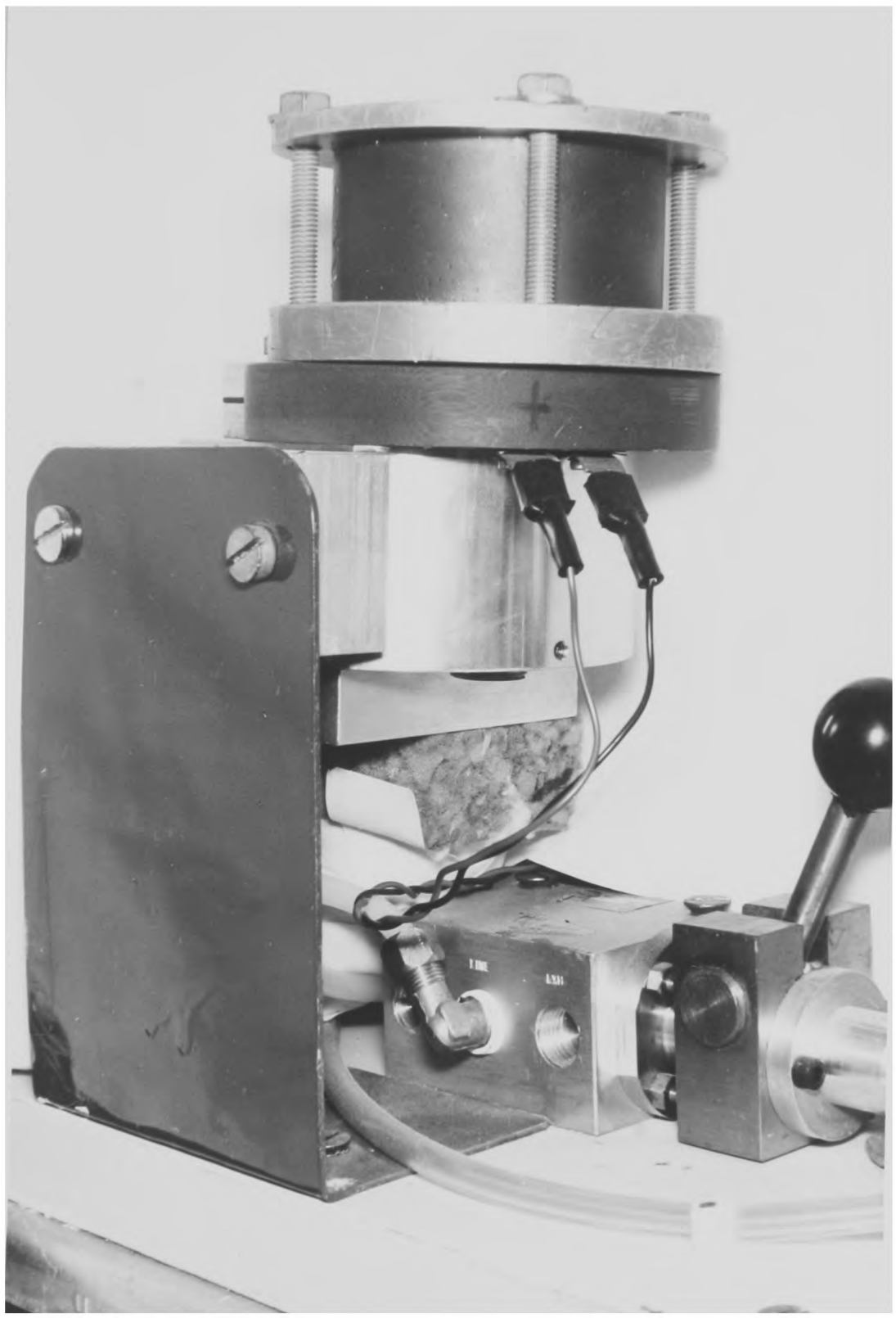


Fig. 3(a):4 Electropneumatic converter.

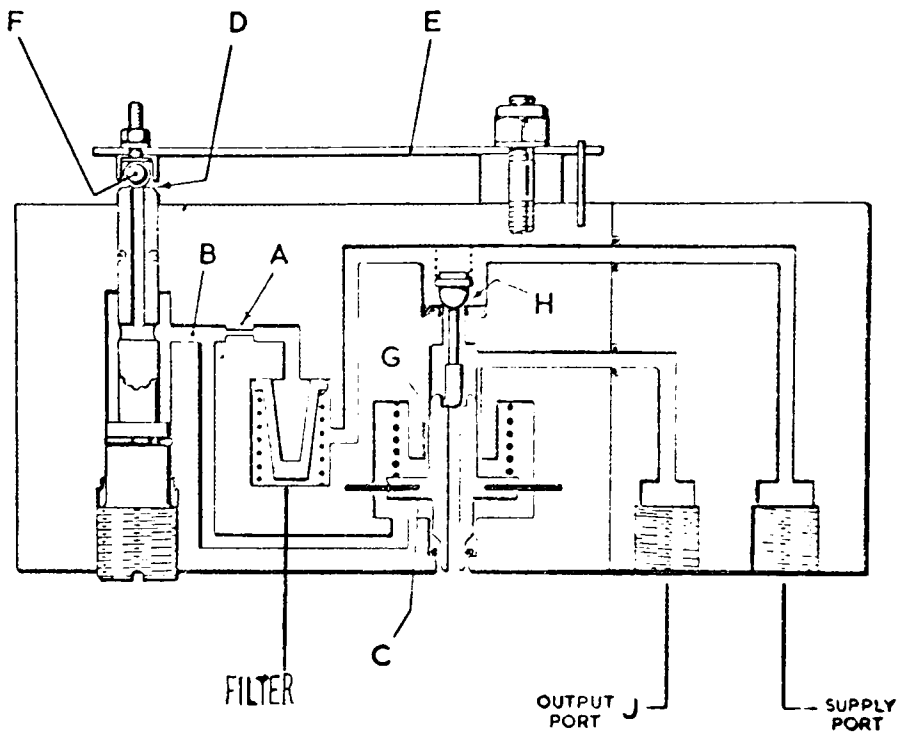
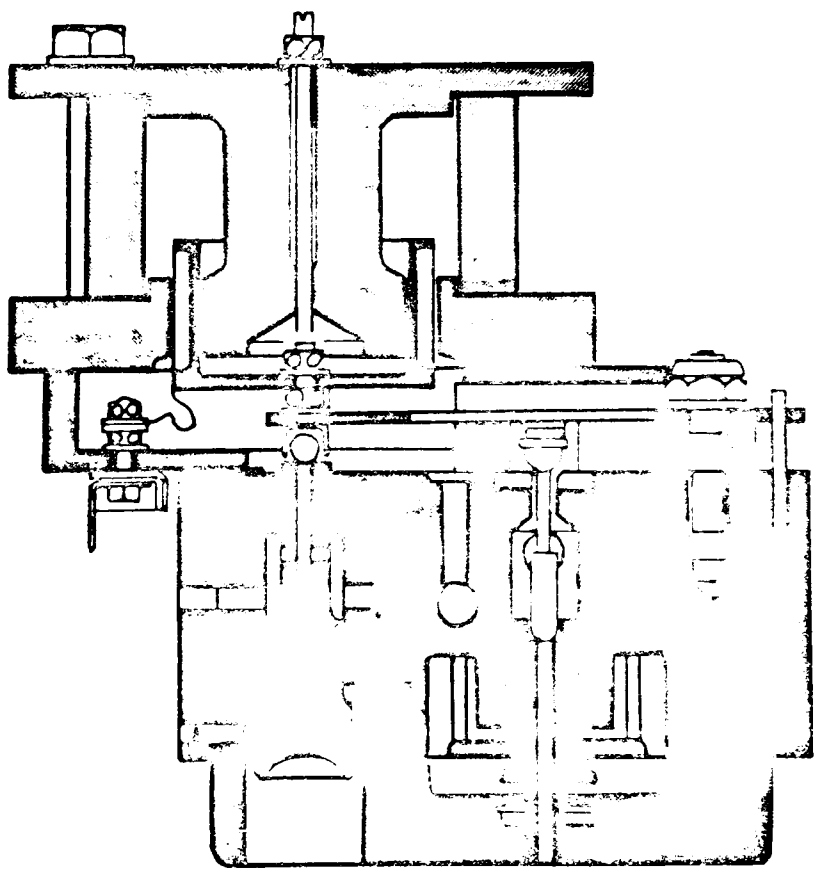


Fig. 3(a):5 Schematic diagram of electropneumatic converter. (A= fixed choke; B = small pressure reservoir tube; C = high pressure side of control relay valve; D = seating for ball-bearing F; E = torsion-bar balance for ball-bearing F; F = ball-bearing; G = low pressure side of control relay valve; H = output valve; J = outlet port). See discussion in text.



BASIC CONVERTER WITH MAGNET

Fig.3(a):6 Section diagram of electropneumatic converter.

until the outlet pressure becomes great enough to balance the relay valve or until the ball returns to its former position. The ball is held in a cage on a spring arm and is moved by a coil in a permanent magnet assembly (Fig. 3(a):6.).

The electropneumatic converter was subjected to static and dynamic tests to judge its performance under conditions likely to be met in practice. A plot of the static pressure output against input current is shown in Fig. 3(a):7. It will be seen that there is a linear relationship between current and pressure when the output pressure is less than 85% of the input line pressure. Thus, if the converter is supplied by 120 p.s.i. and if the maximum output pressure required is less than 85 p.s.i., a fall of even 20 p.s.i. in the supply will not affect the output pressure. Fluctuations in input pressure are lessened by using a very stable reducing valve, and a reservoir in the input line. The supply of high pressure air to the electropneumatic converter is obtained from cylinders through a stable 120 p.s.i. reducing valve (167/10B Power Dome Controller, I.V. Pressure Controllers Ltd.) and is controlled by a pilot operated spool valve immediately upstream from the converter.

The ventilator is designed to produce a predetermined gas flow waveform and it must be established that the dynamic conditions of gas flow encountered in practice do not influence the capability of any part of the ventilator. The ability of the electropneumatic converter to maintain a steady output pressure for a given current, when there is a gas flow, was tested by gradually increasing the outlet flow by means of a needle valve and measuring this flow with a pneumotachograph calibrated against an accurate rotameter which in turn had been calibrated against a Tissot spirometer. The results

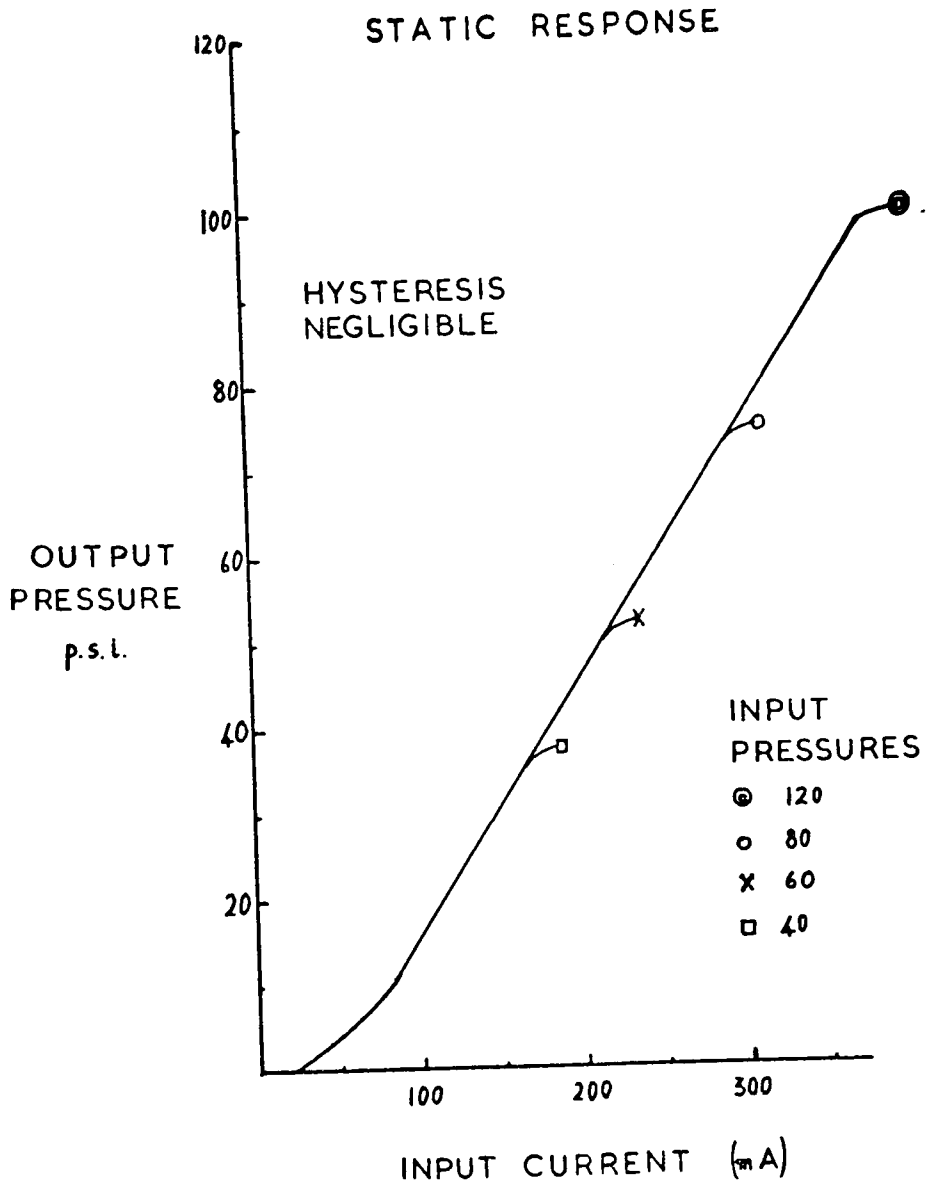


Fig. 3(a):7 Static output pressure response of the electro-pneumatic converter to input current showing the linear response from 10 p.s.i. to within 15% of the input gas pressure.

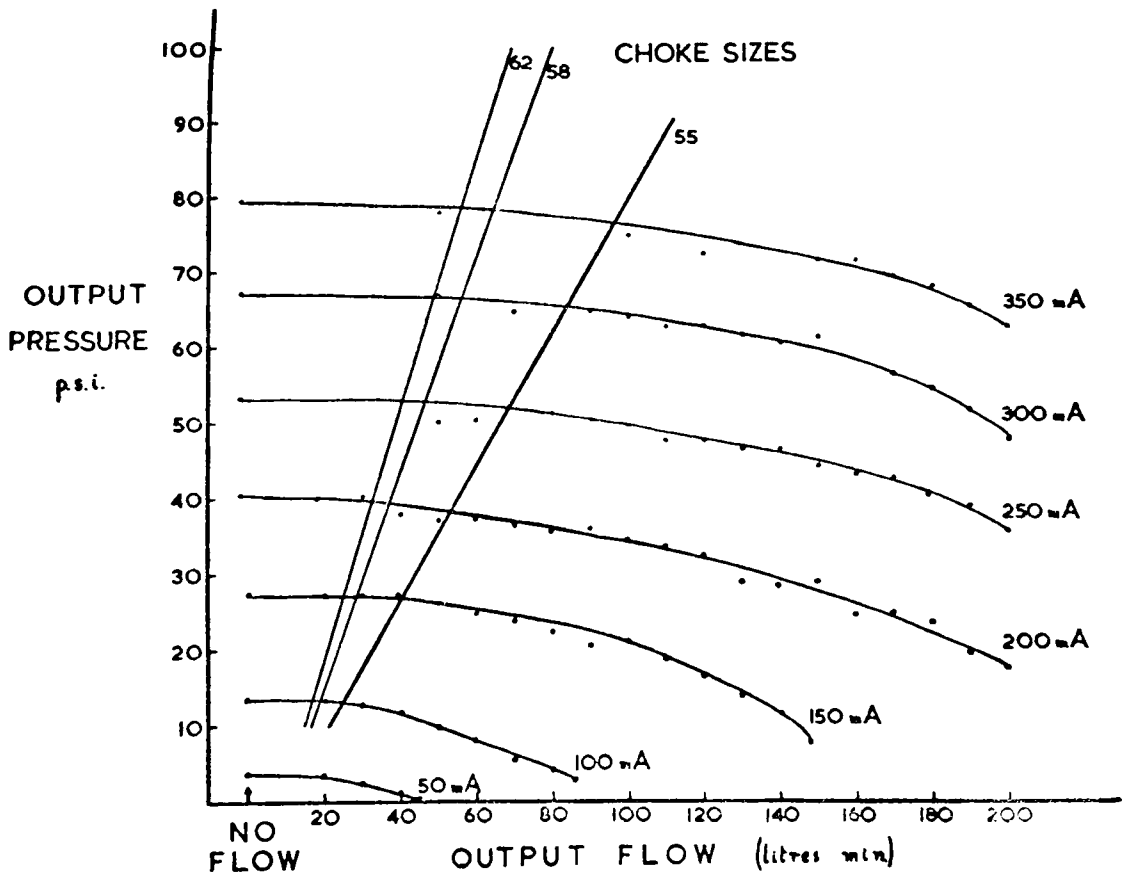


Fig. 3(a):8 Dynamic output pressure response of the electro-pneumatic converter at various fixed current inputs when the flow output is gradually increased. Three choke responses derived from Fig.3(a):11 are superimposed to show the outlet flows to be expected in use.

are shown in Fig. 3(a):8 which illustrates the fall-off in pressure as the flow rate increases. The converter was further tested by connecting the output to a 80 cm^3 reservoir and measuring the pressure changes in the reservoir with a piezo-electric transducer (Kistler 7031 SN 29846). The frequency response of the electro-pneumatic converter to a sine-wave input allowed complete reproduction to 2.5 Hz and a 'flat' response (at the 3 db level) to 6.5 Hz (Fig. 3(a):9). The phase delay with this frequency testing was linear to 6 Hz demonstrating that no deformation of the waveform pattern would occur to at least 6 Hz (Fig. 3(a):10). These values are adequate for the complete reproduction of respiratory patterns of gas flow.

To convert the pressure output of the converter to a flow, the output is led directly to one of a number of chokes. The flow/pressure characteristics of these chokes are shown in Fig. 3(a):11 and at pressures above 10 p.s.i. the relationship of flow to pressure is linear. These chokes are pieces of brass rod 1.5 cm long drilled to a number drill size shown in Table 3(a):1, and threaded to fit a connector.

The overall performance of the collected pieces of interface equipment was tested by arranging the pins in the matrix board of the signal generator to give step changes in the electrical signal, and resultant flow was measured using the calibrated pneumotachograph. Fig. 3(a):12 shows the correlation between pin position and flow. It follows that changes in the selected waveform will result in proportional changes in the flow produced from the choke, and so variable flow patterns may be produced. The duration of gas flow is determined by the "on" setting of the signal generator and the whole system acts as an integrator of flow against time to give a "tidal volume".

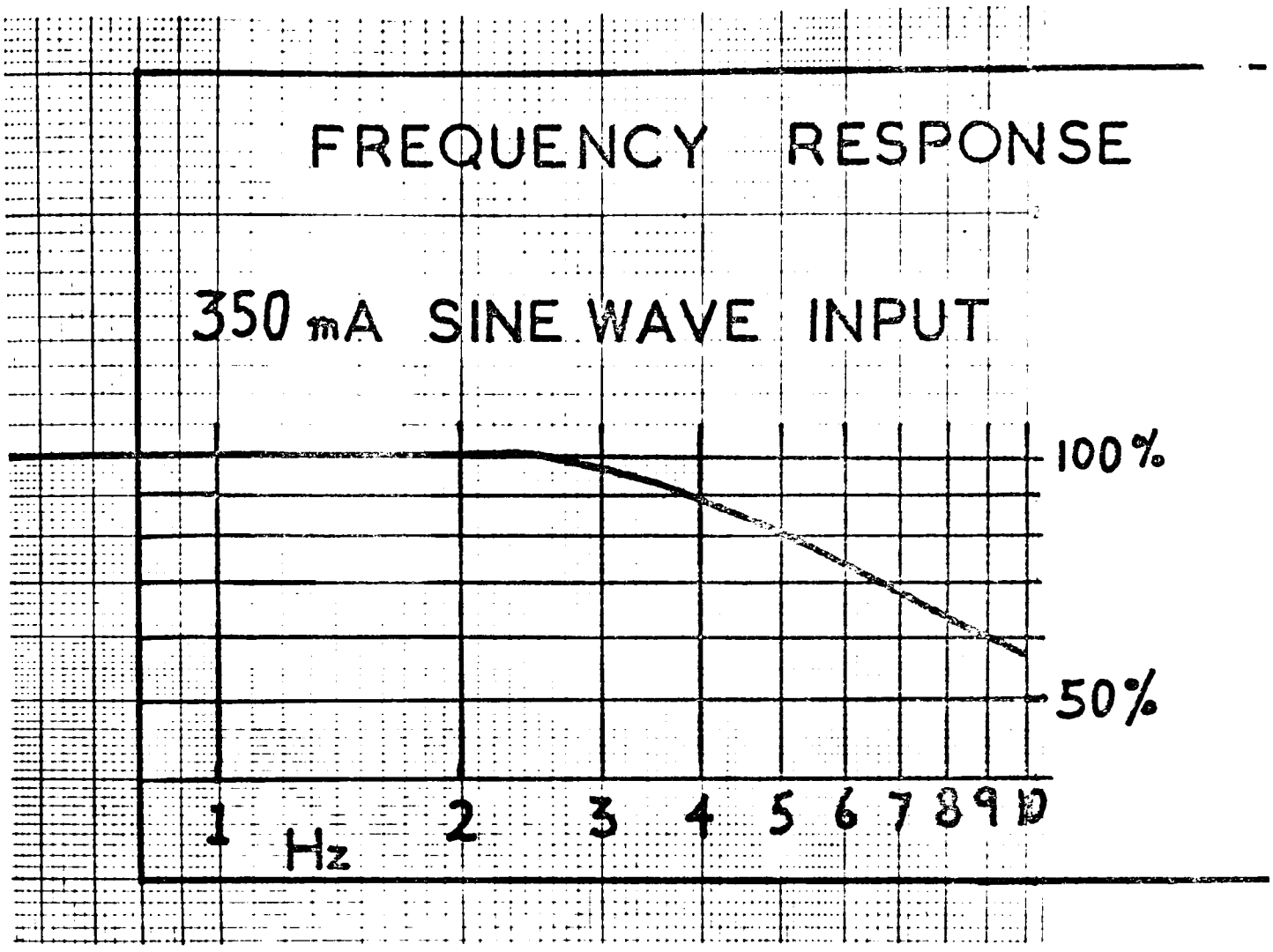


Fig.3(a):9 Frequency response of the electropneumatic converter demonstrating complete reproduction to 2.5 Hz and a "flat" response (at the 3 db level) to 6.5 Hz.

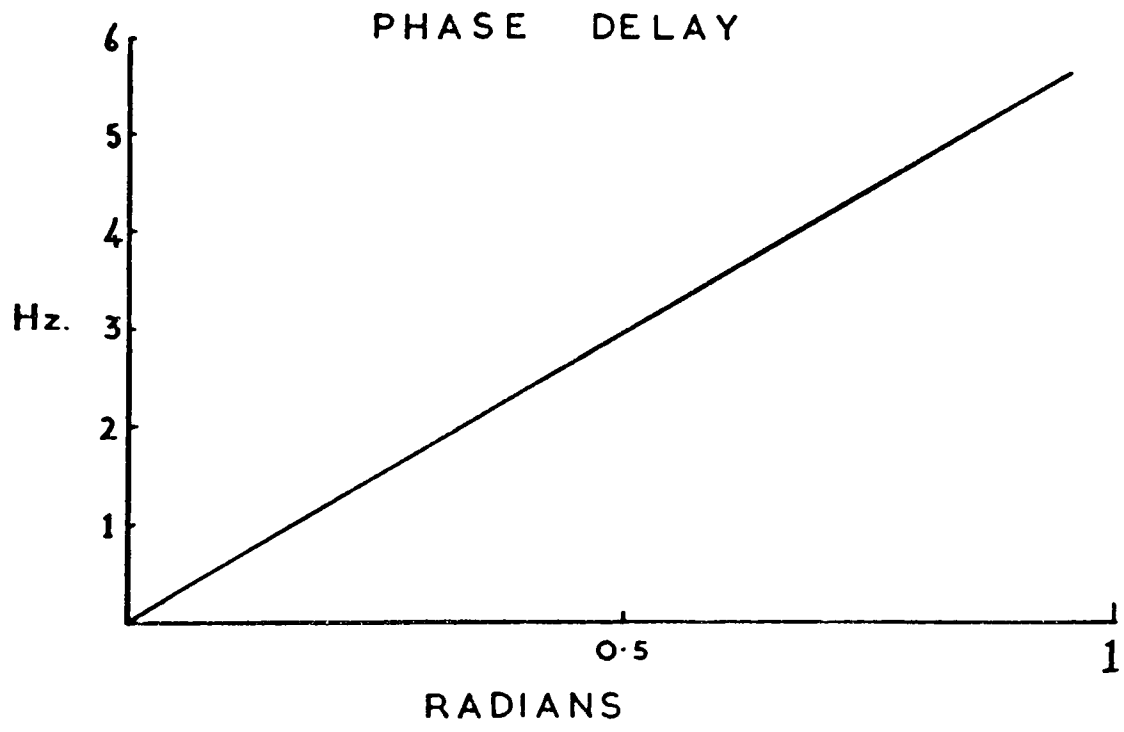


Fig.3(a):10 Phase response of the electropneumatic converter showing a linear phase delay to 6 Hz. No deformation of the waveform pattern will occur to at least 6 Hz.

TABLE 3(a):1

Choke Sizes used to Transfer the Pressure Signal to a Flow

Drill Size	Diameter (Thousandths of an inch)	Diameter (mm)
42	93.5	2.655
50	70	1.988
55	52	1.477
58	42	1.193
62	38	1.079

Choke size 55 was the choke size used for all the animal experiments described in Chapter 6.

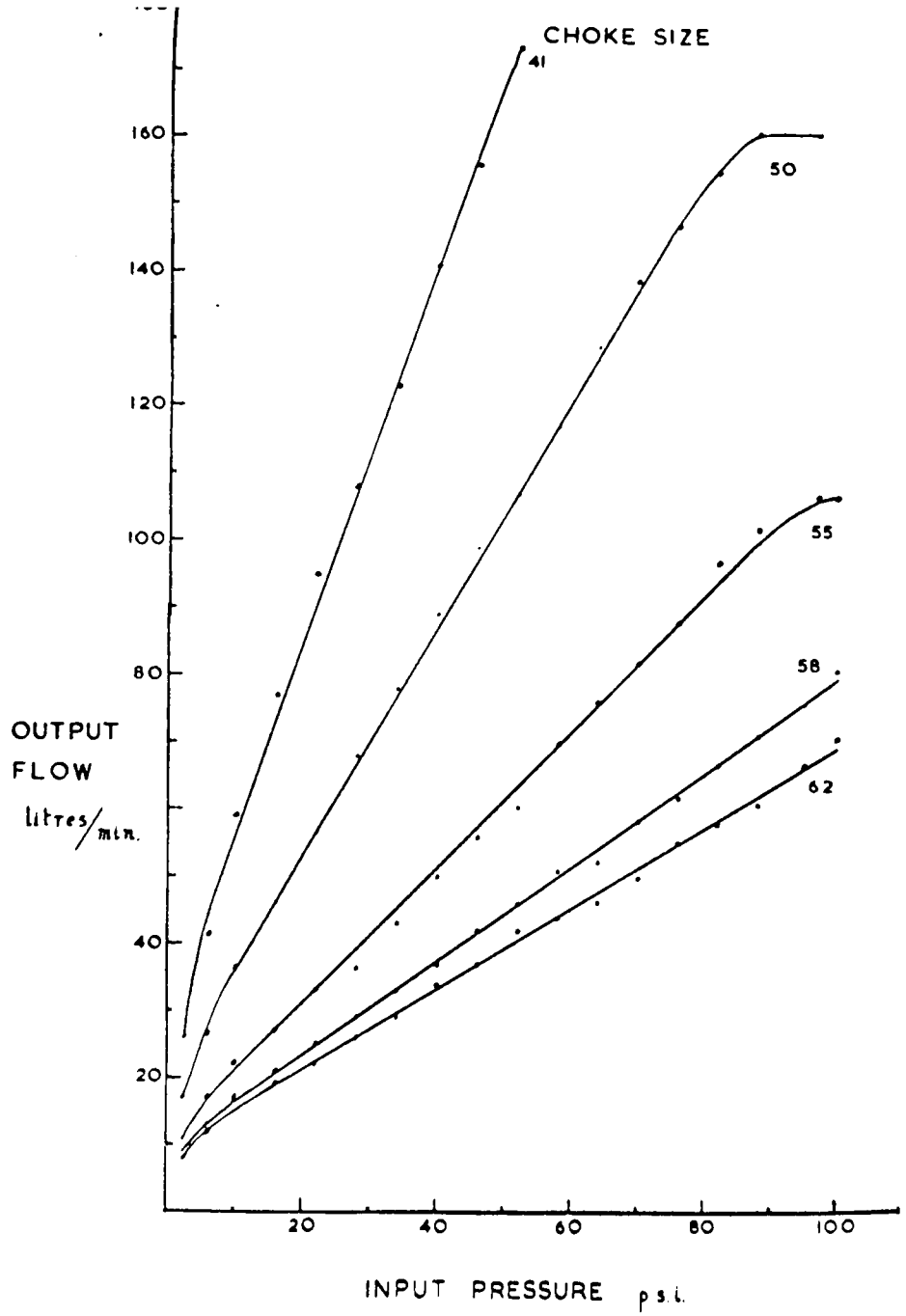


Fig. 3(a):11 Dynamic output flow response of brass chokes (see Table 3(a):1) for a given input pressure showing a linear relationship above 10 p.s.i. to a critical pressure depending upon the individual brass choke.

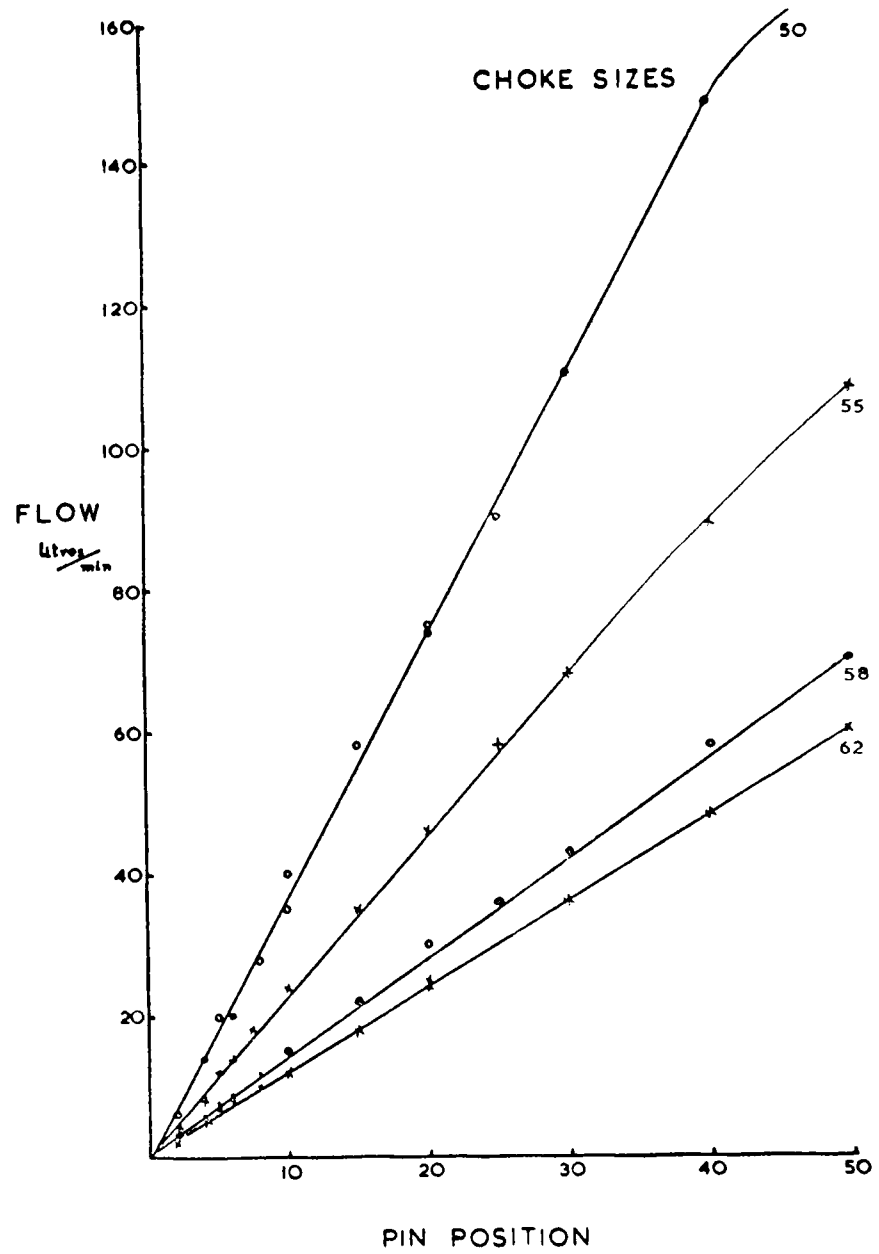


Fig. 3(a):12 Total dynamic output flow response of the ventilator compared to pin position on the matrix board. This shows the linearity of the ventilator response for a given electrical signal.

This tidal volume may be changed by adjusting the gain of the power amplifier. Because of the linearity of this system, integration of the signal to the electropneumatic converter is directly proportional to tidal volume and thus the volume may be adjusted in a controlled manner. The potential driving pressure is so high (85 p.s.i.) that back pressure of up to 50 Torr (1 p.s.i.) from a patient with severe respiratory disease will produce an average of only 4% fall in selected driving pressure (Fig. 3(a):7). There is, therefore, no need for a feed-back circuit to be used in this ventilator.

PATIENT VALVE

A light, rapidly acting inspiratory-expiratory respiratory valve located close to a patient and which can be activated remotely would have many applications in aneasthesia and intensive therapy. If this valve had the additional facility of independent control of inspiratory and expiratory pathways, it would be also very useful as a research tool. Such a valve is not commercially available though Hill and Hook (1959) have described a valve with these attributes.

A valve has been designed (Figs. 3(a):13 and 14) which is remotely activated with independent control of both inspiratory and expiratory pathways. Rapid gas-tight closure of these pathways is achieved by remote control of solenoid operated pistons (Fig. 3(a):14). Solenoids may be very powerful if operated by 240 volts A.C. but these could be dangerous to patients and operator should any defect occur. Such valves have, however, been described (Thornton, 1969 and Lyager, 1970). Electrical hazards may be avoided by using low voltage D.C. solenoids but these solenoids have the disadvantage of being comparatively less powerful. This disadvantage may be overcome by designing the valve so that gas flow is

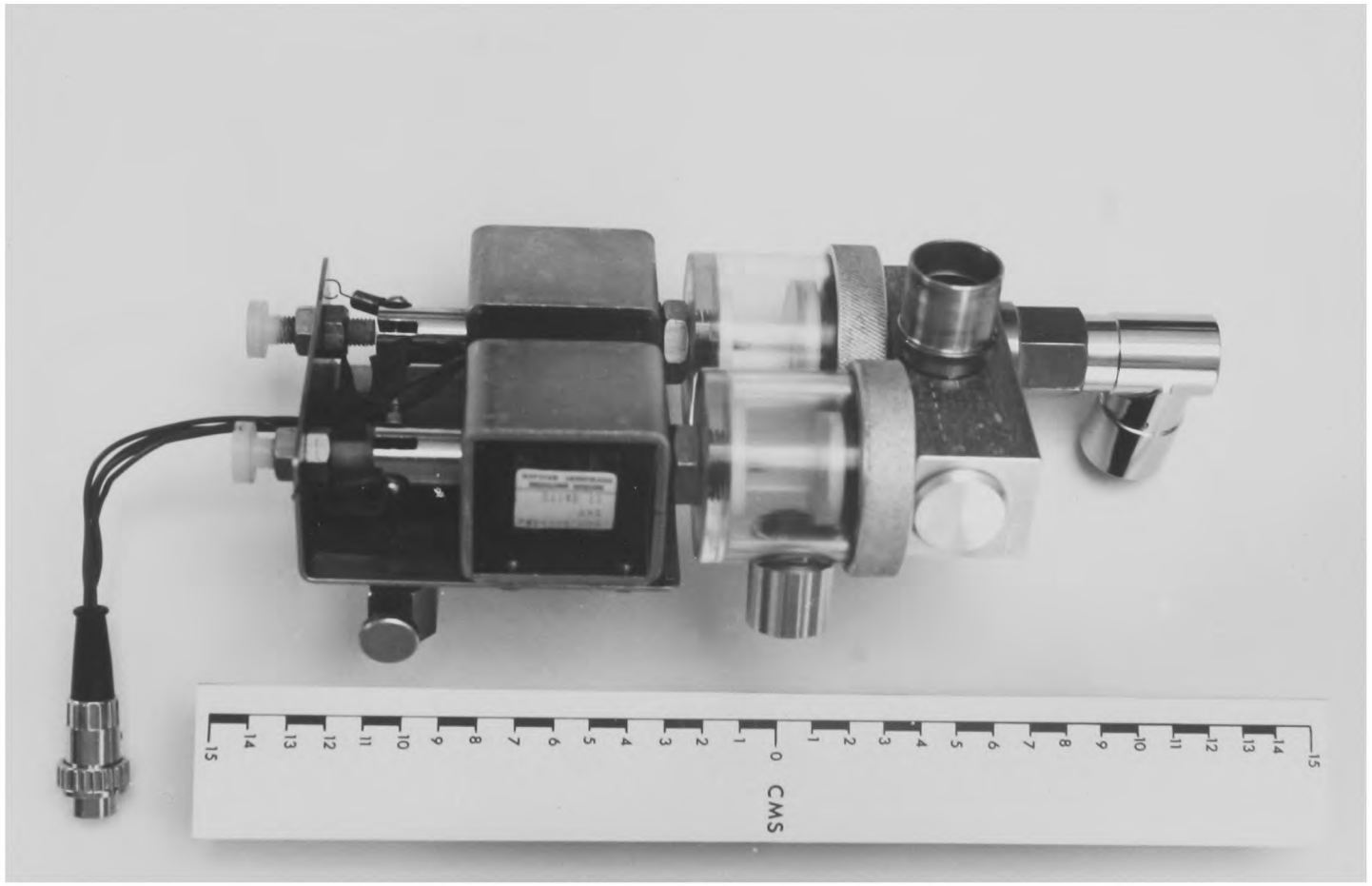


Fig. 3(a):13 Photograph of the complete solenoid operated inspiratory/expiratory valve.

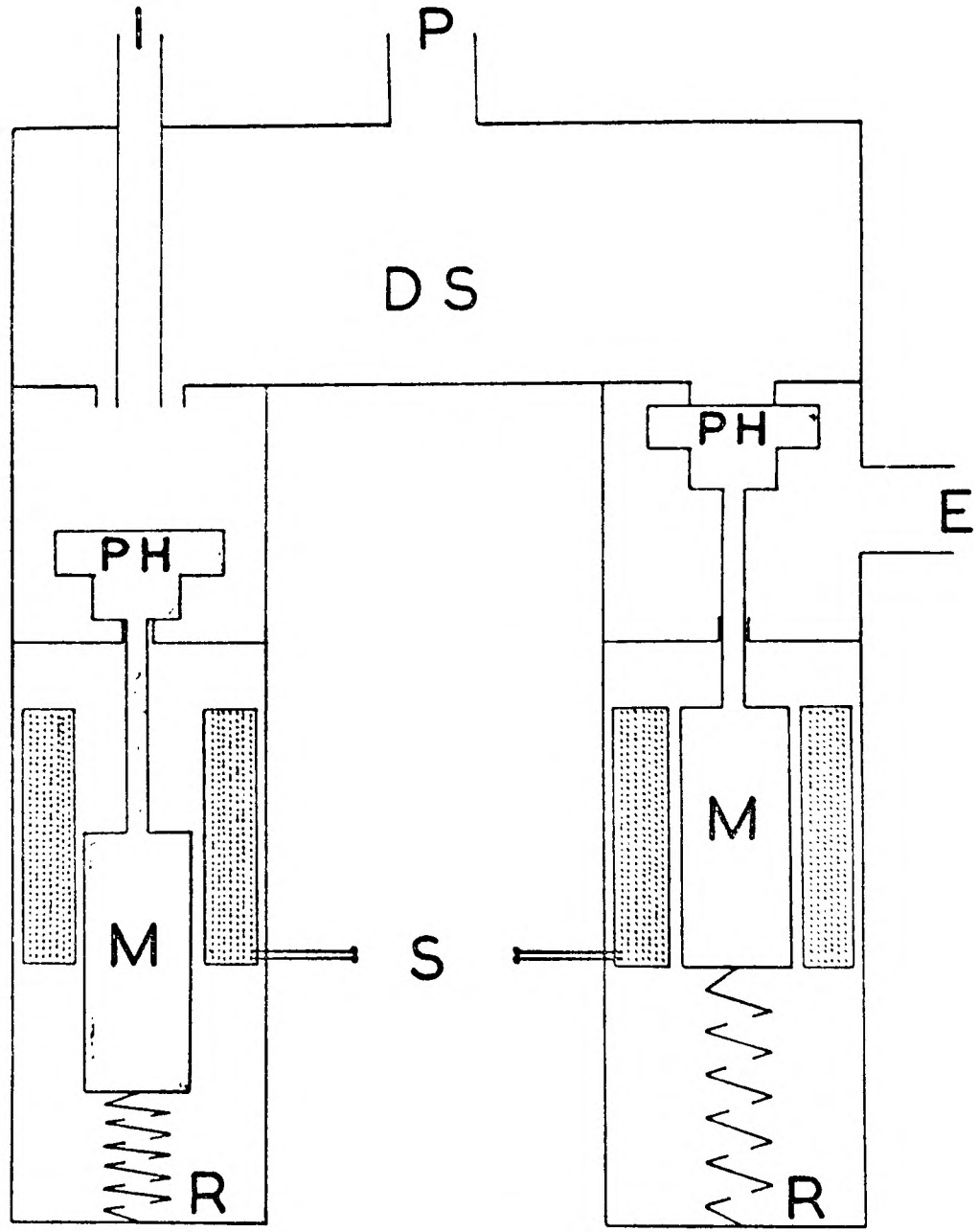


Fig. 3(a):14 Schematic diagram of the valve. I = inspiratory gas port; P = patient gas port; E = expiratory gas port; D.S. = dead space of valve; S = solenoid leads; M = metal piston body; PH = piston head faced on both sides by compressible PVC foam to provide gas-tight closures; R = return spring for recoil of the piston during its off period.

used to assist the recoil of the pistons; elaborate recoil mechanisms are consequently unnecessary and the solenoids may be less powerful. Experience with a prototype of this valve suggested that the valve described by Hill and Hook (1959) might have the disadvantage that at rapid inspiratory flow rates the inspiratory pathway would be forcibly closed.

The solenoids (Benson Bros., Exning Road, Newmarket, Suffolk - BD5 24 volts/11 watts) used in the valve described are powered by a 24 volt D.C. supply and synchronised with the ventilator to prevent any spill of gas from inspiratory to expiratory limb. In addition both inspiratory and expiratory pathways of this valve may be independently controlled allowing both pathways to be closed simultaneously for measurements of airways resistance and compliance. As the pathways are closed by an electrical signal, a power failure "fails safe" leaving both gas ports open. Dead space of this valve has been reduced to 20 ml by suitable moulding, and the expiratory resistance is 2 cm H_2o/1/sec at a flow rate of 2 1/sec.

SAFETY DEVICE

In the system described, the very high driving pressure necessary to operate the electropneumatic converter is separated from the patient only by a choke. If the waveform generator failed to cycle the solenoid operated inspiratory/expiratory valve it would be possible for the patient's airways to be exposed to the driving pressure and to exclude this hazard a safety device has been developed (Fig. 3(a):15). The device consists of two fluidic Schmitt triggers (Dummer and Robertson, 1968) which drive an or/nor gate. The bias pressure of the triggers is selected to equal the greatest permissible pressure in the airways and is provided by an electric compressor working through a low pressure regulator. The output from the or/nor gate switches the spool valve which

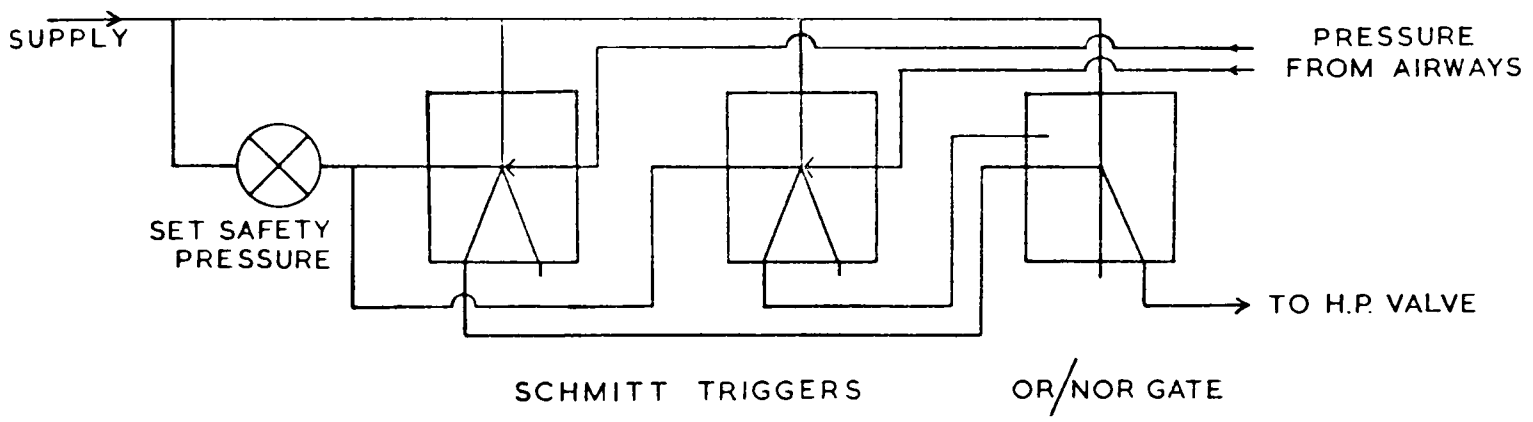


Fig.3(a):15 Block diagram of fluidic safety device.

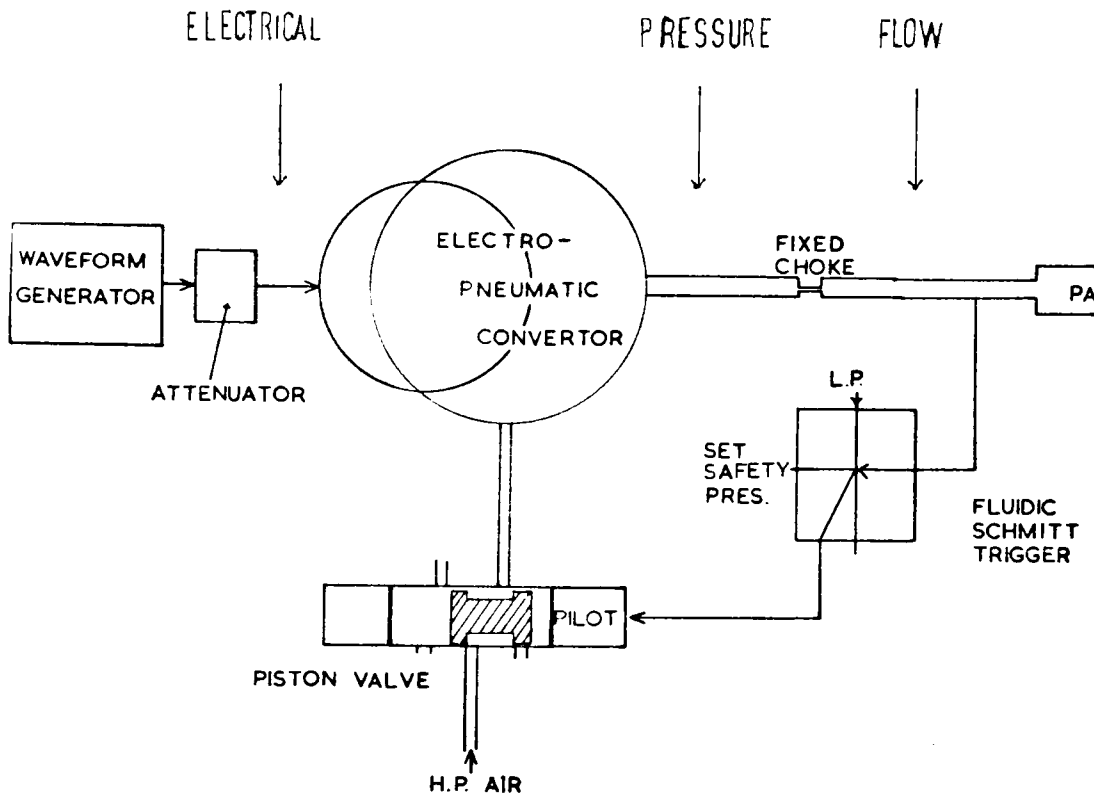


Fig.3(a):16 Block diagram of ventilator.

controls gas entry to the electropneumatic converter. It should be emphasised that if the gas pressure providing the bias fails the system is so balanced that the spool valve will drop to the safe position.

The safety device is very sensitive and has a rapid response. Complete occlusion of the breathing tube at a flow rate of 2 1/sec. causes shutdown with reduction of pressure in 125 m sec. This means that at this flow rate a maximum of 250 ml of gas could be injected following the generation of the set pressure. As an additional precaution a mechanical safety valve of the McKesson type is added in series between the patient valve and the patient.

VENTILATOR PERFORMANCE

The ventilator (outline diagram shown in Fig. 3(a):16) has been tested against an artificial lung system* with a compliance of 100ml/cm H_2O and a variable resistance. Examples of flow and pressure tracings are compared with the original electrical signals in Figs. 3(a):17 and 18, and flow waveform closely follows the electrical signal even under load conditions. The driving gas in this ventilator is also the gas supplied to the patient. However, the system is capable of being purged of air so that anaesthetic gas mixtures may be used., including volatile anaesthetic agents if vaporisers are used that are built for operation with high pressure gases (Bracken et al, 1968). The machine may also be used to drive a bag-in-bottle ventilating system, but this adds a capacitance which can influence the wave produced.

* The artificial lung system was made of copper and exhibited isothermal compliance characteristics. The variable resistance showed laminar flow characteristics when open to atmosphere, but, as can be seen from Figs. 3(a): 17 and 18, this laminar flow characteristic is not maintained when there is a back-pressure through the resistance.

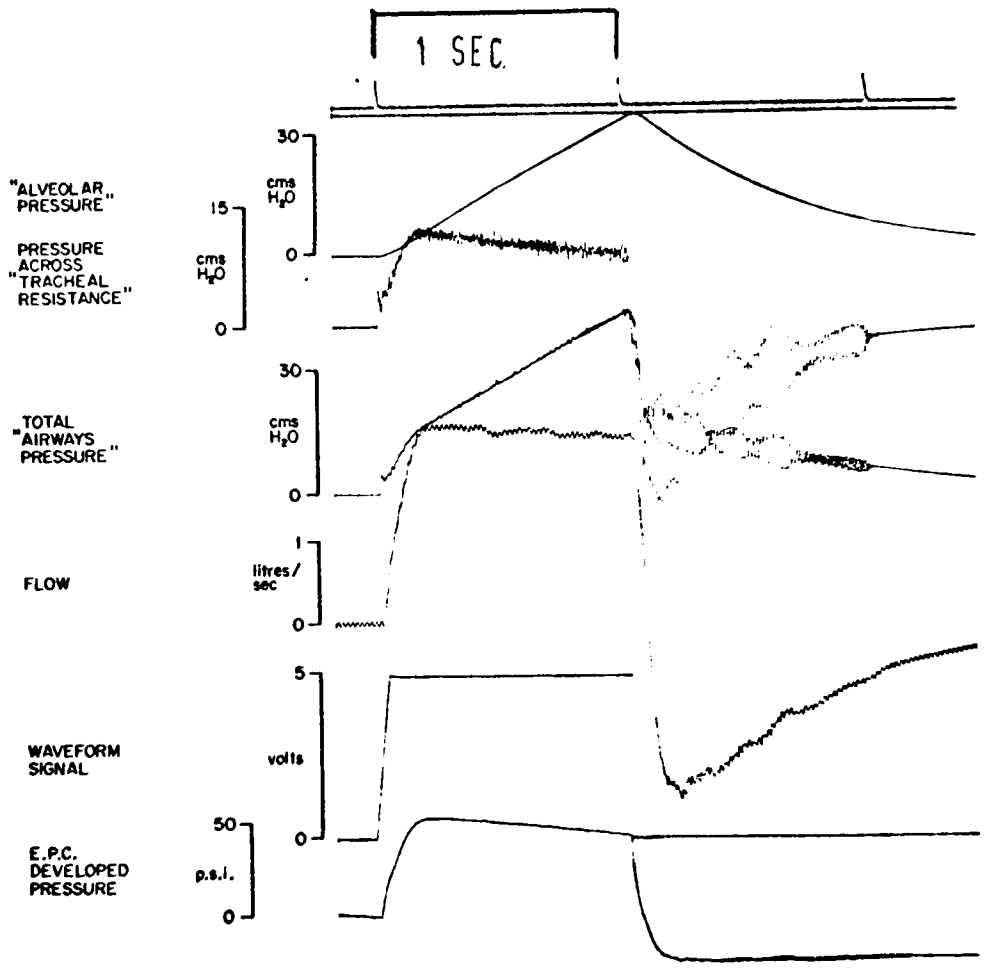


Fig.3(a):17 Test-lung responses of "alveolar pressure", pressure across "tracheal resistance" and total "airways pressure" with flow and electropneumatic converter developed pressure for a tophat electrical signal from the waveform signal generator.

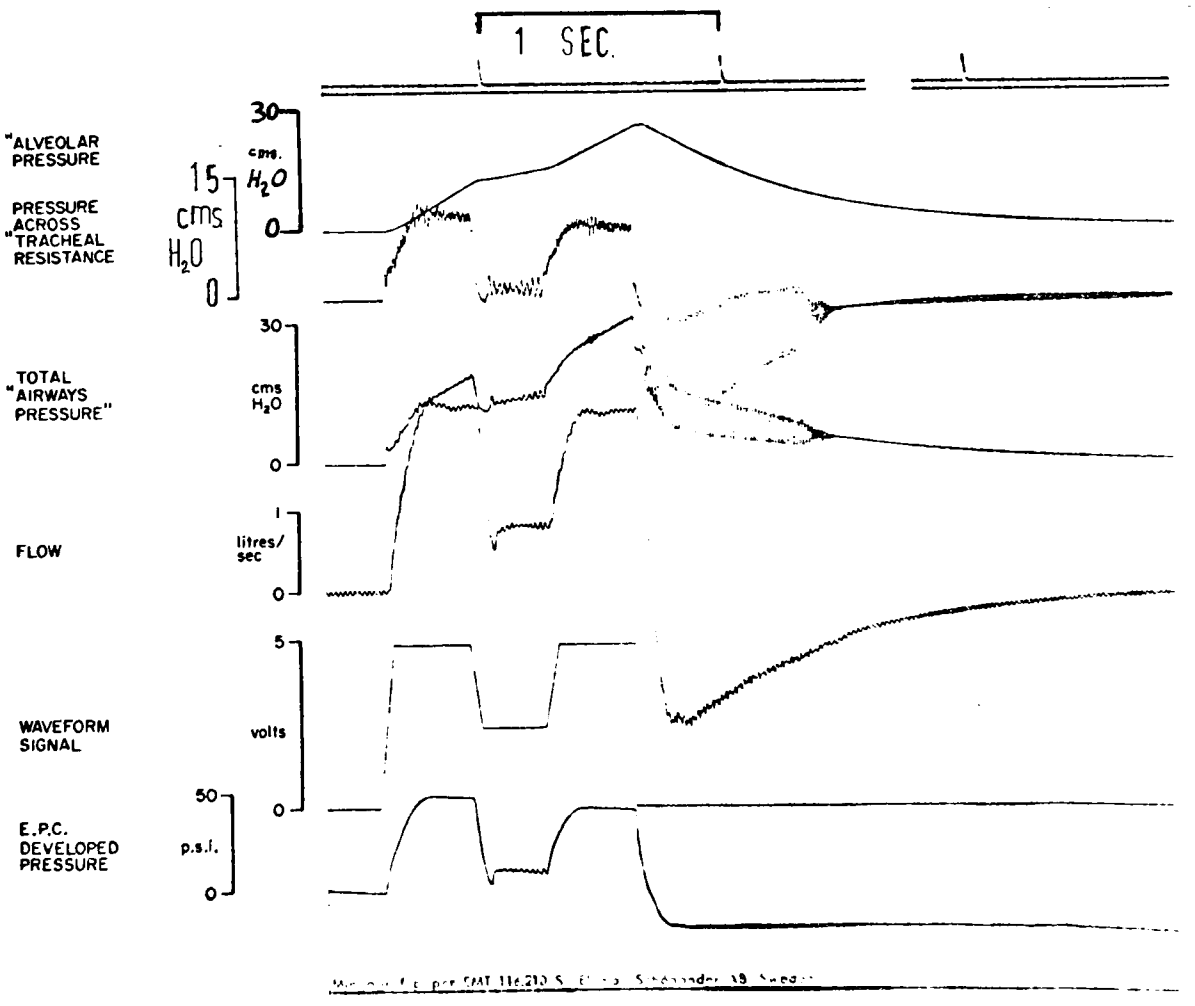


Fig. 3(a):18 Test-lung responses of "alveolar pressure", pressure across "tracheal resistance" and total "airways pressure", with flow and electropneumatic converter developed pressure for a saddle electrical signal from the waveform signal generator.

CHAPTER

3(b)

LABORATORY METHODS

CHAPTER 3(b)

LABORATORY METHODS

The observations on which this thesis is based required the measurement of a number of physiological variables in dogs and humans. The most important included the measurement of gas volumes, the fractional concentrations of O_2 and CO_2 in gas mixtures, and the partial pressures of O_2 and CO_2 in blood. Airway pressures, oesophageal pressures, pleural pressures, blood pressures and cardiac output were also measured. In order to complete the necessary calculations and apply correction factors, measurements of the concentration of haemoglobin in blood, barometric pressure and temperatures were made, and heart rate was calculated using an electrocardiograph. When appropriate, these measurements were recorded on apparatus of a frequency response and pen amplitude suitable for the signal concerned.

RECORDING APPARATUS

Mingograph 81 (Elema-Schonander, Stockholm, Sweden)

The Mingograph 81 Recorder uses galvanometer amplifiers to move an inkjet across recording paper. The inkjet reduces the inertia of the system and also the errors introduced by the arc of a pen of any length. The result is a fast response recorder with acceptable linearity at full-scale deflection.

Step function increments of voltage were introduced into the galvanometer amplifiers of the recorder from a D.C. voltage calibrator (Type 127, G. and E. Bradley, London, U.K.) which has an accuracy of 0.02%. The recorder showed a linear response of up to 7 cm, the full-scale deflection of the jet of each channel, and no

evidence of hysteresis was found. The Mingograph Recorder, when tested with an EMT 39 strain gauge matching unit and an EMT 31 pre-amplifier, had an amplitude frequency response flat to 12 Hz (95% at 17 Hz, 70% at 42 Hz) and the phase delay was linear at 1.5° per Hz to 4 Hz. Gersh (1970) showed by Fourier analysis that this degree of damping did not alter the amplitude of the pressure signals he recorded from the left ventricle, aorta, or left atrium, and it can be assumed that the same damping would not have influenced any of the results obtained in these studies (Geddes and Baker 1968). In the Mingograph 81 recorder, if a test signal is fed directly to the final amplifiers (EMT 7) the amplitude frequency response is flat to at least 100 Hz.

Devices M.4 with D.C. 6 Pre-Amplifier (Devices Instruments Incorporated, Cambridge, U.K.)

This hot stylus recorder has a linear response to step function increments in input voltage at full-scale deflection. This apparatus was only used to record the output from an end-tidal CO_2 analyser and its frequency response was well in excess of that of the analyser used in the studies.

SARGENT M.R. (E.H. Sargent & Co., Chicago, Illinois, U.S.)

This apparatus was used for recording dye dilution cardiac output curves and, intermittently, the end-tidal CO_2 concentration. The particular quality of this potentiometric recorder is its extreme linearity over an 8 inch pen deflection. On testing, the recorder's dynamic response was flat only to 0.4 Hz at full-scale deflection but its response to step increases in voltage was indeed linear.

LAN OSCILLOSCOPE 419A (Lan Electronics Ltd., Slough, Bucks U.K.)

Pulmonary artery pressure, arterial pressure, tracheal

pressure and airway gas flow were continuously displayed on this oscilloscope throughout the animal experiments.

END-TIDAL CARBON DIOXIDE

The fractional concentration of CO_2 in expired gas was measured continuously with an infra-red CO_2 analyser (Uras M; Hartmann and Braun, Frankfurt/Main, Germany), which is based on the principle of interference spectrometry described by Luft (1943). Gas was sampled by a suction pump (Dymax Mk.II, Charles Austin Pumps, Byfleet, Surrey U.K.) which withdrew gas continuously at 250 ml/min. from the region of the carina. This gas was subsequently returned to the system to avoid errors in the measurement of respiratory minute volume, and the system was intermittently checked for leaks throughout experiments to avoid errors in volume measurement by Douglas bag collection (Douglas, 1911). The analyser signal was recorded intermittently on the Sargent recorder and continuously on the Devices recorder, and the system was calibrated between 0 and 5% CO_2 in air, in steps of 1% CO_2, at the beginning and end of each experiment with a Wösthoff gas mixing pump (SA 27/3-F; H. Wösthoff, H.G. Bochum, West Germany). The gas mixtures delivered by this mixing pump were confirmed at the time of the experiments described with a Lloyd/ Haldane apparatus (Gallencamp, London U.K.). (Lloyd, 1958) Fig. 3(b):1). This calibration procedure together with the large pen amplitude of the Sargent recorder allowed a reading accuracy of $\pm$ 0.025% CO_2. The alinearity and hysteresis of the infra-red analyser were minimised by generating a 'line of best fit' for the calibrating points for each experiment, and the final accuracy of the system was $\pm$ 0.05%. This is approximately equivalent to a partial pressure of $\pm$ 0.5 Torr P_{CO_2}. The partial pressure of CO_2

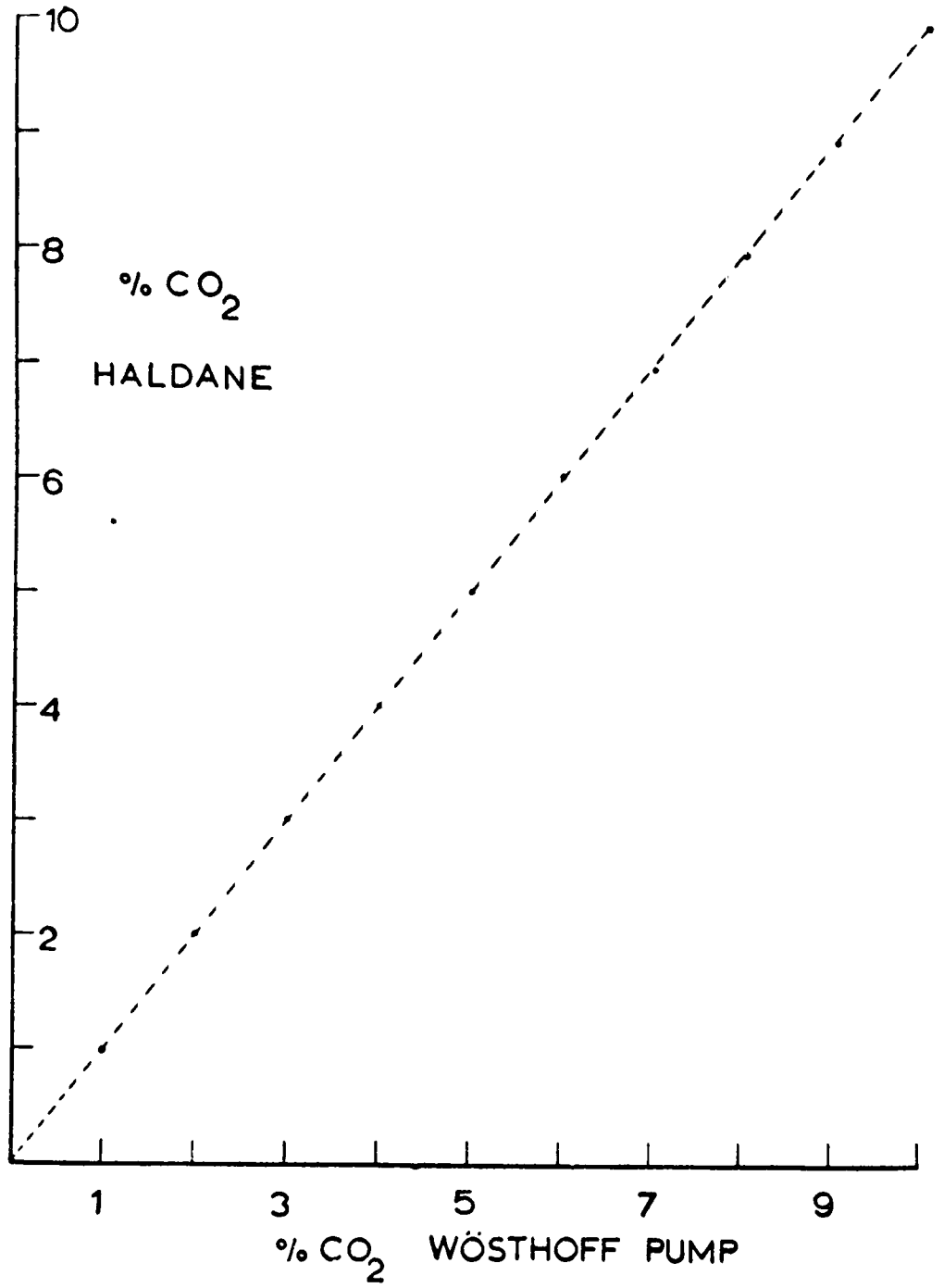


Fig. 3(b):1 Calibration of the Wösthoff pump delivery of % CO_2 with Haldane analysis.

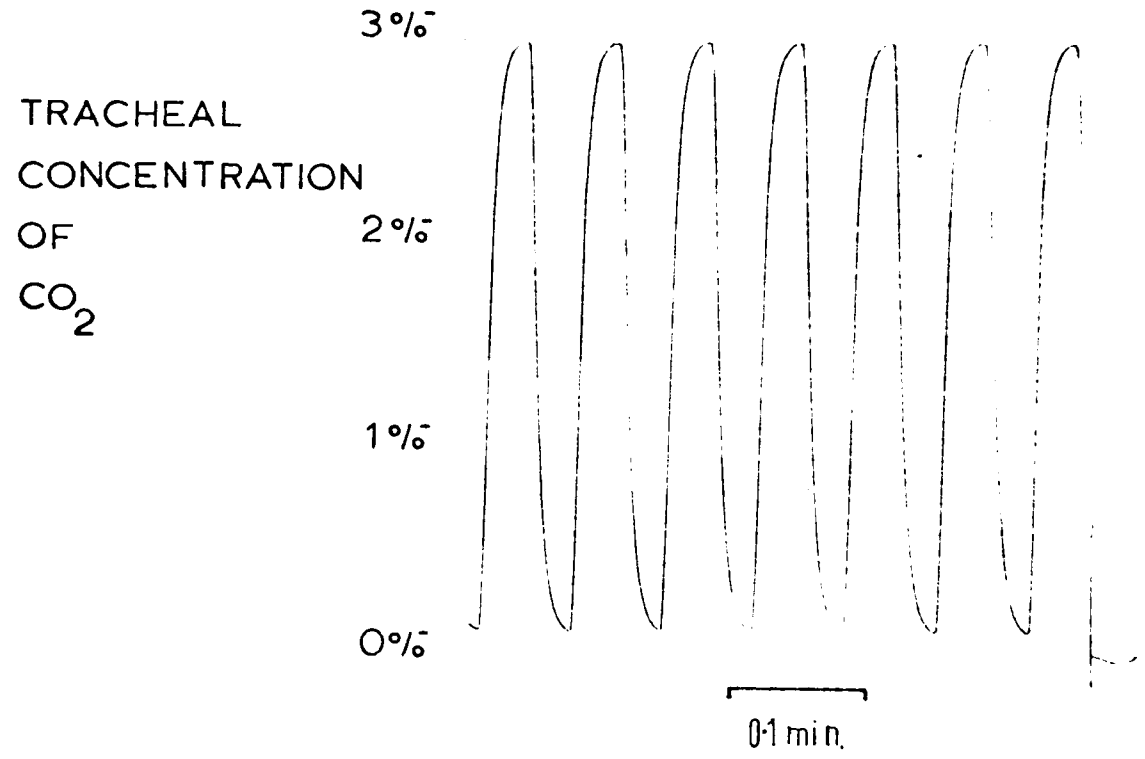


Fig. 3(b):2 Experimental recording of end-tidal CO_2 concentration from Dog 13.

in the end-tidal gas was given by the following equation:

$$P_{CO_2} = \frac{\text{vols. \% } CO_2 \ (P_b - 2.454\ T + 43.43)}{100}$$

where P_b = barometric pressure; T = temperature of the experimental animal, and the equation 2.454 T - 43.43 represents a linear regression to calculate the saturated water vapour pressure at the temperature of the animal between 31°C and 42°C.

The fractional concentration of CO_2 displayed on the Devices recorder was used during the studies to indicate the approximate P_{a,CO_2} (Ramwell 1958; Nunn and Hill, 1960). This display was used to decide when a steady state had been reached so that a new series of measurements could begin; at least ten minutes of stable concentration of end-tidal CO_2 were allowed to elapse. More accurate recording on the Sargent recorder was performed only intermittently and synchronised with arterial sampling of blood, (Fig. 3(b):2). This record was later used for comparison with calculated P_{A,CO_2} (approx.).

VOLUME AND FLOW MEASUREMENT

Volume.

The reference standard used in this study was a wet gas meter (Type A, Parkinson and Cowan Ltd., London U.K.) which is periodically (approximately every three years) checked by the makers for accuracy which is stated at ± 0.1% of the volume measured. This wet gas meter was used to calibrate a Tissot Spirometer (P.K. Morgan Ltd., Chatham, Kent, U.K.) (Tissot, 1904) (Fig. 3(b):3). Calibration was performed in two ways, first by filling the bell of the spirometer with air and allowing the air to pass out through the wet gas meter and then by pumping air at 8 l/min through the gas meter into the spirometer. The

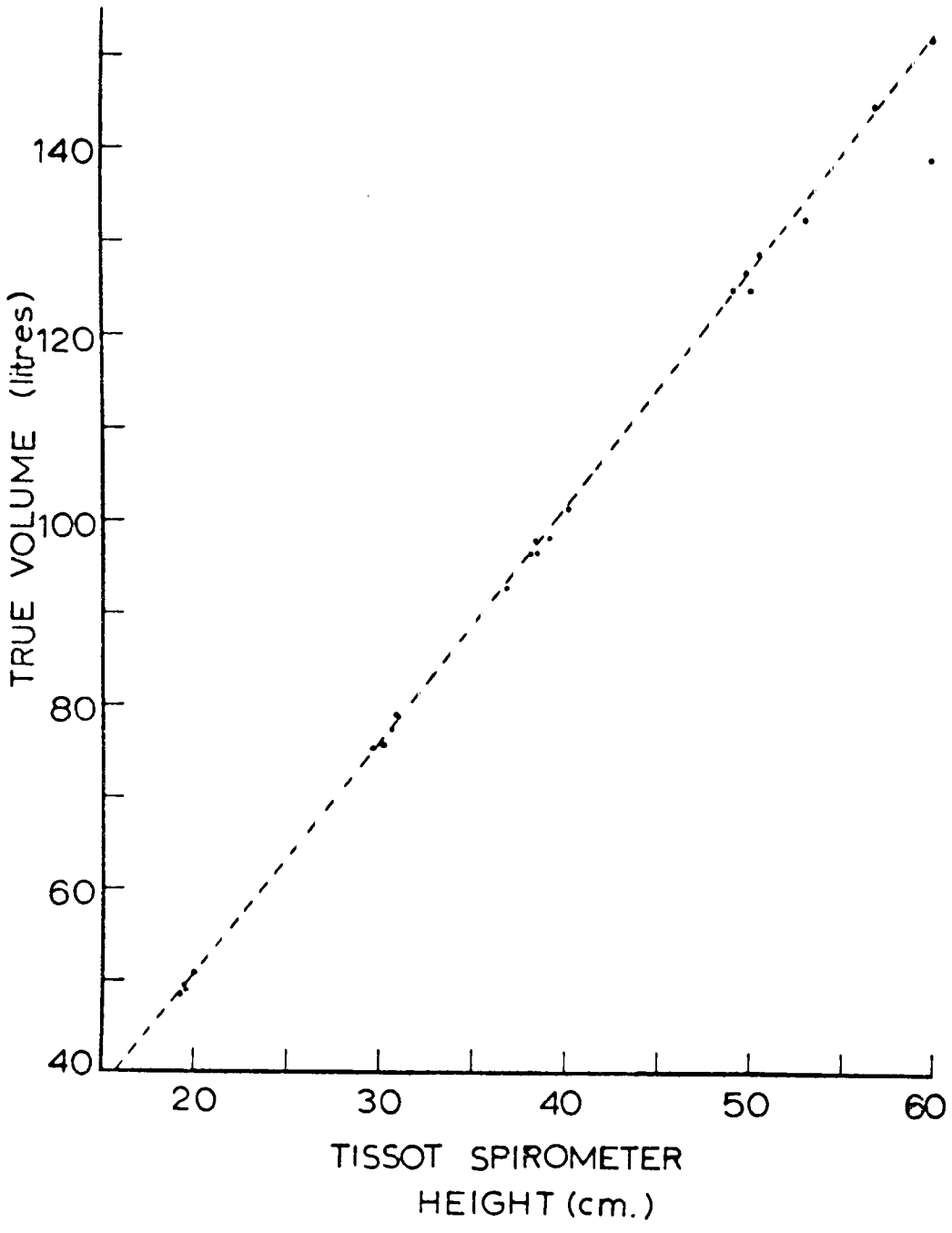


Fig.3(b):3 Calibration of Tissot spirometer. Volume(litres) = 2.54 x Tissot scale in cm.

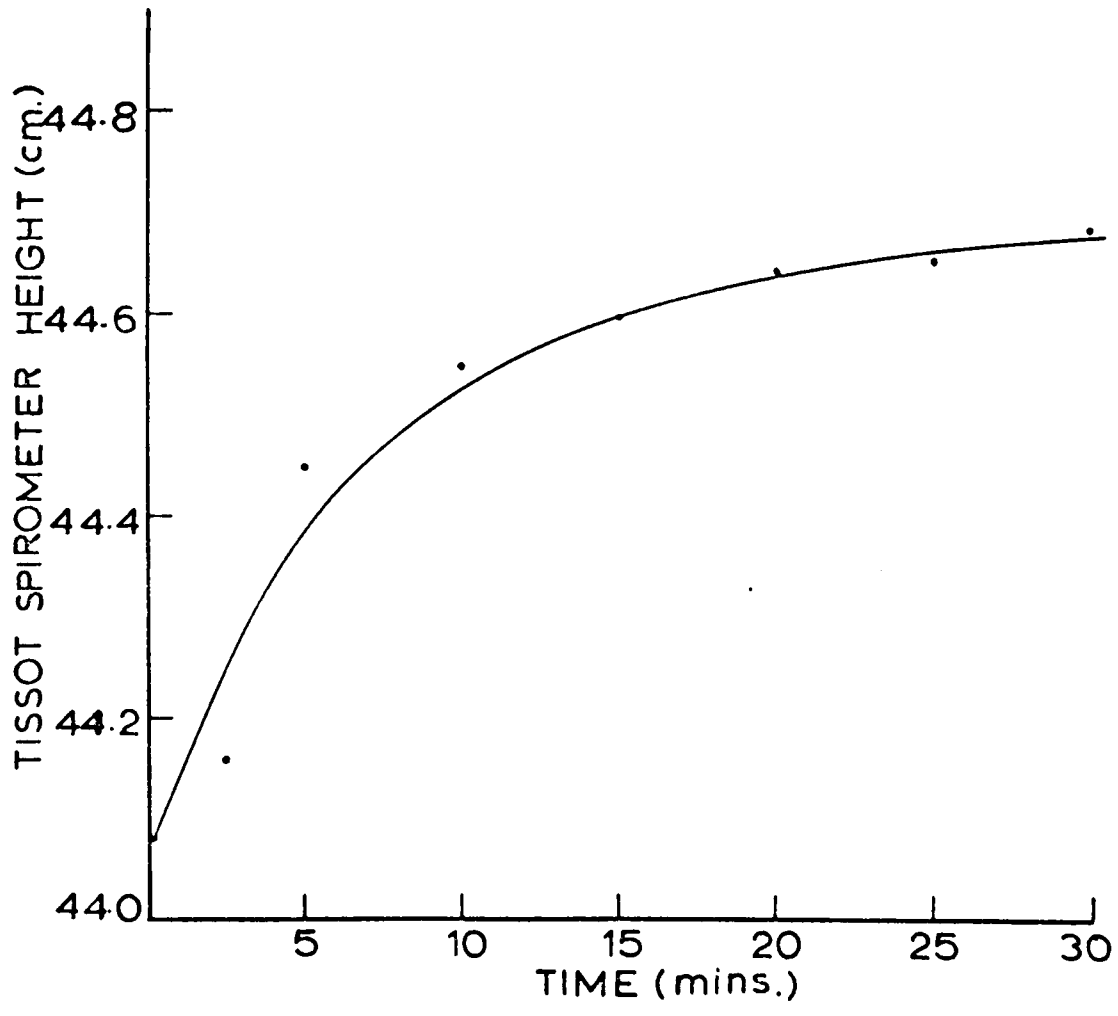


Fig. 3(b):4 Graph of alteration of the gas volume of the Tissot spirometer with time.

gas volumes in the spirometer were assumed to be saturated with water vapour at room temperature and to assess the time necessary for saturation to occur in the first procedure, tests were performed to find out when the bell stopped rising. Fig. 3(b):4 shows that ten minutes was sufficient time to allow for effective equilibration. As gas passed through the wet gas meter must pass through water, saturation with water vapour can be assumed. All volumes were corrected to 20°C and 760 torr. Repeated measurements of the volume contained in the Tissot spirometer when exhausted from the same displacement height was $\pm$ 25 ml in 100 l.

The Tissot spirometer was then used to calibrate the dry gas meter (Type CDI, Parkinson and Cowan Ltd., London, U.K.) used to measure ventilation volume in the studies. Calibration was performed at the flow rate chosen to evacuate the Douglas bags used in the studies (Adams et al, 1967). Again, calibration was performed in two ways - first by filling the spirometer by allowing time for saturation of air, and by sucking the air through the dry gas meter, and second, by pumping room air through the gas clock, at the flow rate used in practice. The measurements made in the second calibration procedure were corrected for the relative humidity of room air by the equation:

$$V_D = V_W \left[1 - \frac{P_W}{P_b} \right]$$

where V_D = gas volume at relative humidity necessary, V_W = moist gas volume, P_b = barometric pressure, P_W = water vapour pressure necessary. The correction factor was calculated to be 0.981. The dry gas meter was then used to measure the collected expired volumes in all

physiological studies. Large volumes were always measured and the overall accuracy of volume measurement was ± 100 ml in 20 L.

Expired gas was collected from the expiratory port of the solenoid-operated valve in a 30 litre P.V.C. Douglas Bag (Plysu Industrial Ltd., Bletchley, Bucks, U.K.). These bags were fitted with large-bore two-way taps (Siebe-Gorman and Co., Chessington,Surrey, U.K.) and with a small two-way tap on a sampling tube. Before collection the bag was evacuated to - 10 cm H_2O of pressure. Collection was started during inspiration and continued for thirty breaths which always occupied 120 seconds because of the accurate timing of the ventilator. Measured samples were taken from the bag for analysis of the mixed expired P_{O_2} and P_{CO_2}, and the bag was again evacuated through the dry gas meter to - 10 cm H_2O pressure. To check for diffusion of CO_2, the bags were filled with a known concentration of about 5% CO_2 in air and the contents reanalysed after one hour. No measureable difference occurred.

In some of the studies volumes were also measured by integration of the flow signal from a Fleisch pneumotachograph by a Godart Integrator, and by planimetry of the flow signal. Calibration of this system will be described in the section on flow measurement.

Flow.

In the studies described gas flow was measured using a Fleisch transducer, (Fleisch, 1925) and a differential pressure transducer (Godart Pneumotachograph, Godart Manimex de Bilt, Holland). This system uses the principle of laminar flow through fine capillary tubes to give a pressure differential across the capillaries by the Hagen-Poiseuille Law (Hagen, 1839; Poiseuille, 1840/41).

$$\text{Pressure drop} = F \times \text{viscosity} \times \frac{\text{length}}{(\text{diameter})^4} \times \text{flow rate}$$

(F is a factor depending upon the units used).

For any one Fleisch head the length and diameter of the capillary tubes are constant so that the only variable affecting the pressure differential and flow rate is the viscosity of the gas flowing through the head. Thus, if differing gas viscosities are to be used, the transducer must be calibrated with each gas and this creates problems in the accurate measurement of mixed expired gas, the composition of which varies throughout expiration (Smith, 1964; Hobbes, 1967). In these studies the accurate measurement of flow was only performed during inspiration when gas concentration and hence viscosity was constant. The head was heated to 35°C to avoid condensation in the capillary tubes of the transducer. Calibration checks at various times throughout a study did not reveal any alteration of the calibration due to mucus deposition or other time dependent degeneration. Between studies the pneumotachograph head was cleaned with "Decon 75" (Medical Pharmaceutical Developments Ltd., Portslade, Sussex, U.K.) and before use on patients was cleaned with Decon 75 and sterilised with "Cidex" (Arbrook Products, Edinburgh, U.K.).

Calibration of the Fleisch head was performed using a high pressure air source (70 psi) and a needle valve to produce a constant flow of gas. This air flow was passed into a large reservoir, through the Fleisch head and through a two-way tap (Siebe-Gorman) to atmosphere or the Tissot Spirometer. After a constant flow had been established the tap was turned at zero time and a timed volume was allowed to enter the spirometer. Calculation of flow then depended on volume

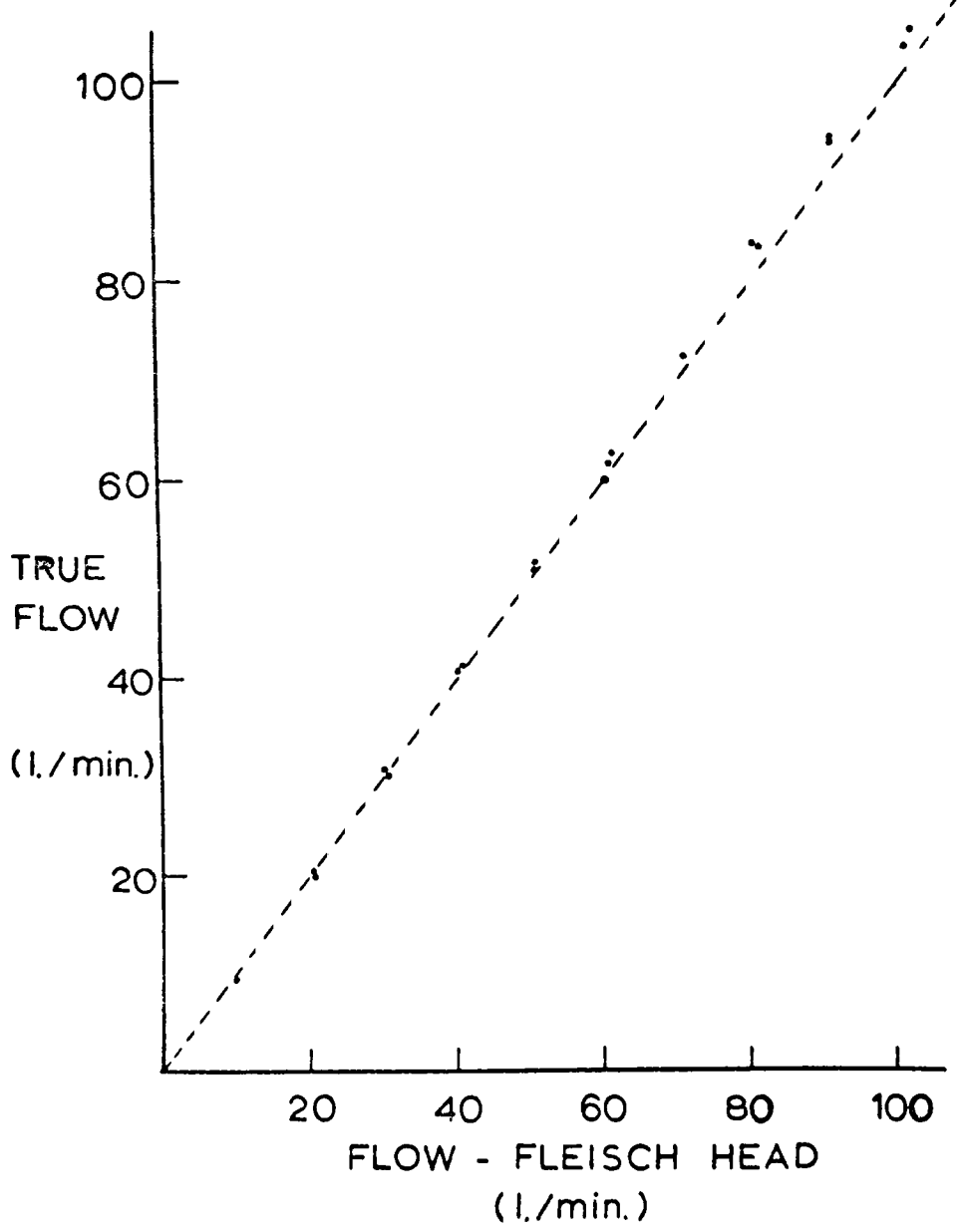


Fig. 3(b):5 Calibration of the Fleisch pneumotachograph head for flow.

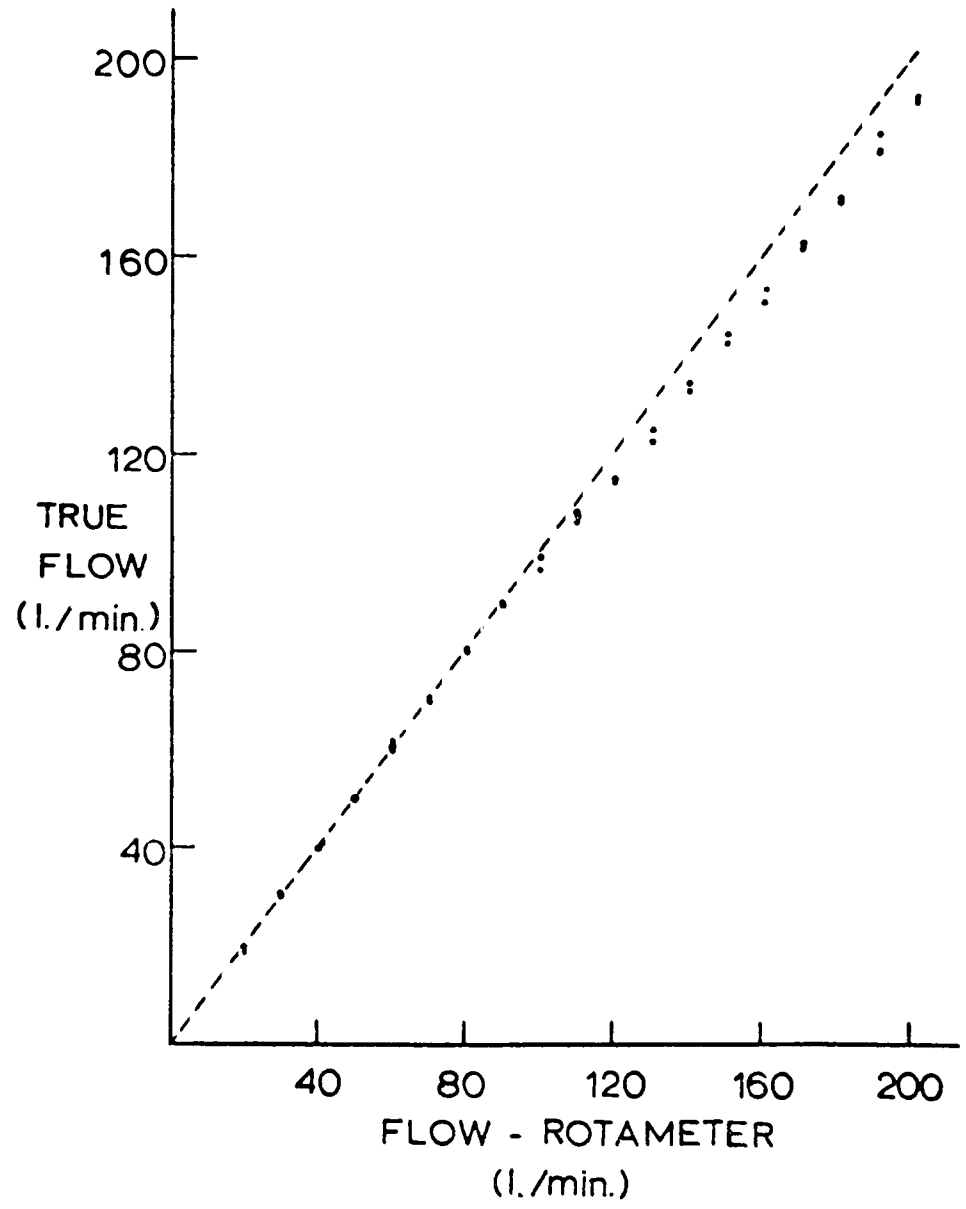


Fig. 3(b):6 Calibration of the rotameter for flow.

divided by time with corrections for the fact that dry gas flowed through the transducer while saturated gas was measured in the spirometer. The calibration curve is shown in Fig. 3(b):5 and the accuracy of the system was estimated to be $\pm$ 2%. By an identical technique a rotameter (Rotameter Manufacturing Co.Ltd., Croydon, Surrey,U.K.) was calibrated (Fig. 3(b):6). This flow-meter was subsequently used to calibrate the pneumotacho-graph. During studies the Godart Amplification system was calibrated with zero flow and a flow of 1 l/sec, delivered through the previously calibrated rotameter. The calibration did not alter on re-checking at the end of the studies.

With I.P.P.V. extreme care must be taken to position the Fleisch head correctly and connect it by tubes of suitable capacitance to the differential manometer, otherwise the turbulence which may occur at the beginning of square gas flow patterns may cause large deflections in the opposite direction to the normal signal. This turbulence is more pronounced with high airway resistance and high flow rates suddenly passed through the head. It may present an insoluble problem in artificial ven-tilation when short inspiratory times are being used and consequently gas is flowing at high velocity through the head.

When the Godart pneumotachograph was used for integration of the flow signal for volume measurement, further calibration was undertaken with the Tissot spirometer in the same manner as for the calibration of the pneumotachograph for flow. In this investigation different, but constant, flow rates were used and the re-zeroing integration signal was displayed continuously on the Mingograph recorder. The full-scale deflection of the signal varied with the flow rate and the pneumot-achograph head as shown in Fig.3(b):7. This effect

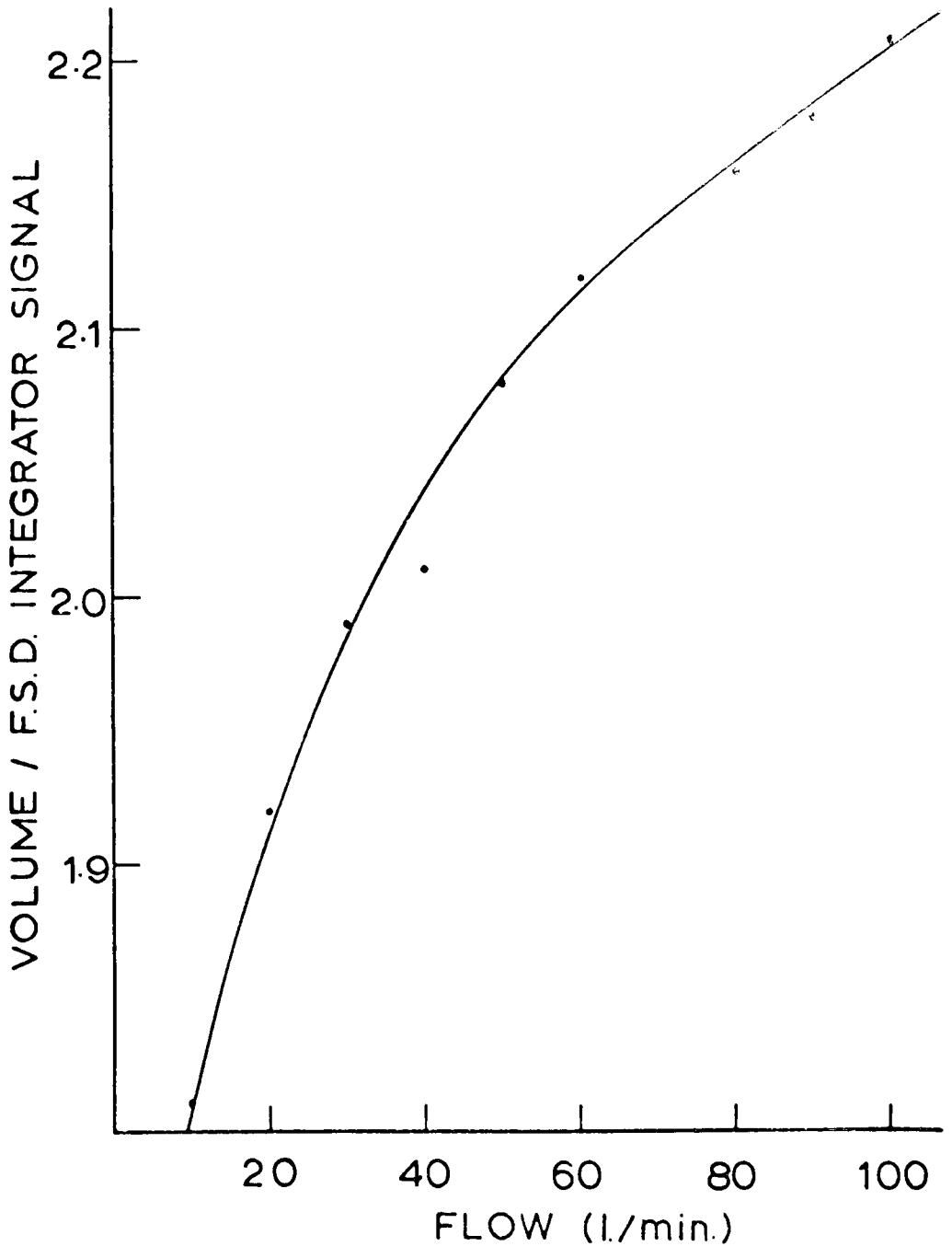


Fig. 3(b):7 Calibration of the Fleisch pneumotachograph head and Godart integrator for volume at different gas flows.

is not due to alinearity of the differential inductive transducer which was tested and found to be linear, nor to the integrator which was found to be accurate, but the finding complicates the measurement of volume by this method, as a changing flow rate will change the calibration. This method of measuring ventilation volume was only used during the study of the alveolar pressure response to a constant gas flow during inspiration (Chapter 5).

CARDIAC OUTPUT

Dye.

Cardiac output was measured by an indicator dye dilution technique (Prys-Roberts, 1969) derived from the development of Stewart (1897) and Hamilton et al. (1932) of the original principle described by Hering (1829) and Fick (1870). Indocyanine Green (Cardiogreen Hynson, Wescott and Dunning, Incorporated, Baltimore, Maryland, U.S.A.) was the dye chosen because its peak light absorption of 800 nanometers is isobestic for both reduced and oxyhaemoglobin (Fox et al., 1957), because of its non-toxicity[1]. (Fox and Wood, 1960), and because its short half life of 3 - 10 minutes (Table 3(b):1) allows measurements of cardiac output at frequent intervals (Edwards et al., 1960; Benchimol et al., 1964).

A bolus of dye was rapidly injected into the right ventricle through a catheter (I.D. 0.975 mm, O.D. 1.34 mm, length 60 cm) using a self-loading constant volume syringe (Scientific Instruments Incorporated, Springfield, Mass., U.S.A.) attached to the dye deservoir. By keeping

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1. Only one case of sensitisation response is known to the manufacturers, and this was thought to occur because of iodine sensitivity, small traces of iodine being present in the dye (Miskin, M.E. quoted by Wollenweber and Komber, 1968).

TABLE 3 (b) : 1

Author	Estimated half-life of indocyanine green (minutes)
Cherrick et al. (1960)	3.0
Ketterer et al. (1960)	10.8
Hunton et al. (1960)	9.1
Krasavage and Michaelson (1965)	5.6 - 7.0

Table: Determinations of the plasma half-life of indocyanine green obtained from the literature.

the dye catheter full at all times it was possible to ensure rapid entry of the dye bolus into the circulation. Injection of dye was always made during the same phase of ventilation (early in the expiratory phase) to avoid errors due to variation in cardiac output during the ventilatory cycle (Charlier, 1968). Blood was withdrawn from the iliac artery at a constant rate (38.5 ml/min) by means of a Gilford Pump Constant Flow System (Gilford Instruments, Incorporated, Oberlin, Ohio,U.S.A.). This blood was withdrawn through the cuvette of a Gilford Densitometer (Model 103 IR) which gave an electrical signal recorded on the Sargent Recorder at a speed of ten inches per minute.

The linearity of the cuvette-densitometer-recorder system was checked by serial dilutions of freshly prepared dye in expired human blood-bank blood. These dilutions proved linear through zero to 40 mg/1 (Fig. 3(b):8). This finding disagrees with recent spectrophotometric analysis of dye in blood (Simmons and Shepherd, 1971). These authors believe that serial dye dilutions exhibit different photometric characteristics at different dilutions. Further evidence of the linearity of the system was the calibration procedure for dye concentration which occurred at the end of every experiment. This procedure is described below, and in these cases linearity was exhibited up to 7.5 mg/1.

At the end of each experiment 100 ml of blood was taken and was divided into three aliquots of 20 ml and one of 40 ml. 0.2 ml of dye was placed in one of the 20 ml aliquots, 0.4 in another and 0.6 in the third. Each dye aliquot and the control aliquot were then separately and thoroughly mixed and drawn through the densitometer system, the controls of which were left exactly as they were during the study concerned. By

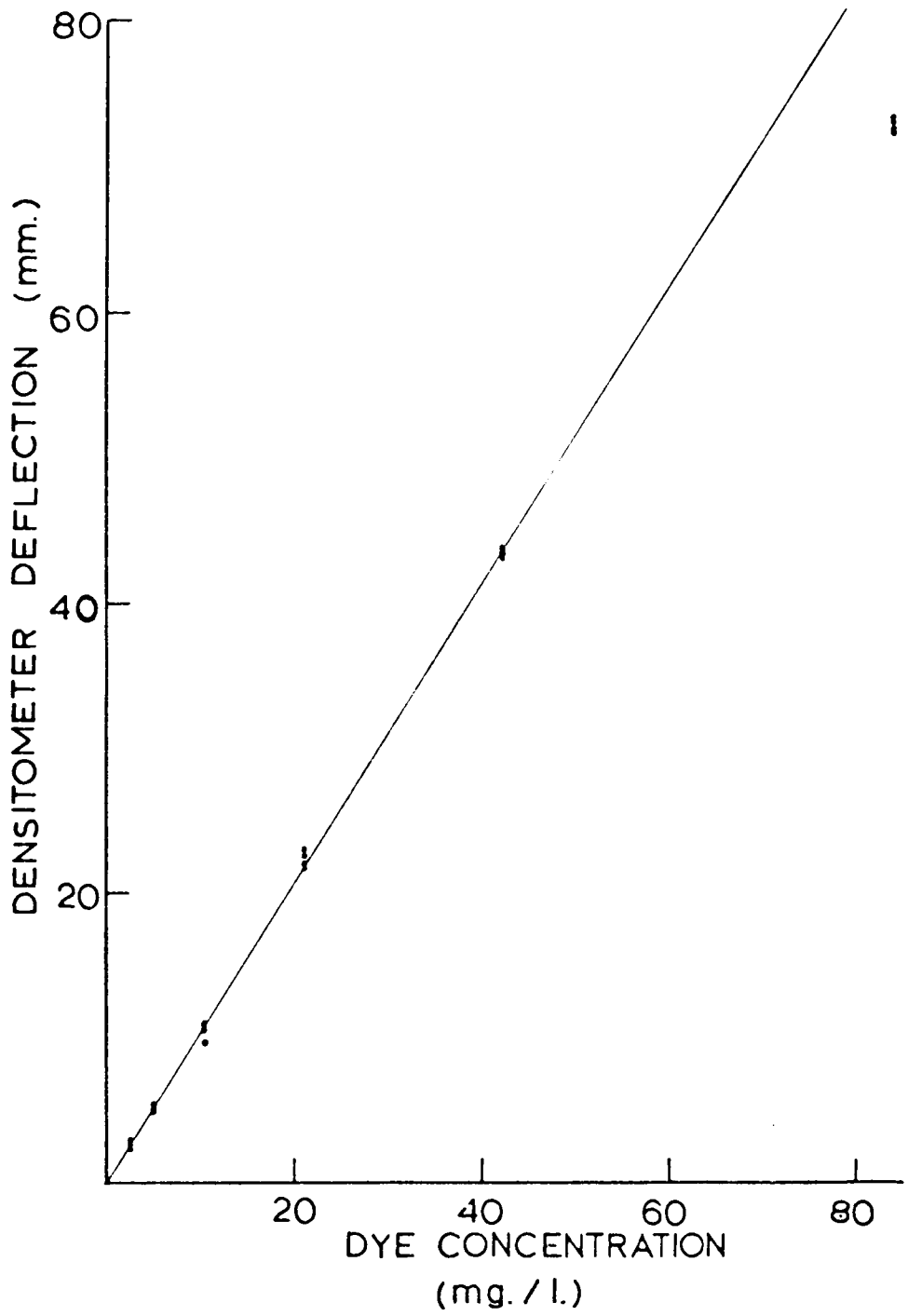

Fig. 3(b):8 Linearity of the Gilford cuvette - densitometer system with increasing dye concentrations of indocyanine green in whole blood.

this means a calibration deflection was obtained for each dye concentration. The volume of dye injected at each cardiac output measurement was measured by weighing the dye expelled by the system for a number of "injections", and by calculating the mean weight. This was compared with single weights and found to correspond.

The area under the dye curve was calculated as shown in Fig. 3(b):9. The following formulae were used to derive the cardiac output:

$$A = a \times dt + \frac{y_n (t_b - t_a)\, dt}{\log_e y_a - \log_e y_b}$$

where a =

$$\frac{y_o}{2} + y_1 + y_2 + \ldots\ldots\ldots\ldots y_{n-1} + \frac{y_n}{2}$$

$$\dot{Q} = \frac{60 \times \text{vol. of dye injected} \times \text{conc. of dye in bottle}}{A \times \text{calibration factor}}$$

where calibration factor =

$$\frac{1000 \times \text{concentration of dye in bottle}}{1000 \times \text{mm. deflection for the conc. of dye in bottle}}$$

The above equations for the area are derived from the trapezoid rule for the area under a curve, and from the extrapolated exponential to estimate the decay area if recirculation had not taken place (Kelman, 1965).

In the early studies in this series, when the animals end-tidal CO_2 had stabilized after a change in

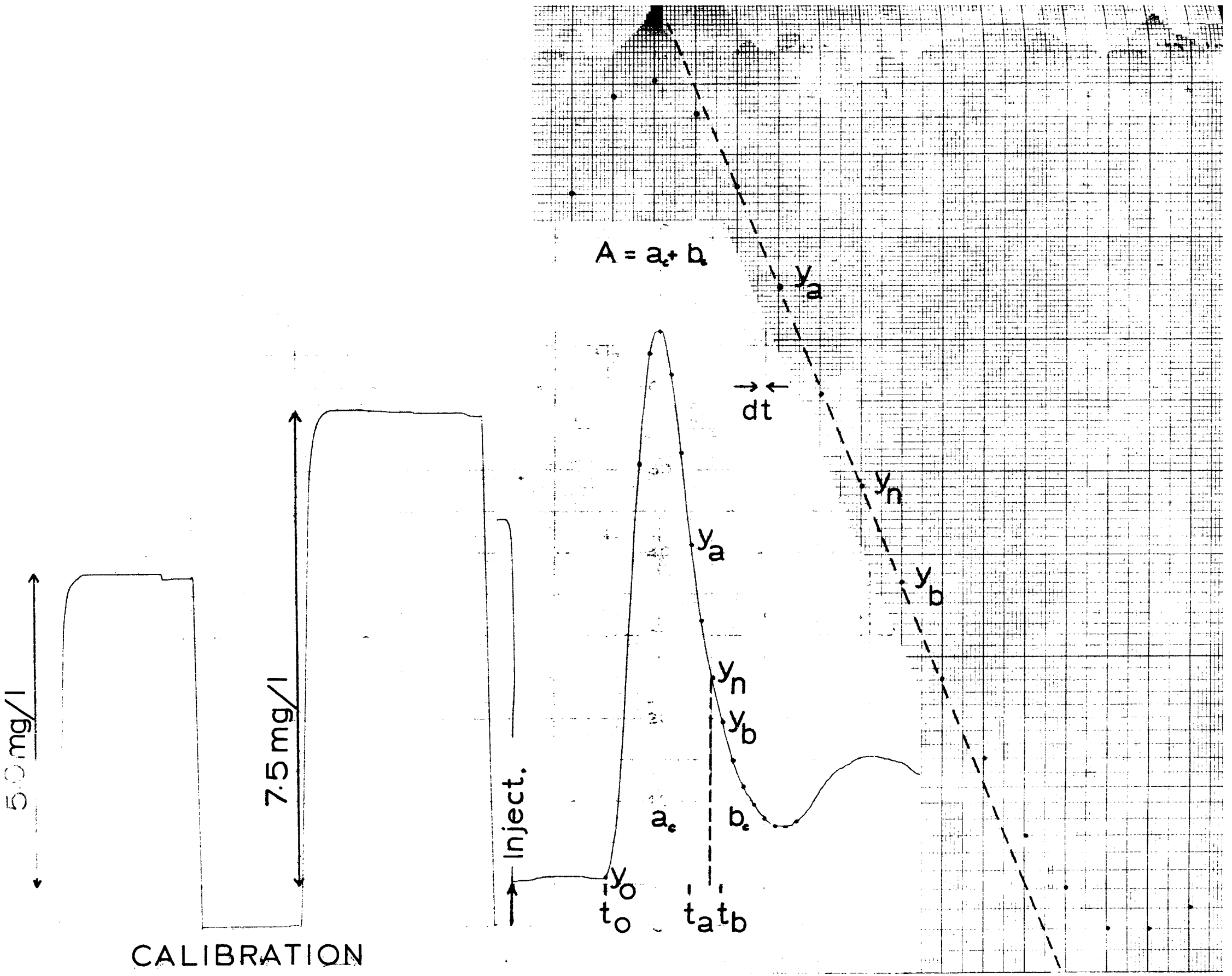

Fig. 3(b):9 Example of a dye dilution curve from Dog 24 with a semi-log plot to show the exponential relationship used to calculate the area under the second part of the curve. The points marked are used in the calculations detailed in the text to calculate the cardiac output.

ventilation, two measurements of cardiac output were made with an interval of ten minutes between them and the overall linear correlation coefficient between replicates was 0.952 (Fig. 3(b):10). These results were so similar that only one measured dye dilution cardiac output measurement was regarded as necessary after each change in ventilation, especially as it was being compared on each occasion with a cardiac output calculated by the direct Fick procedure. This allowed the number of ventilatory changes in later experiments to be increased.

Direct Fick Principle.

Cardiac output was also calculated by the measurement of oxygen utilisation, the so-called Fick Principle (Fick, 1870). This is based on the formula:

$$\dot{Q} = \frac{\dot{V}_{O_2} \quad STPD}{10\,(C_{a,O_2} - C_{\bar{v},O_2})}$$

The exact derivation of the various terms of the above equation is shown in the section on theoretical methods.

The experimental requirements are for expired gas volume measurement and analysis of the mixed expired gas concentration of O_2 and CO_2. The inspired O_2 concentration, and measurements of the partial pressure of O_2 and CO_2 in arterial and mixed venous blood, of room temperature, and of barometric pressure are also required. These measurements are all discussed in the appropriate sections.

Earlier studies (Hamilton et al., 1948; Etsten and Li, 1954) suggested that there is a discrepancy between the results of cardiac output measured by the

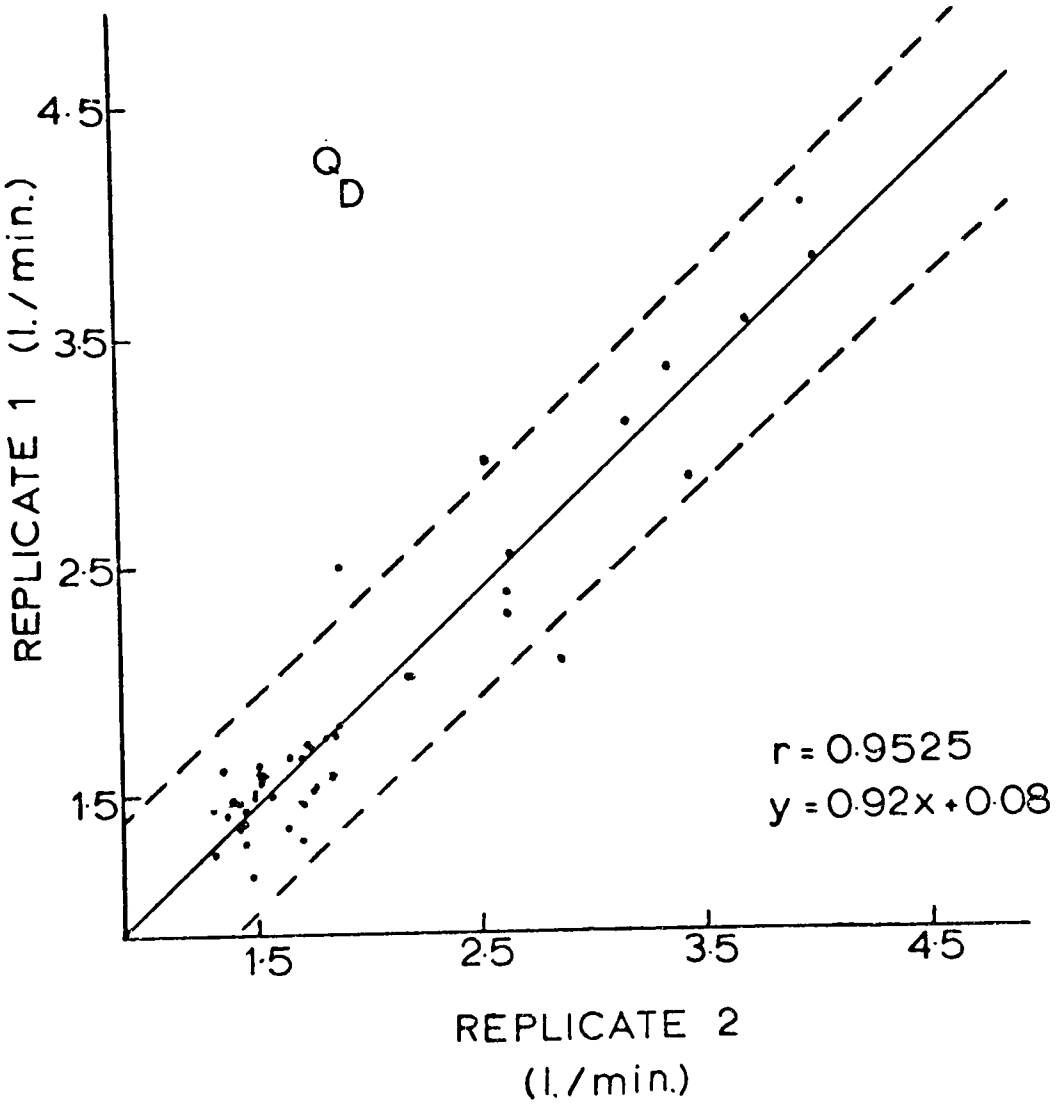

Fig. 3(b):10 Comparison of the replicates of measurements for cardiac output by dye dilution. The straight line of best fit is drawn, together with the 95% confidence limits.

Fick method and those measured by dye dilution, whereas more recent studies (Theye et al. 1964; Grenvick 1966) have suggested that this is not so. This study confirms the latter reports (Table 3(b):2, Fig. 3(b):11) but there are, however, very likely to be small discrepancies between the two methods because of normal variations in the composition of arterial blood. This variation may affect the results of estimation by the Fick method by up to 4%. (Wood et al. 1955). At low cardiac outputs measured by dye dilution, there is a possibility that recirculation may occur before all the dye has circulated, thus giving a falsely low reading (Oriol et al. 1967). This error may be reduced by central (pulmonary arterial or right ventricular) injection of dye.

PRESSURE MEASUREMENT

Measurements were made of airway pressure, oesophageal pressure, intrapleural pressure, arterial pressure and pulmonary artery pressure.

Airway Pressure.

Pressure was measured at the level of the carina with a Statham strain gauge transducer (P.M. 5 or P.M. 6) and an air-filled catheter (I.D. 1.5 mm, O.D. 2.1 mm). In some patients the measuring catheter was pushed as far as possible into the endobronchial lumen.

Oesophageal Pressure.

In this study, oesophageal pressure has been regarded as representative of intrathoracic pressure (Milic-Emili et al. 1964). Saline-filled oesophageal catheters have been used by several workers (Dornhorst and Leathart 1952; Rutishauser et al. 1966 and 1967; Banchero et al. 1967) to measure oesophageal pressure, but all used very narrow-bore catheters of I.D. 0.5-1.5 mm

TABLE 3(b) : 2

Author	Type	Fick	Dye	r	Slope	No.	Animal
Moore et al. (1929)	p-t-p-s	3.41 ± 0.78	3.24 ± 0.85	0.878	0.95	6	humans
Hamilton et al.(1948)	E.B.	6.59 ± 3.05	6.87 ± 3.43	0.930	1.05	46	humans
Werkö et al. (1949)	E.B.	5.87 ± 1.94	6.11 ± 1.57	0.865	0.70	68	humans
Kopelman & Lee(1951)	E.B.	4.47 ± 1.72	4.45 ± 1.81	0.967	1.02	27	humans
Johnson (1951)	E.B.	7.09	7.25				humans
Eliasch (1952)	E.B.	5.88 ± 1.87	6.60 ± 1.92	0.742	0.76	66	humans
Doyle et al. (1953)	E.B.	3.5 ± 0.3	3.2 ± 0.2	0.73		152	humans
Etsten & Li (1954)	E.B.	3.71 ± 0.85	3.50 ± 0.84	0.870	0.85	15	dogs
Eliasch et al. (1954)	E.B.	6.39 ± 2.48	6.14 ± 2.26			352	humans
Neely et al. (1954)	E.B.	6.03 ± 1.96	6.45 ± 1.83	0.448	0.42	31	humans
Smith et al. (1954)	E.B.	5.46	5.24			19	humans
Shepherd et al.(1955)	E.B.	3.92 ± 1.51	3.87 ± 1.77	0.941	1.10	21	humans
Korner & Shillingford (1955)	E.B.	4.28 ± 0.77	4.62 ± 0.67	0.853	0.74	18	humans
Falholt & Fabricius (1956)	I.C.G.	3.05 ± 0.77	2.85 ± 0.82	0.628	0.67	18	humans
Sekelj et al. (1958)	E.B.	3.79 ± 2.01	4.23 ± 2.32	0.888	1.03	28	humans

Table continued on following page

continuation of Table 3(b):2 from previous page

Author	Type	Fick	Dye	r	Slope	No.	Animal
Richardson et al. (1959)	I.C.G.	2.44	2.36			48	humans
Taylor & Shillingford (1959)	C.B.	5.80 ± 2.44	5.85 ± 2.74	0.900	1.01	53	humans
Miller et al. (1962)	I.C.G.	5.28	5.09		1.04	34	humans
Smulyan et al. (1962)	I.C.G.	3.06	2.51			10	dogs
Phinney et al. (1963)	C.B.	4.2	4.2	0.93		27	humans
Theye et al. (1964)	I.C.G.	2.77 ± 0.88	2.75 ± 0.96	0.954	1.04	24	dogs
Grenvick (1966)	I.C.G.	3.59 ± 1.31	3.67 ± 1.25			26	humans
The Author (1971)	I.C.G.	3.35 ± 1.81	3.21 ± 1.71	0.871	0.92	405	dogs

Table: Comparisons of paired cardiac output determinations performed by the direct Fick method and a dye-dilution method. The results are given, wherever possible, as mean ± standard deviation. Type refers to type of dye used for the dye-dilution technique. E.B. = Evans Blue; C.B. = Coomassie Blue; I.C.G. = Indocyanine Green; p-t-p-s = phenol-tetroid-phenthalein-sodium. r = linear correlation coefficient; Slope = slope of straight line fitted to the data by the method of least squares best fit; No. = number of paired readings.

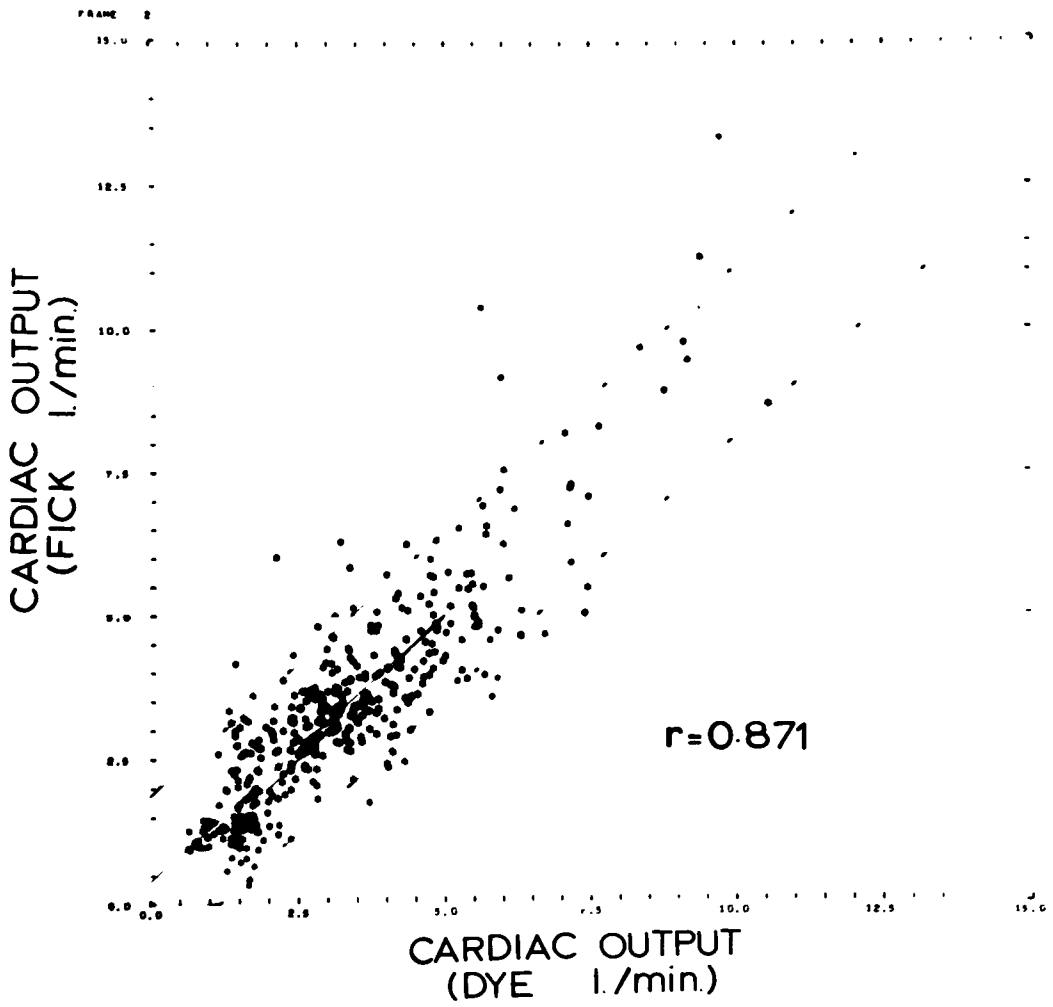

Fig. 3(b):11 Comparison of simultaneous cardiac output measurements by the direct Fick method and by the dye dilution method. The straight line of best fit is marked together with the line of identity and 99% confidence limits. This result indicates that there is no difference between the identity line and the line of best fit at the 0.01 probability level.

and O.D. 1 - 3 mm. Because the animals and patients were anaesthetised in this study, a firm wide-bore catheter (I.D. 5 mm, O.D. 6 mm) could be used which had better dynamic response characteristics than a narrow-bore catheter system. (Table 3(b):3).

The catheter was placed with its tip approximately in the middle third of the oesophagus at a point where cardiac pulsations on the pressure record were minimal. The pressure transducer was aligned on each occasion at approximately the same level, established by taking a point at the junction of the anterior three-fifths and the posterior two-fifths of the thoracic antero-posterior diameter. Results with this method were very repeatable whereas results were less satisfactory using air-filled oesophageal baloons (Milic-Emili et al. 1964).

Intra-pleural Pressure.

Pressure in the pleural space was measured with a Statham P.M. 131 transducer and an air-filled catheter (I.D. 1.85 mm, O.D. 2.4 mm). In patients where this technique was used the catheter was inserted through the intercostal space which was later to be used for a thoracotomy incision. No significant pneumothorax was demonstrated at thoracotomy in any patient.

Arterial and Pulmonary Artery Pressures.

Arterial - A C.E.D. (Consolidated Electrodynamics Division, Bell and Howell Ltd., Basingstoke, U.K.) transducer and a fluid-filled nylon catheter (I.D. 1.79 mm, O.D. 2.76 mm, length 30 cm) were used.

Pulmonary Artery - An Elema-Schonander transducer (EMT 33) and a fluid-filled catheter (I.D. 0.975mm, O.D. 1.34 mm, length 75 cm) were used.

The transducers were aligned with a point at the

junction of the posterior three-fifths and anterior two-fifths of the antero-posterior diameter of the chest (Guyton and Greganti, 1956). Signals were recorded on the Mingograph 81 recorder previously described.

Static Calibration for Pressure.

The stability of the transducer-amplifier-recorder systems was observed for 48 hours and found to be acceptable except for minor alterations in the balance of the EMT 39 strain gauge matching unit. The reference D.C. voltage produced by the recorder was found to be very stable and once set could be relied upon for calibration of pressure signals. During studies, the balance and calibration of the systems were repeatedly checked.

A mercury manometer (Airflow Developments Ltd., High Wycombe, Bucks, U.K.) and a blended paraffin manometer (Airflow Developments Ltd.) were used for static calibration of the systems which were found to have a linear response to step increments of pressure with no hysteresis at the gain amplitudes used.

Dynamic Calibration of Catheter Systems.

The strain gauge pressure transducers used in the studies were kept 'wet' with a mixture of aqueous glutaraldehyde ("Cidex", Arbrook Products, Edinburgh, U.K.) and normal saline between experiments or for two days before experiments. This facilitated the preparation of transducer-catheter systems so that, as far as possible, bubbles were removed before measurements were made.

All fluid-filled catheter systems were submitted to dynamic testing, using an hydraulic pressure generator, a sine-wave signal generator and the strain gauge amplifier (Type Q) of a Tektronix storage oscilloscope

(Tektronix Inc., Beaverton, Oregon, U.S.A.) (Gersh 1970). This apparatus was adapted to the larger catheter system used for oesophageal pressure measurement by replacing the reference transducer by a large seal. The full frequency response characteristics of the three systems are shown in Table 3(b):3). These show that the frequency response of the arterial system was adequate for the reproduction of systolic and diasystolic pressures, the response of the pulmonary artery system was adequate only for the mean pressure, and the oesophageal system was satisfactory for the reproduction of slow respiratory responses but step function increases would be slightly damped.

BLOOD GAS ANALYSIS

Blood was taken for analysis from the iliac artery and the pulmonary artery. Sometimes it proved impossible to aspirate blood through the pulmonary artery catheter, so another catheter was routinely passed into the right ventricle through the external jugular vein (I.D. 1.15 mm, O.D. 1.65 mm, length 30 cm). Mixed venous blood was thus either pulmonary artery blood or blood from the right ventricle. Adams (1970) found that the partial pressure difference for O_2 and CO_2 between these two sites was negligible. The blood was then placed in iced water to reduce metabolism (Greenbaum et al., 1967) and analysed by technicians in the Department following the usual procedure.

Oxygen Partial Pressure.

The partial pressure of O_2 in whole blood was measured using an oxygen electrode (Type E5046, Radiometer A/S, Copenhagen, Denmark) based on the original design by Clark et al, (1953) which in turn was based upon the polarographic principle of Heyrovsky (1922). The

TABLE 3 (b) : 3

Pressure System	Dynamic frequency response			
	Flat (100%)	95%	70%	Resonance
Arterial	20 Hz	33 Hz	70 Hz	136 Hz
Pulmonary artery	1.5 Hz	2.5 Hz	5 Hz	6.5 Hz
Oesophageal	4 Hz	6 Hz	18 Hz	50 Hz

Table: Dynamic pressure response characteristics of the liquid systems used to measure pressure.

electrode has a platinum wire cathode of 20μ diameter, the tip of which is covered with a polypropylene membrane of 20μ thickness and is bathed in a buffer solution of Na_2HPO_4, KH_2PO_4 and KCl. The anode is of silver/silver chloride.

The electrode is negatively polarised with a voltage of 700 mV and the current flowing in the circuit was measured in these studies with a current amplifier (Hahn 1969) and a digital voltmeter VT 200 (Honeywell, Hemel Hempstead, Herts, U.K.). Calibration of the electrode was performed using three gas mixtures:

1. Oxygen-free nitrogen "Whitespot" (B.O.C. London,U.K.).

2. Air.

3. Approximately 50% oxygen with CO_2 and N_2. The oxygen percentage was accurately measured with a Servomex Oxygen Analyser (Type OA 101 Servomex Controls Ltd., Crowborough, Sussex, U.K.) with a digital readout (VT 200 Honeywell). The electrode span was calibrated initially with both air and oxygen to establish linearity, but, as no O_2 was ever added to the air used for ventilation, the electrodes were calibrated only with air during studies. The blood/gas correction factor used was 1.04 (Adams and Morgan-Hughes, 1967). Accuracy of oxygen partial pressure measurement was $\pm$ 0.5 - 1.0 torr (Hahn 1971a).

Hydrogen Ion Concentration (pH).

pH of whole blood was measured with a capillary glass electrode (Type G 297, Radiometer A/S, Copenhagen, Denmark) described by Siggaard-Andersen et al, 1960 and based on earlier work by Thompson (1875), Cremer (1906) and Haber and Klemensiewicz (1909). The electrode

circuit is completed by a calomel-saturated KCl reference electrode and by a liquid junction in the capillary glass electrode. Changes in electrode potential were measred with a pH measuring unit (E.I.L. Measuring Unit C33B-2 Electronic Instruments Ltd., Richmond, Surrey U.K.) and read out on a Vibron Electrometer (Model 33B-2, E.I.L.). The electrode was calibrated against standard buffers of pH 6.841 $\pm$ 0.005 at 37°C and pH 7.383 $\pm$ 0.005 at 37°C (Radiometer A/S, Copenhagen, Denmark), so that the measurement accuracy was $\pm$ 0.005 pH units.

Carbon Dioxide Partial Pressure.

CO_2 partial pressure was measured with a standard 'Severinghaus' CO_2 sensitive electrode (D616 Unit, Electrode E5036/0, Radiometer A/S, Copenhagen, Denmark) using nylon mesh as a separator instead of 'Joseph' paper. The design of this electrode was first described by Severinghaus and Bradley (1958) and Gertz and Loeschcke (1958) following work by Stow and Randall (1954) and Stow et al. (1957) on physical principles first enunciated by Gesell and McGinty (1926). The CO_2 electrode response is read out in the same manner as the pH electrode.

Calibration was with known gas mixtures of CO_2 and O_2 with a 'hinge' gas from a cylinder of known gas composition previously analysed with a Lloyd-Haldane apparatus and a low and a high CO_2 gas mixture from Wösthoff pumps the output of which had been analysed in the same way. Calibration of CO_2 electrodes with gas assumes no blood/gas difference for CO_2 (Adams and Morgan-Hughes 1967) and that the pH/log P_{CO_2} response is linear (Crampton Smith and Hahn 1970). The accuracy of CO_2 partial pressure measurement with this electrode is $\pm$ 0.1 torr (Hahn 1971b).

Thermostatic Control of Electrode Temperatures.

All electrodes were kept at 37°C (New York Academy of Sciences 1966) by a Radiometer VT S 13 Water Thermostat with the sensing thermometer probe placed in the CO_2 electrode water-bath so that the electrode temperature itself was controlled to 37°C.

ELECTROCARDIOGRAPH

Continuous monitoring of lead II of the electrocardiogram (E.C.G.) was performed during each study. The E.C.G. was recorded on the Mingograf 81 recorder via an EMT 18 pre-amplifier, and the heart rate was calculated using the R - R interval of this trace.

HAEMOGLOBIN MEASUREMENT

Haemoglobin concentration (Hb) was measured by using a spectrophotometer (Spectronic 20 Bausch and Lomb, Rochester, New York) to compare a blood sample with a solution of standard reagent (International Cyanohaemoglobin B.S. 3985: 1966) (Nature 1965). Estimations of Hb were made at least twice at the beginning and end of each study, and did not differ by more than 10%. The mean of the results was taken as the standard for the study.

BAROMETRIC PRESSURE

The barometric pressure was measured at the time and place of blood gas analysis and gas measurement, with a continuously recording anaeroid barometer (Microbarograph, Short and Mason, London, U.K.), which agreed exactly with a Fortin barometer (Gallenkamp, London, U.K.).

TEMPERATURE

Both body temperature and room temperature were

measured with thermistor probes (400 series, Yellow Springs Instruments, Yellow Springs, Ohio, U.S.A.) and a Digitec digital thermometer (United Systems Corp., Clayton, Ohio, U.S.A.). The probe used for measurement of body temperature in the animal studies was placed in the superior vena cava through an external jugular vein. An electro-thermal pad (Electrothermal Rubber Sheeting, Electro Thermal Engineering Ltd., London, U.K.) was placed under the operating table to keep the animal's temperature as close as possible to 38°C (Friedman and Bennett 1943). The room temperature probe was situated close to the gas meter used for measurement of expired gas volumes.

ANAESTHESIA AND DRUGS

The dogs were premedicated with morphine (1.5 mg/Kg) and chlorpromazine (1 mg/Kg) and anaesthesia was induced with thiopentone sodium (20-25 mg/Kg) injected intravenously. A Magill endotracheal tube of 9 - 12 mm I.D. was inserted and the animal ventilated with air. Anaesthesia was maintained with a mixture of chloralose (1%) and urethane (5%) warmed to 40°C.

Van Citters et al. (1964) in a study of chronic animal preparations (dogs) demonstrated the superiority of chloralose to pentobarbitone for stability of the cardiovascular system during induction and maintenance of anaesthesia. Urethane causes little change in cardiac output as measured by the pressure-pulse contour method (Remington et al. (1949) and either no change or a slight increase in blood pressure with normal doses (Greisheimer 1965; Giles et al. 1969). Giles et al. (1969) further showed a constant cardiac output over a period of 30 minutes. In studies done in 1969 in association with Gersh (1970) there was found to be a

drop in blood pressure and left ventricular dP/dt after injection of a chloralose-urethane mixture, but both variables returned to normal within ten minutes. Important evidence confirming the relatively non-cardiotoxic effect of chloralose-urethane is provided by Bruce and Chapman (1965) who showed that the left ventricular residual volume measured by angiocardiography was raised with pentobarbitone but not with chloralose-urethane mixtures. Rapaport et al. (1962) also noticed the reduction of left ventricular residual volume, measured by thermo-dilution, to normal levels with chloralose-urethane as opposed to pentobarbitone anaesthesia. Figs (3(b):12-18) show that in the animals studied there was no systematic deterioration of variables with time even up to nine hours.

In experiments requiring blockade of the autonomic nervous system of the experimental animal, atropine (0,1 mg/Kg) was injected to obtund the responses of the parasympathetic nervous system (Goodman and Gilman 1970). Propranolol (0.1 mg/Kg) and phenoxybenzamine (1.5 mg/Kg) were injected to obtund the beta and alpha components of the sympathetic nervous system respectively (Goodman and Gilman 1970).

Non-depolarising neuro-muscular blockade was carried out using pancuronium bromide (0.4 mg/Kg). This relaxant was chosen because it does not release histamine in humans or dogs, it does not have vagal blocking effects, and its effect on cardio-vascular stability is minimal (Smith et al. 1970; Kelman and Kennedy 1971).

Human Studies.

Premedication was variable. Induction and endotracheal intubation were performed under thiopentone and suxamethonium chloride. Anaesthesia was maintained with nitrous oxide, oxygen and 0.5 - 1% halothane with neuro-muscular blockade by tubocurarine.

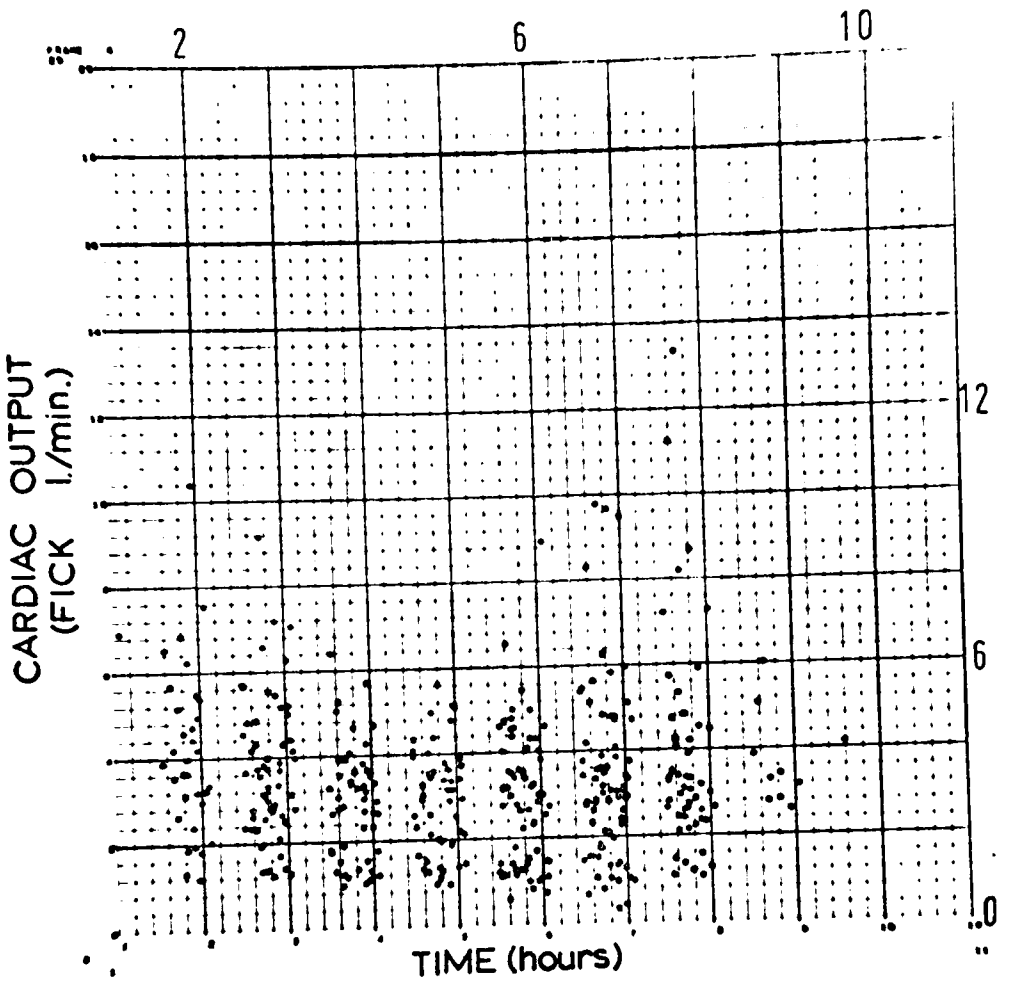

Fig.3(b):12 Graphical representation for all the dog data for cardiac output, by the direct Fick method, versus time since the commencement of the experimental procedure.

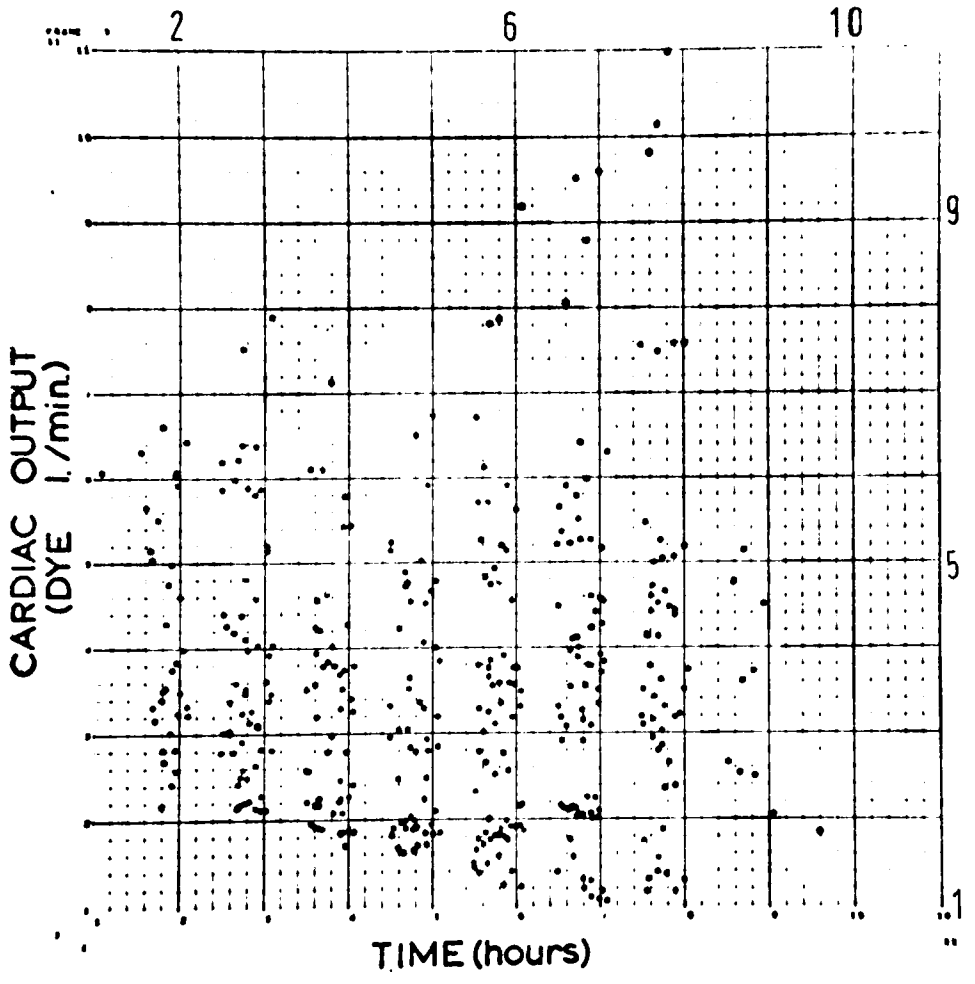

Fig. 3(b):13 Graphical representation for all the dog data for cardiac out-put, by the dye dilution technique, versus time since the commencement of the experimental procedure.

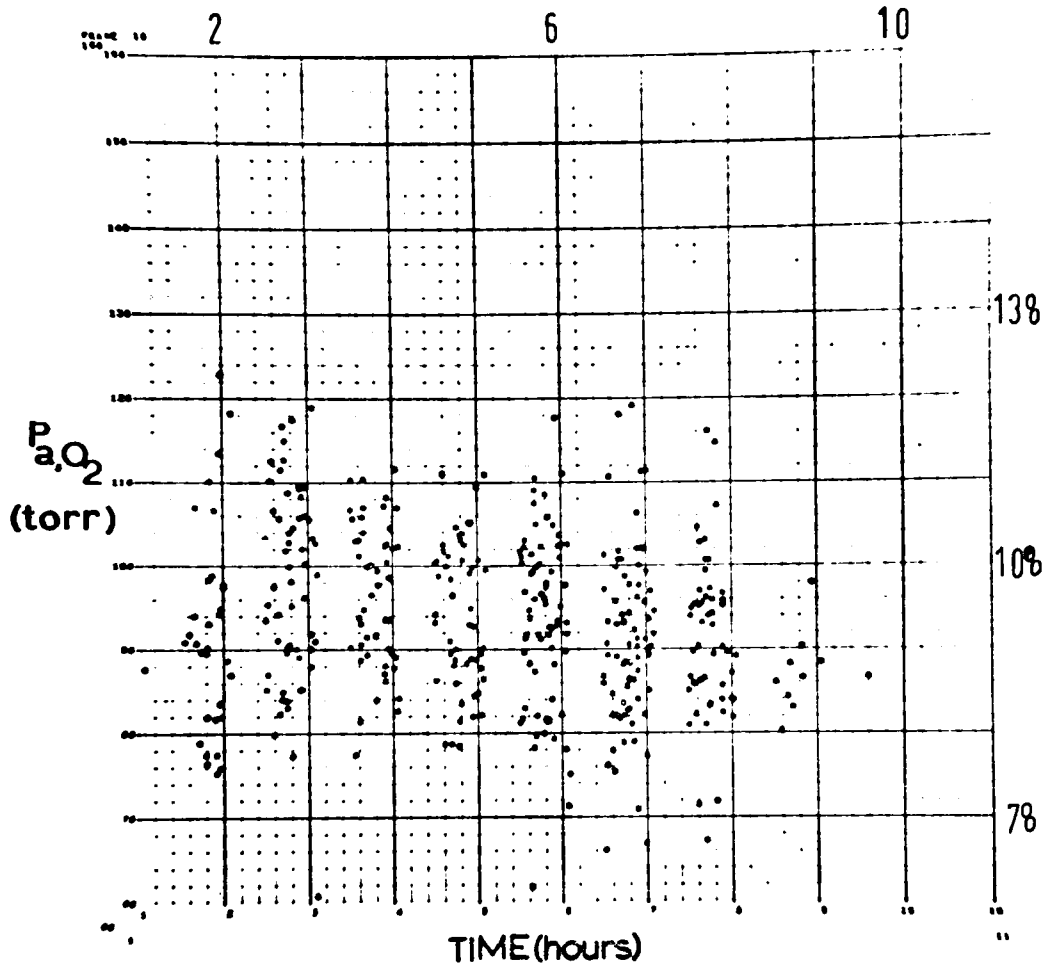

Fig.3(b):14 Graphical representation for all the dog data for arterial P_{O_2} versus time since the commencement of the experimental procedure.

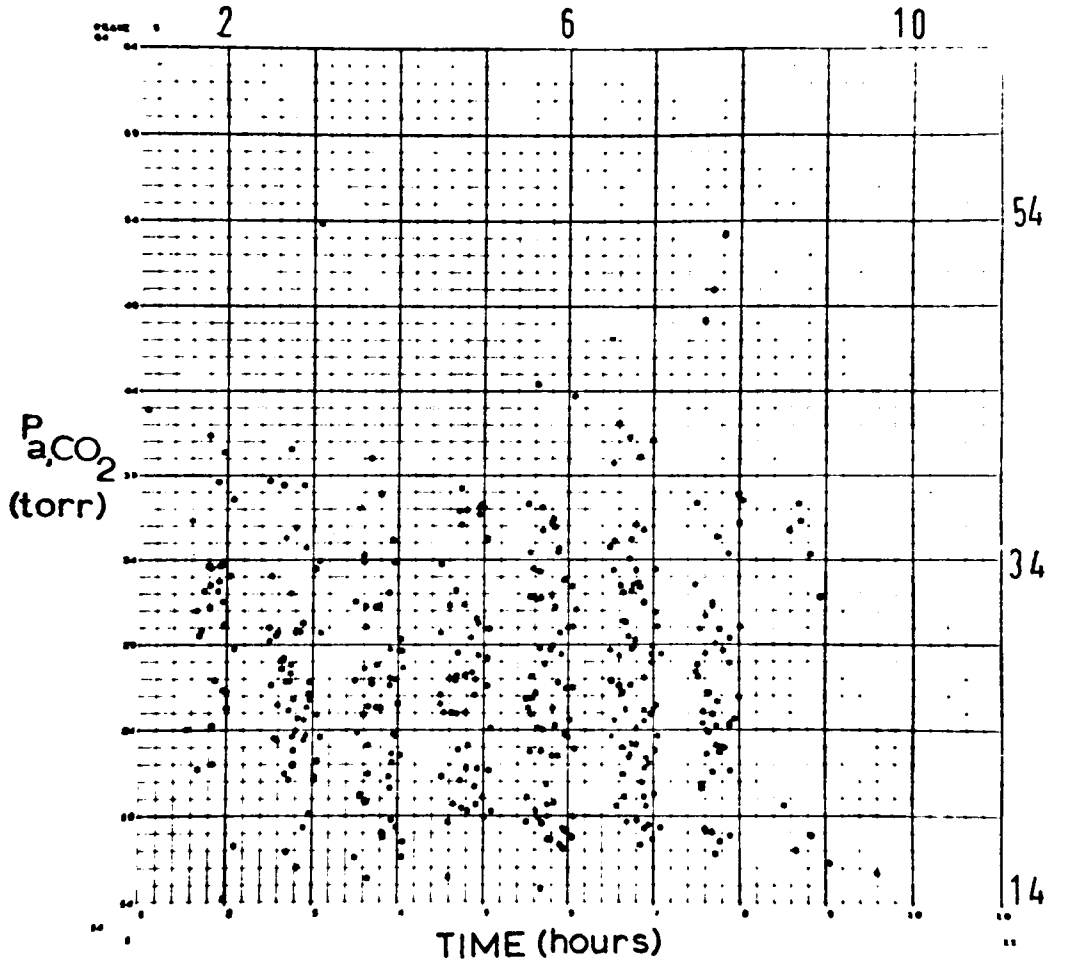

Fig.3(b):15 Graphical representation for all the dog data for arterial P_{CO_2} versus time since the commencement of the experimental procedure.

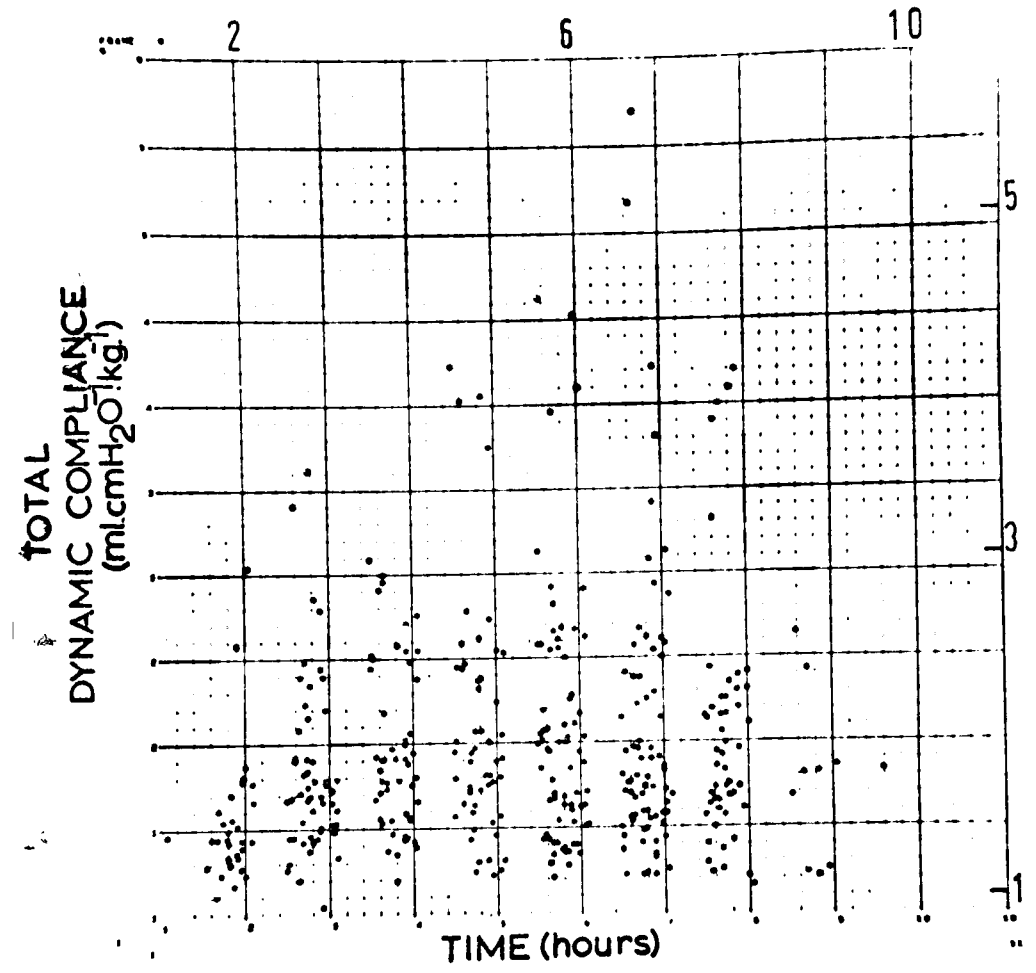

Fig.3(b):16 Graphical representation for all the dog data for total dynamic compliance versus time since the commencement of the experimental procedure.

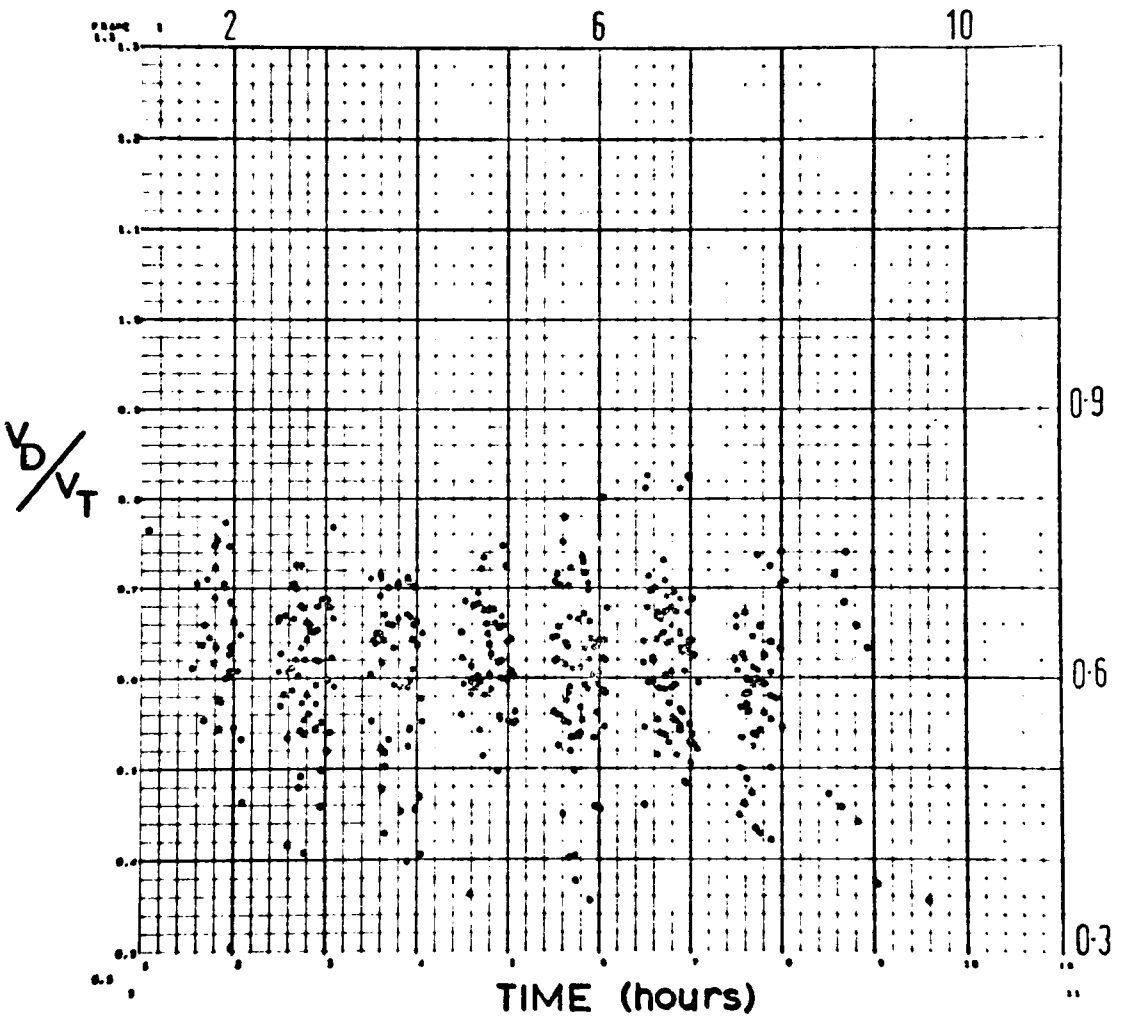

Fig.3(b):17 Graphical representation for all the dog data for physiological dead space to tidal volume ratio versus time since the commencement of the experimental procedure.

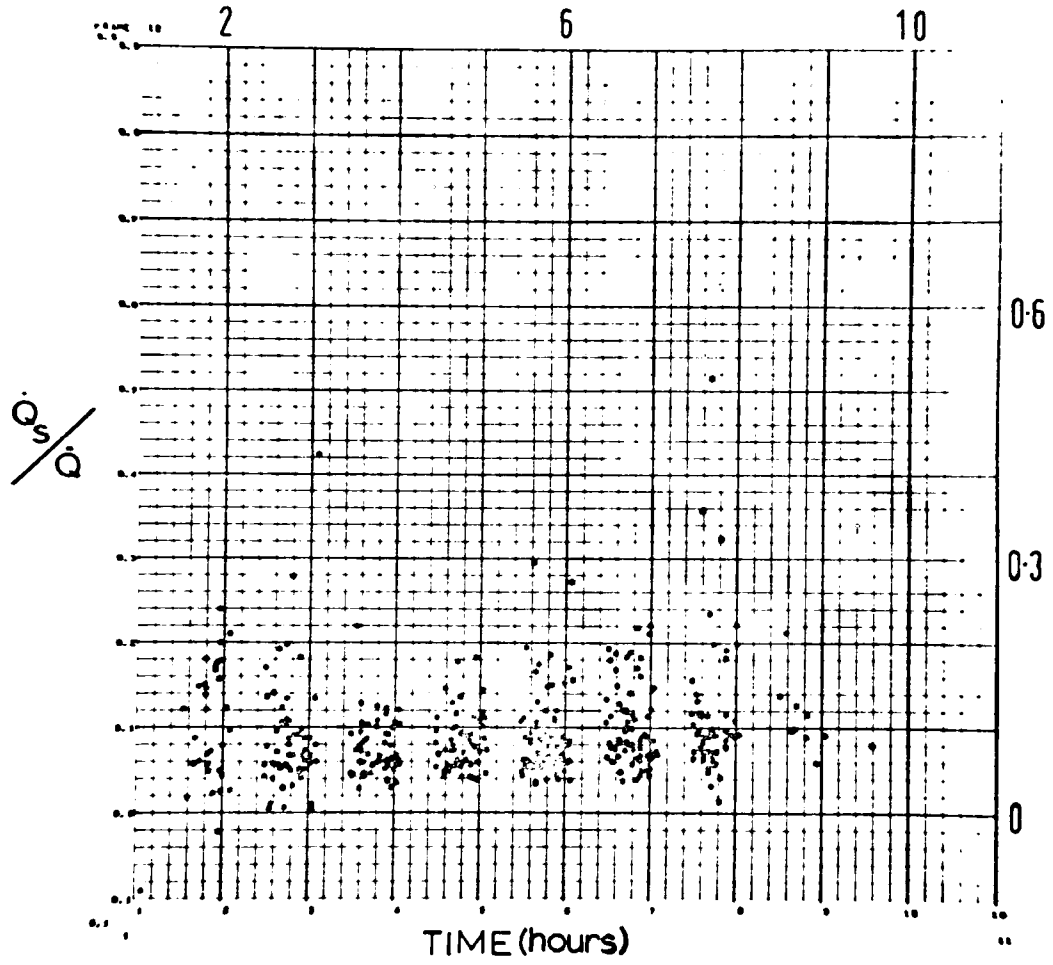

Fig. 3(b):18 Graphical representation for all the dog data for pulmonary venous admixture versus time since the commencement of the experimental procedure.

CHAPTER

3(c)

THEORETICAL METHODS
(used for analysis of physiological data)

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THEORETICAL METHODS
(used for analysis of physiological data)

The raw data were corrected where appropriate, and then subjected to a full 'Riley-Cournand Analysis' to calculate physiological indices such as dead space to tidal volume (V_D/V_T) ratio, pulmonary venous admixture ($\dot{Q}_s/\dot{Q}$), partial pressure of alveolar oxygen (P_{a,O_2}), the difference between the partial pressures of alveolar and arterial oxygen ($A\text{-}aP_{O_2}$), etc.. The calculations were performed on the Atlas Computer at Harwell.

BLOOD GAS CORRECTIONS

The general form of the corrections used by Kelman and Nunn (1966) for the delay time before analysis, and the temperature differential between animal and electrode temperatures was adopted with some modifications. The equations used with their sources were:-

Delay time correction for CO_2

$$P_{CO_2} = P_{CO_2\,(measured)} - 0.1 \times \text{delay time in minutes}$$

(Kelman and Nunn 1966)

When the blood samples were stored on ice all delay times for P_{CO_2}, and P_{O_2} and pH were divided by 10 (Kelman and Nunn 1966).

Delay time correction for pH

$$pH = pH_{(measured)} + 0.00094 \times \text{delay time in minutes}$$

(Greenbaum et al. 1967)

Correction for heparin effect on P_{O_2}

$$P_{O_2} = P_{O_2}(\text{measured}) + \frac{0.0393 \times 0.02387(P_{O_2} - 150)}{10 \times 0.023}$$

$$= P_{O_2} \times 1.00408 - 0.6118$$

(McDowall et al. 1968)

0.0393 = volume of heparin in the average sample; 0.02387 = solubility coefficient of O_2 in heparin at 37°C; 0.023 = solubility coefficient of O_2 in blood at 37°C.

Delay time correction for O_2

$$C_{O_2} = C_{O_2}(\text{calculated}) + 0.00794 \times \text{delay time in minutes}$$

(Greenbaum et al. 1967)

where,

$$C_{O_2} = (\alpha \times P_{O_2}) + (\text{Hb} \times \text{capacity} \times \frac{S_{O_2}}{100})$$

where α is the solubility coefficient of O_2 in blood and equals $0.0059519 - 0.0001266\ T + 0.0000013\ T^2$ (Kelman 1966b) and S_{O_2} = % saturation of O_2 in blood, and capacity = 1.30 ml/g Hb (Foëx 1971) or 1.34 ml/g Hb (Hüffner 1894) or 1.39 ml/g Hb (Adams 1970). In the final analysis of the results a value of 1.34 ml/g Hb for the O_2 combining capacity of Hb has been used following studies on the O_2 capacity of Hb in normal acid-base balance by Theye (1970 and 1971), Foëx et al. (1970) and Prys-Roberts et al. (1971).

Temperature correction for CO_2

$$P_{CO_2} = P_{CO_2}(37°C) \times 10^{0.021(T - 37)}$$

(Nunn et al. 1965; Bergman 1968; Siggaard-Andersen 1963)

The equation initially derived by Nunn and his colleagues used a value of 0.019 instead of 0.021. The value 0.021 was obtained experimentally by Bergman (1968) and agrees with the theoretical value calculated by Siggaard-Andersen (1963).

Temperature correction for pH

$$pH = pH_{(37^{\circ}C)} - \left[0.01963 - 0.003038 \log_{10}(P_{CO_2(37^{\circ}C)} \times 10^{0.021})\right] (T - 37)$$

This equation is a modified form of the equation proposed by Burton (1965) which was based on an electrode temperature of 38°C. It has been modified to conform to the present standard temperature for electrodes of 37°C (Gambino et al. 1966).

Temperature correction for O_2

$$P_{O_2} = P_{O_2(37^{\circ}C)} \times 10^{(T - 37)} \left[0.0052 + 0.0268(1 - e^{-30 \{1 - S_{O_2}\}})\right]$$

The experimental work on which the equation is based was carried out by Nunn et al. (1965). The actual mathematical derivation was performed by Kelman (1966b) from these results, and the equation was independently derived by Bergman (1968).

Oxygen Dissociation Curve

The O_2 dissociation curve used in this series of animal experiments was that described by Rossing and Cain (1966). Fig.3(c) 1) demonstrates the difference between this curve and the accepted theoretical curve for humans (Kelman 1966a). The equation used for dogs was:-

$$S_{O_2} = \frac{100z}{1 + z}$$

where

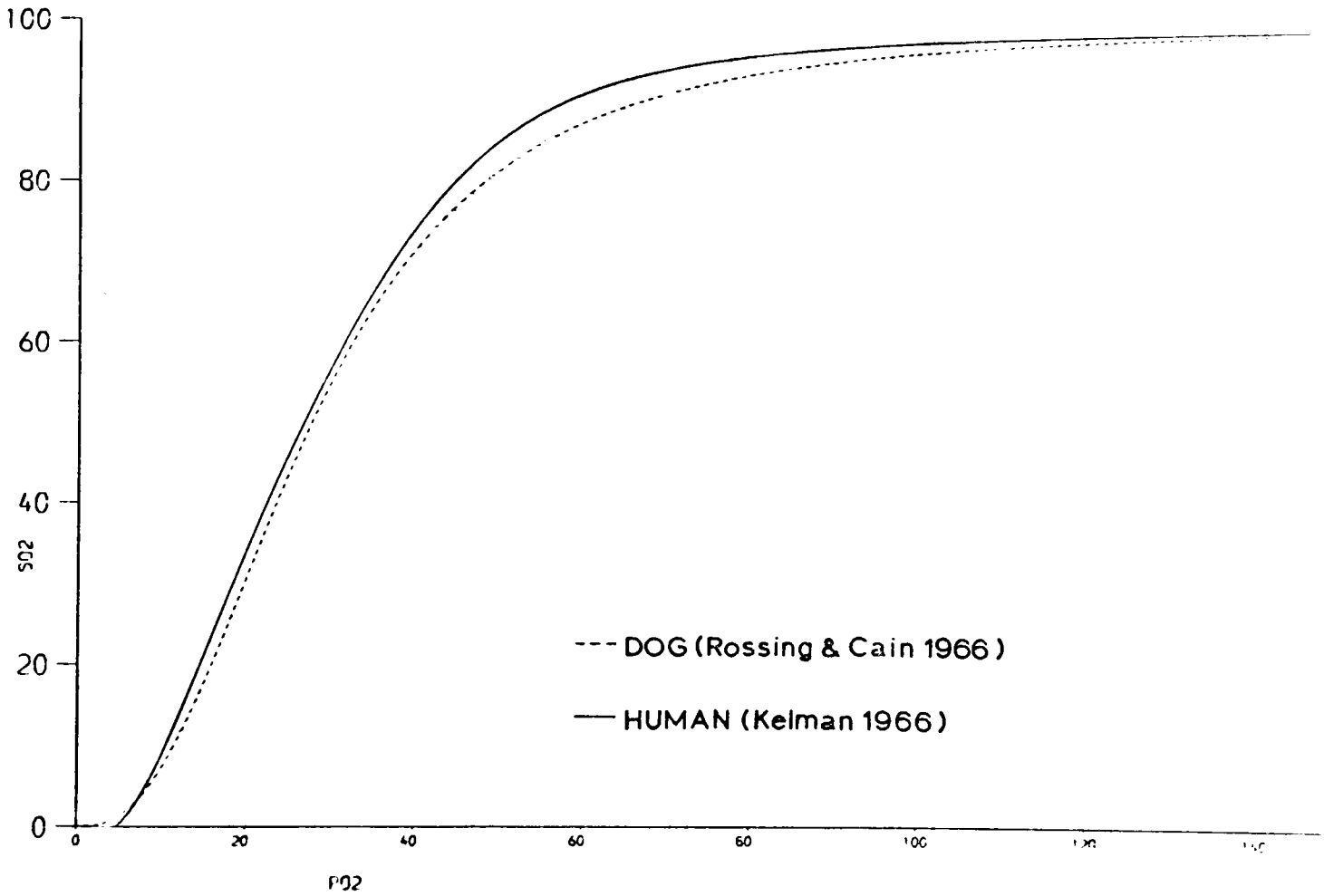


Fig. 3(c):1 Theoretical oxygen dissociation curves calculated from the equations described by Kelman (1966) for human blood, and Rossing & Cain (1966) for dog blood.

$$S_{O_2} = \frac{100z\left[z\left(z\left\{z - 6.7074\right\} + 21.214\right) - 8.53223\right]}{z\left[z\left(z\left\{z - 6.71044\right\} + 23.9617\right) - 31.3463\right] + 93.5961}$$

(rearranged from Kelman 1966.)

$$z = \frac{P_{O_2}}{10} \times 10^{\left[0.4(pH - 7.4) + 0.06(\log_{10}40 - \log_{10}P_{CO_2}) + 0.024(37 - T)\right]}$$

The temperature (T) is again constant and the last term within the power brackets may be ignored.(Kelman 1966 after Adair 1925 and Severinghaus 1965)."

$$z = \text{antilog}_{10}\left[2.5198 \log_{10} P_{O_2} + 1.1804(pH - 7) - 0.047234\ T - 2.3621\right]$$

In these series of experiments the pH and P_{O_2} of blood were always measured at a temperature (T) of 37°C and consequently the last two terms of this equation become constant. For completeness the human dissociation curve was also included in the computer program:-

$$S_{O_2} = \frac{P_{O_2}}{10} \times 10^{\left[0.4(pH - 7.4) + 0.06(\log_{10}40 - \log_{10}P_{CO_2}) + 0.024(37 - T)\right]}$$

The temperature (T) is again constant and the last term within the power brackets may be ignored. (Kelman 1966 after Adair 1925 and Severinghaus 1965).

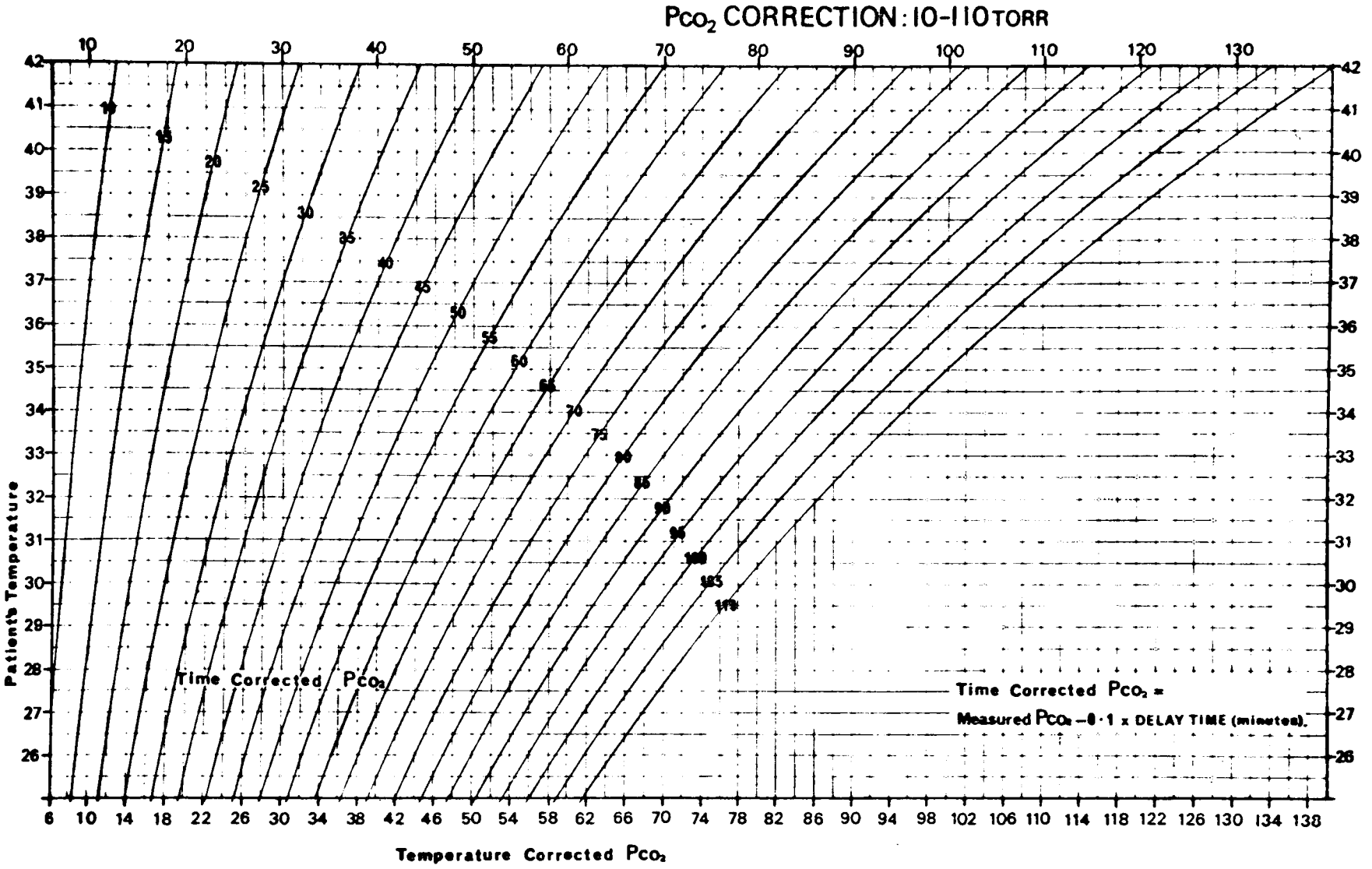
Blood gas correction nomograms which were designed by the author of this thesis for clinical use were used as a rough check on the calculated results. The nomograms are shown in Fig. (3(c):2).

GAS COMPRESSION CORRECTIONS

The measured volume of expired gas includes some gas compressed in the apparatus dead space which does not take part in ventilation. Correction is made for this using Boyle's Law (1662),

$$V_T = V_{T(measured)} \frac{V_c P_x}{1000 P_b}$$

where V_c = compressible volume; P_x = peak pressure in upper airway at the end of inspiration; P_b = barometric pressure. The expired O_2 and CO_2 partial pressures were then corrected for this compression effect as shown:-



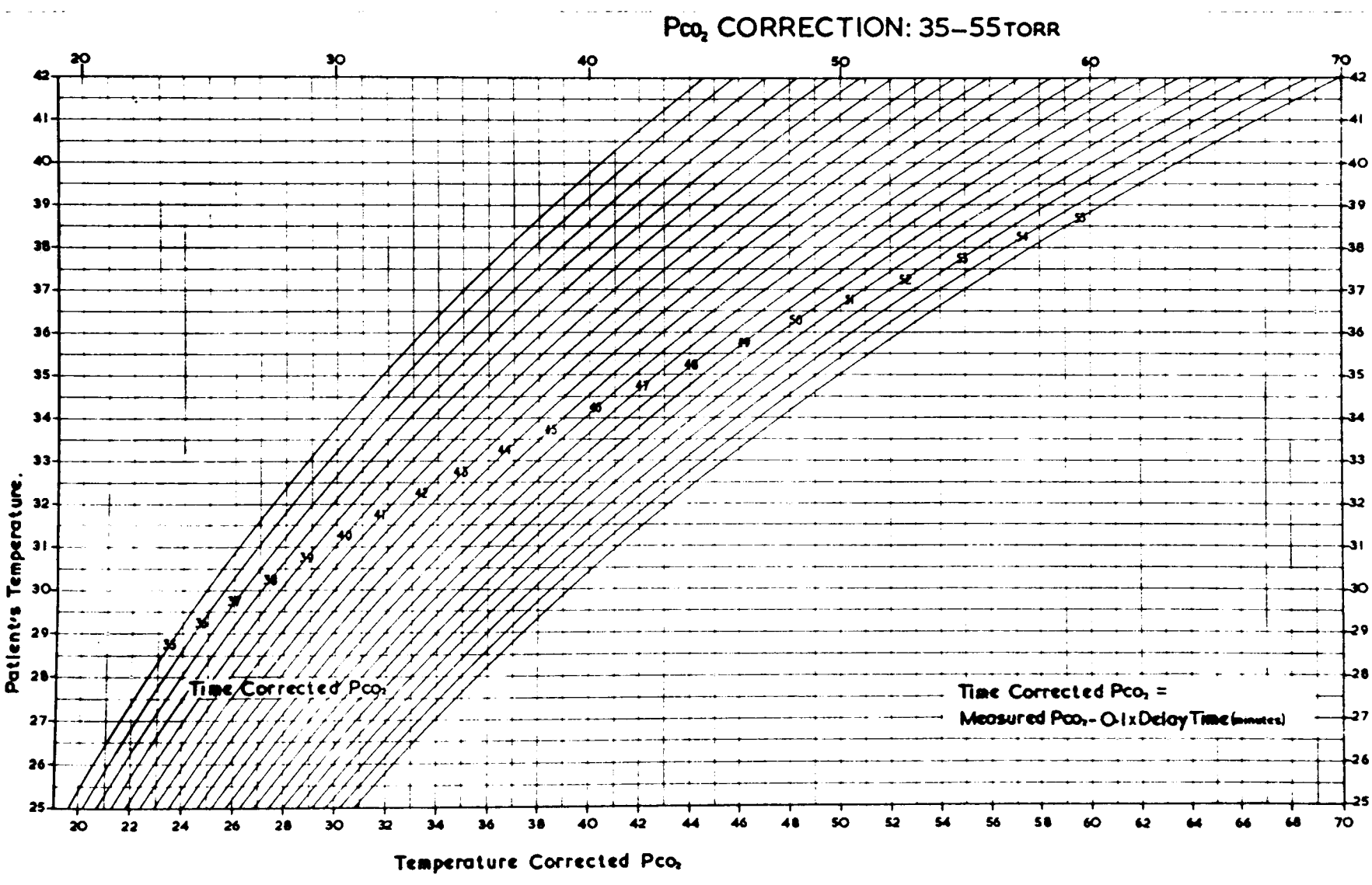
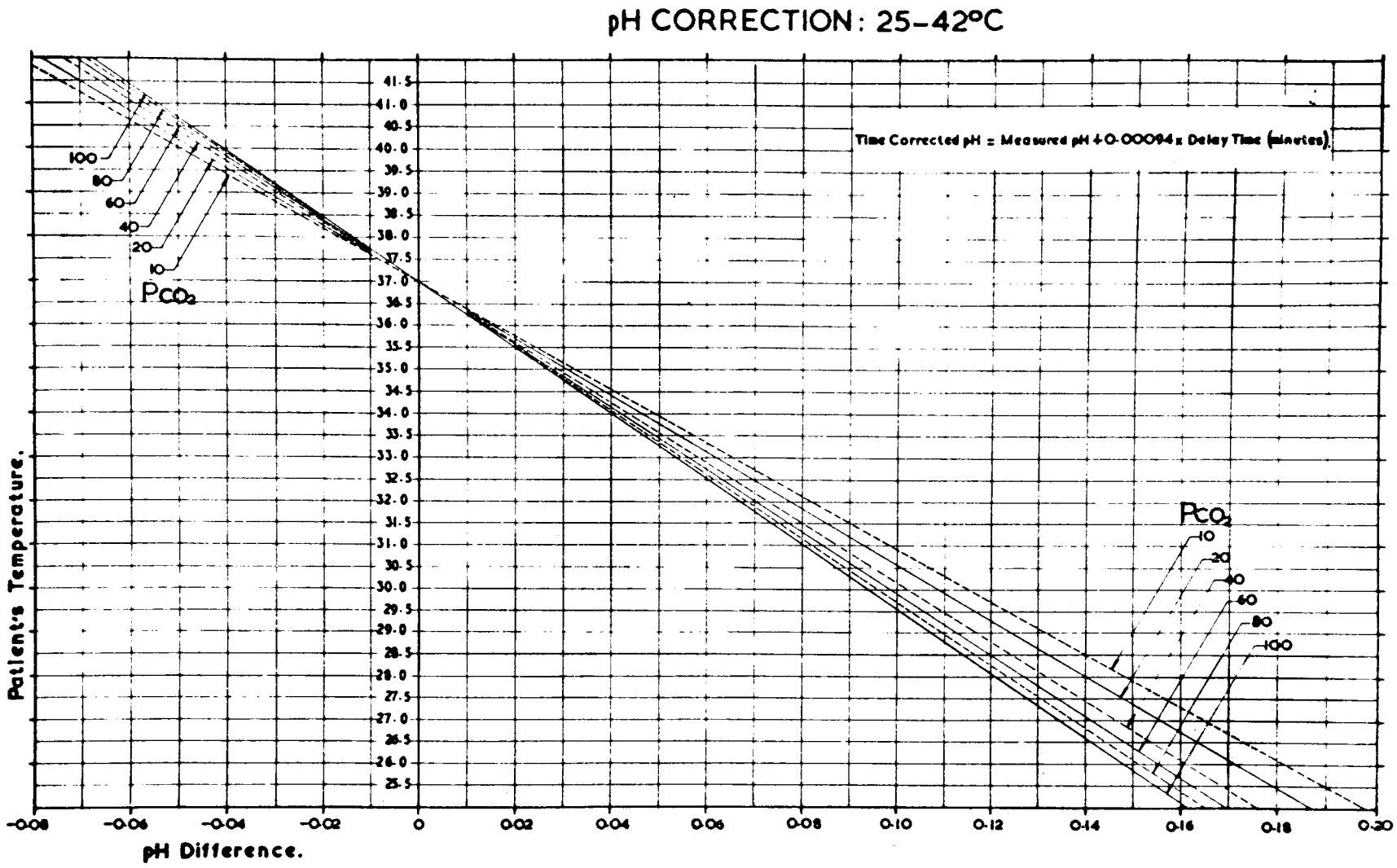


Fig. 3(c):2(i) Nomograms for P_{CO_2} delay time and patient temperature correction.



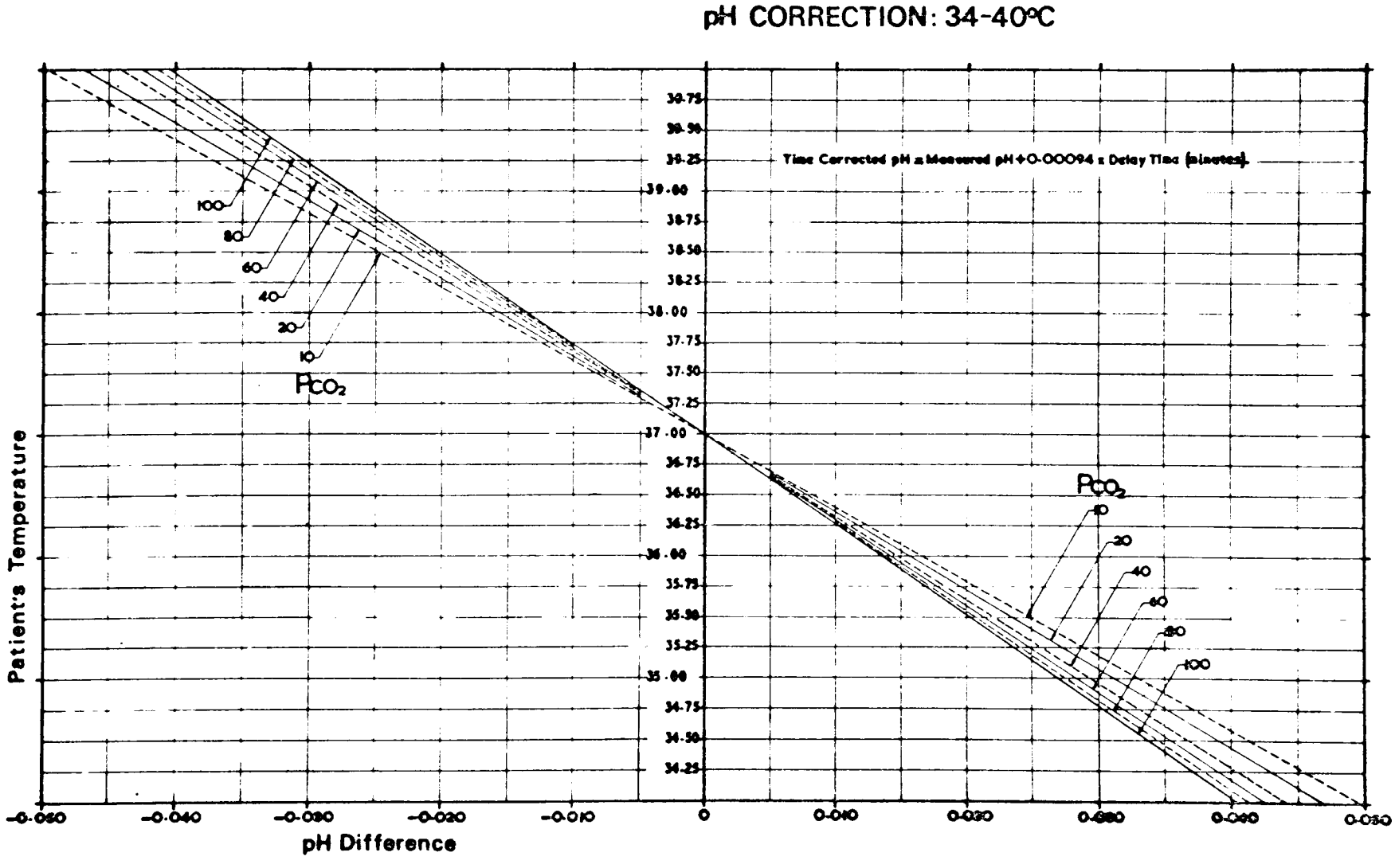


Fig. 3(c):2(ii) Nomograms for pH delay time and patient temperature correction.

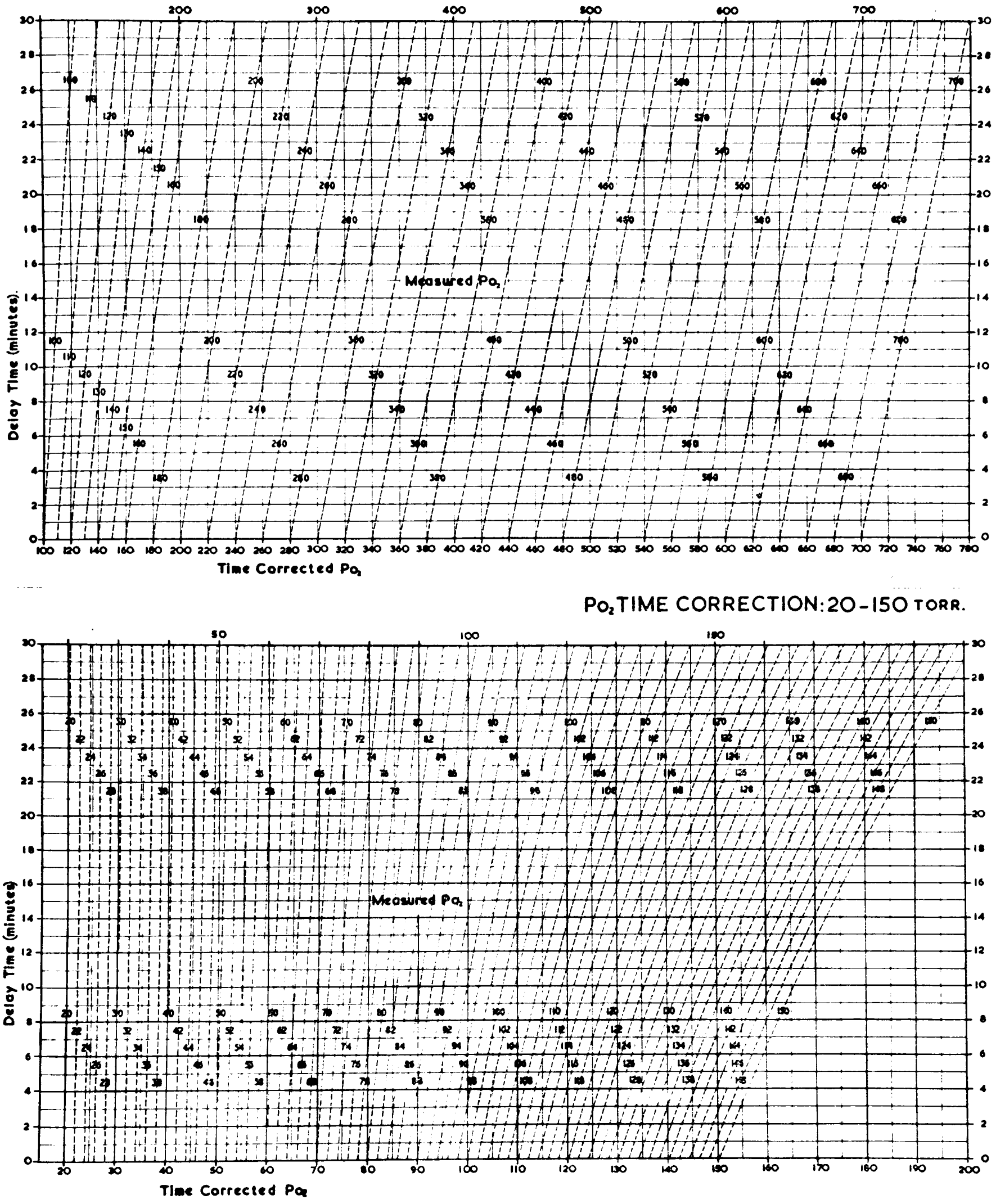


Fig. 3(c):2(iii) Nomograms for P_{O_2} delay time correction.

PO_2 CORRECTION FACTORS FOR THE DISSOCIATION CURVE

PCO_2-FACTOR

	+0	+1	+2	+3	+4	+5	+6	+7	+8	+9
10	1.087	1.081	1.075	1.070	1.065	1.061	1.057	1.053	1.049	1.046
20	1.042	1.039	1.037	1.034	1.031	1.029	1.026	1.024	1.022	1.019
30	1.017	1.015	1.013	1.012	1.010	1.008	1.006	1.005	1.003	1.002
40	1.000	0.999	0.997	0.996	0.994	0.993	0.992	0.990	0.989	0.988
50	0.987	0.986	0.984	0.983	0.982	0.981	0.980	0.979	0.978	0.977
60	0.976	0.975	0.974	0.973	0.972	0.971	0.970	0.970	0.969	0.968
70	0.967	0.966	0.965	0.965	0.964	0.963	0.962	0.961	0.961	0.960
80	0.959	0.959	0.958	0.957	0.956	0.956	0.955	0.954	0.954	0.953
90	0.953	0.952	0.951	0.951	0.950	0.949	0.949	0.948	0.948	0.947
100	0.947	0.946	0.945	0.945	0.944	0.944	0.943	0.943	0.942	0.942
110	0.941	0.941	0.940	0.940	0.939	0.939	0.938	0.938	0.937	0.937

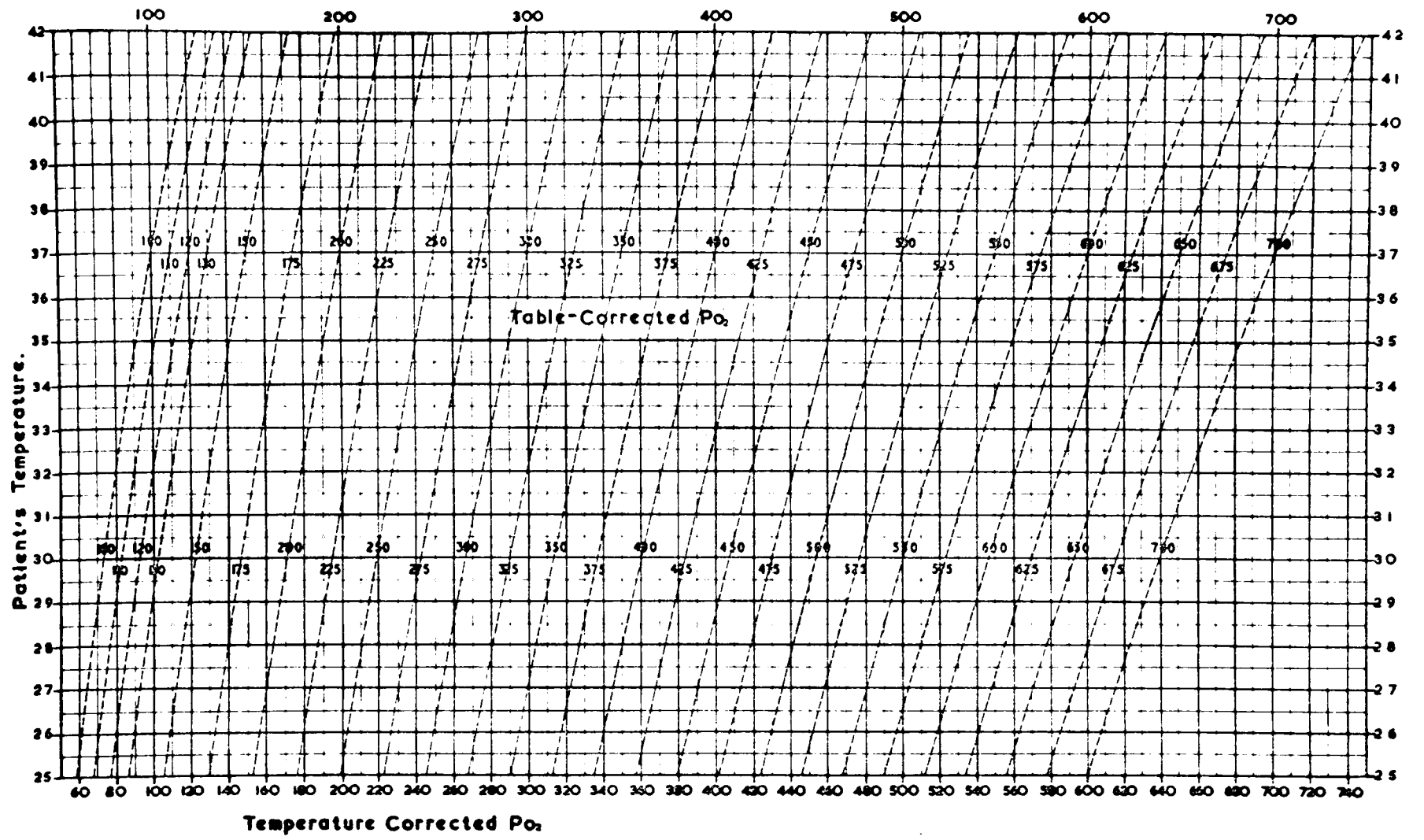
Fig. 3(c):2(iv) P_{CO_2} correction factor for P_{O_2} so that the oxygen dissociation curve may be correctly used.

PO_2 CORRECTION FACTORS FOR THE O_2 DISSOCIATION CURVE

pH - FACTOR

	+0	+.01	+.02	+.03	+.04	+.05	+.06	+.07	+.08	+.09
6.7	0.525	0.530	0.535	0.540	0.545	0.550	0.555	0.560	0.565	0.570
6.8	0.575	0.581	0.586	0.592	0.597	0.603	0.608	0.614	0.619	0.625
6.9	0.631	0.637	0.643	0.649	0.655	0.661	0.667	0.673	0.679	0.685
7.0	0. 692	0.698	0.705	0.711	0.718	0.724	0.731	0.738	0.745	0.752
7.1	0.759	0.766	0.773	0.780	0.787	0.794	0.802	0.809	0.817	0.824
7.2	0.832	0.839	0.847	0.855	0.863	0.871	0.879	0.887	0.895	0.904
7.3	0.912	0.920	0.929	0.938	0.946	0.955	0.964	0.973	0.982	0.991
7.4	1.000	1.009	1.019	1.028	1.038	1.047	1.057	1.067	1.076	1.086
7.5	1.096	1.107	1.117	1.127	1.138	1.148	1.159	1.169	1.180	1.191
7.6	1.202	1.213	1.225	1.236	1.247	1.259	1.271	1.282	1.294	1.306
7.7	1.318	1.330	1.343	1.355	1.368	1.380	1.393	1.406	1.419	1.432
7.8	1.445	1.459	1.472	1.486	1.500	1.514	1.528	1.542	1.556	1.570
7.9	1.585	1.600	1.614	1.629	1.644	1.660	1.675	1.690	1.706	1.722
8.0	1.738	1.754	1.770	1.786	1.803	1.820	1.837	1.854	1.871	1.888

Fig. 3(c):2(v) pH correction factor for P_{O_2} so that the oxygen dissociation curve may be correctly used.



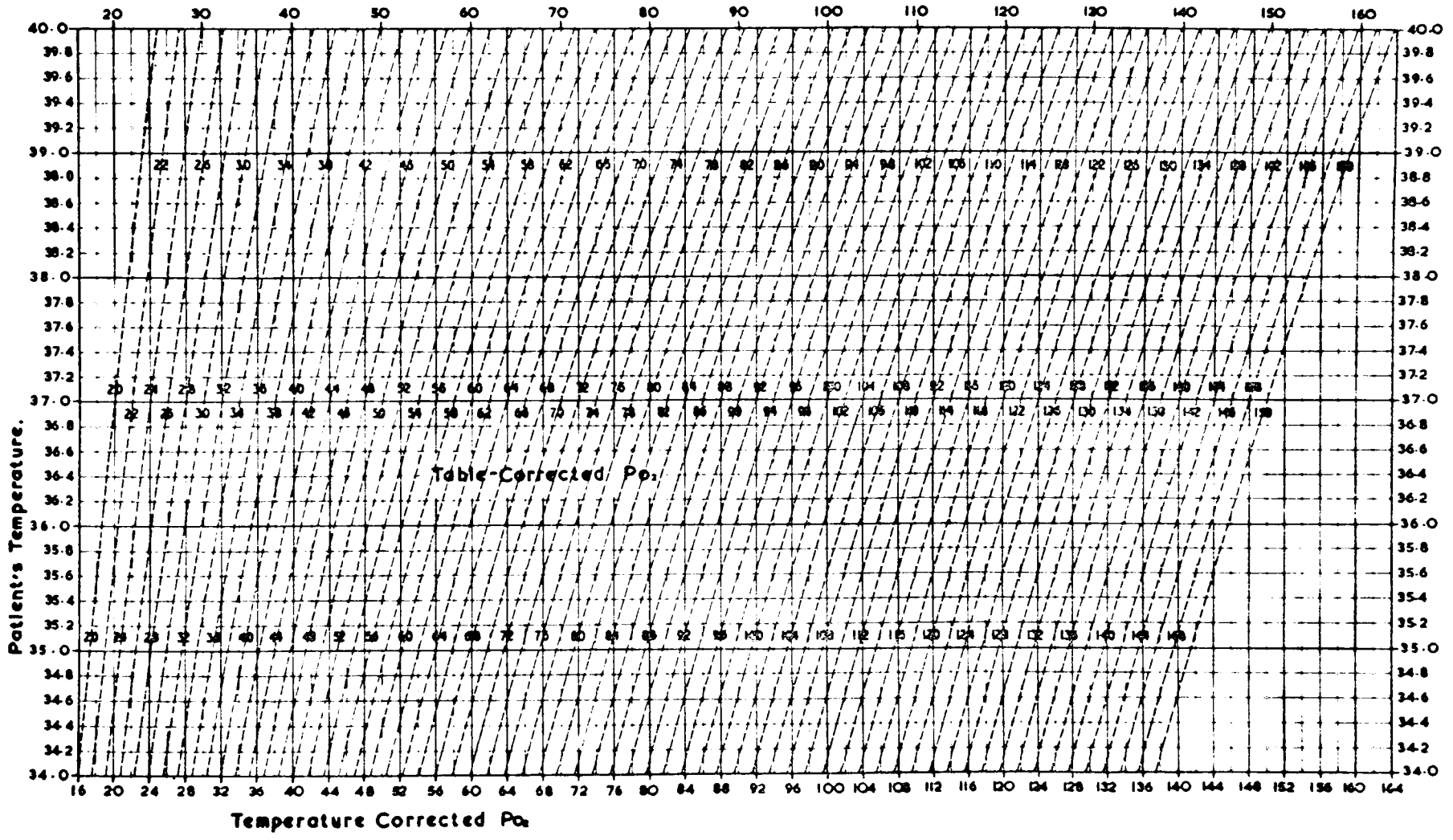


Fig. 3(c):2(vi) Nomograms for P_{O_2} patient temperature correction.

$$P_{\bar{E}O_2} = \frac{P_{\bar{E}O_2(\text{measured})}\ V_{T(\text{measured})}}{V_T}$$

$$P_{\bar{E}CO_2} = \frac{P_{\bar{E}CO_2(\text{measured})}\ V_{T(\text{measured})}}{V_T}$$

RILEY-COURNAND ANALYSIS

This name is given in the Nuffield Department of Anaesthetics to a method of assessing respiratory and cardiovascular efficiency. Measurements are made of V_E, $P_{\bar{E},CO_2}$, $P_{\bar{E},O_2}$, P_{a,CO_2}, P_{a,O_2}, $P_{\bar{v},CO_2}$, $P_{\bar{v},O_2}$, and pH. After suitable corrections have been applied standard equations are used to calculate $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, $\dot{Q}$, $\dot{Q}_s/\dot{Q}$, P_{A,O_2}, V_D/V_T and P_{A,CO_2}. The author has modified the standard equations used to calculate P_{A,O_2}, and P_{A,CO_2}.

This 'analysis' depends on conditions of steady-state exchange of nitrogen and other respiratory gases. Particular care was taken in these studies by allowing at least 15 minutes to elapse after a change in ventilation, to ensure that stable conditions existed before measurements were made.

Standard Equations.

$$\text{'Filley factor'} = \frac{P_{I,O_2} - P_{\bar{E},O_2}}{P_{\bar{E},CO_2}}$$ (Nunn 1963 after Filley et al. 1954)

$$\dot{V}_{O_2}\ \text{STPD} = 1000\dot{V}_E\ \text{STPD}\left[\frac{F_{I,O_2}(1 - F_{\bar{E},O_2} - F_{\bar{E},CO_2})}{1 - F_{I,O2}} - F_{\bar{E},O_2}\right]$$

(derived by many physiologists from the early studies of Geppert and Zuntz 1888 and Douglas 1911).

$$\dot{V}_{CO_2}STPD = \dot{V}_E\ STPD \times F_{\bar{E},CO_2} \times 1000$$

$$\dot{Q} = \frac{\dot{V}_{O_2}STPD}{10(C_{a,O_2} - C_{\bar{v},O_2})} \qquad \text{(Fick 1870)}$$

$$\dot{Q}_s/\dot{Q} = \frac{C_{c',O_2} - C_{a,O_2}}{C_{c',O_2} - C_{\bar{v},O_2}} \qquad \text{(Berggren 1942 after Sackur 1896\& 1897)}$$

$$V_D/V_T = 1 - \frac{P_{\bar{E},CO_2}}{P_{a,CO_2}} \qquad \text{(Enghoff 1938 after Bohr 1891)}$$

Derivation of P_{A,O_2}

The partial pressure of alveolar oxygen used in calculations in this thesis was derived by combining a modification of the Nunn (1963) equation

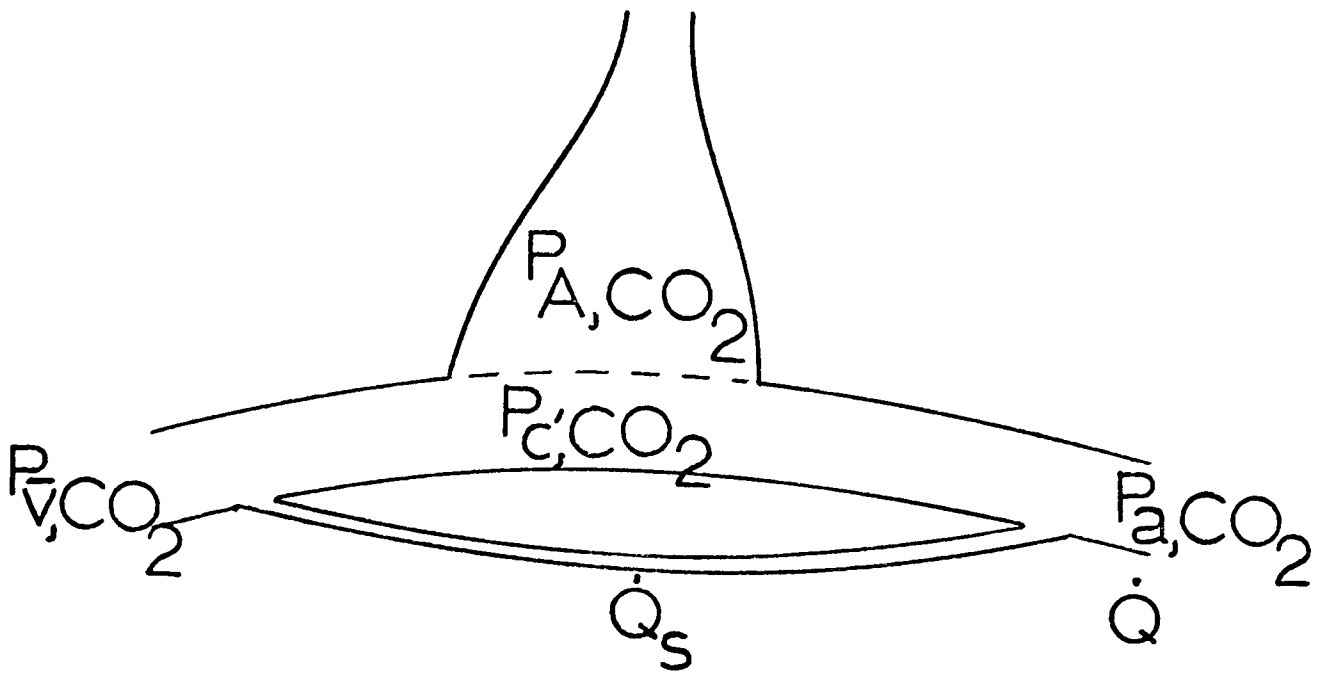
$$P_{A,O_2} = P_{I,O_2} - \text{Filley}\ P_{A,CO_2}$$

with

$$P_{A,CO_2} = P_{\bar{v},CO_2} - \frac{P_{\bar{v},CO_2} - P_{a,CO_2}}{1 - \dot{Q}_s/\dot{Q}}$$

The derivation of the second equation is shown in Fig. 3(c):3, and assumes a linear relationship between P_{CO_2} and C_{CO_2} in the physiological range (Prys-Roberts 1968). The equation for P_{A,O_2} then becomes:-

$$P_{A,O_2} = P_{I,O_2} - \text{Filley}\left(P_{\bar{v},CO_2} - \frac{P_{\bar{v},CO_2} - P_{a,CO_2}}{1 - \dot{Q}_s/\dot{Q}}\right)$$



Let $P_{c',CO_2} = P_{A,CO_2}$

Then

$$P_{a,CO_2}\,\dot{Q} = P_{\bar{v},CO_2}\,\dot{Q}_s + P_{A,CO_2}\,(\dot{Q} - \dot{Q}_s)$$

$$P_{A,CO_2} = \frac{P_{a,CO_2}\,\dot{Q} - P_{\bar{v},CO_2}\,\dot{Q}_s}{\dot{Q} - \dot{Q}_s}$$

$$= \frac{P_{a,CO_2} - P_{\bar{v},CO_2}\,\frac{\dot{Q}_s}{\dot{Q}}}{1 - \frac{\dot{Q}_s}{\dot{Q}}}$$

$$= \frac{P_{a,CO_2} - P_{\bar{v},CO_2}\,\frac{\dot{Q}_s}{\dot{Q}} + P_{\bar{v},CO_2} - P_{\bar{v},CO_2}}{1 - \frac{\dot{Q}_s}{\dot{Q}}}$$

$$= P_{\bar{v},CO_2} - \frac{P_{\bar{v},CO_2} - P_{a,CO_2}}{1 - \frac{\dot{Q}_s}{\dot{Q}}}$$

Fig.3(c):3 Derivation of P_{A,CO_2} used in the calculation of P_{A,O_2}.

where

$$\dot{Q}_s/\dot{Q} = \frac{\alpha P_{A,O_2} + \text{Hb Capac.}\ S_{A,O_2} - C_{a,O_2}}{\alpha P_{A,O_2} + \text{Hb Capac.}\ S_{A,O_2} - C_{\bar{v},O_2}}$$

therefore

$$P_{A,O_2} = P_{I,O_2} - \text{Filley}\left[P_{\bar{v},CO_2} - \frac{P_{\bar{v},CO_2} - P_{a,CO_2}}{1 - \frac{\alpha P_{A,O_2} + \text{Hb Capac.}\ S_{A,O_2} - C_{a,O_2}}{\alpha P_{A,O_2} + \text{Hb Capac.}\ S_{A,O_2} - C_{\bar{v},O_2}}}\right]$$

$$P_{A,O_2} = P_{I,O_2} - \text{Filley}\left[P_{\bar{v},CO_2} - \frac{(P_{\bar{v},CO_2} - P_{a,CO_2})\ (\alpha P_{A,O_2} + \text{Hb Capac.}\ S_{A,O_2} - C_{\bar{v},O_2})}{\alpha P_{A,O_2} + \text{Hb Capac.}\ S_{A,O_2} - C_{\bar{v},O_2} - \alpha P_{A,O_2} - \text{Hb Capac.}\ S_{A,O_2} + C_{a,O_2}}\right]$$

$$P_{A,O_2} = P_{I,O_2} - \text{Filley}\left[P_{\bar{v},CO_2} - \frac{(P_{\bar{v},CO_2} - P_{a,CO_2})\ (\alpha P_{A,O_2} + \text{Hb Capac.}\ S_{A,O_2} - C_{\bar{v},O_2})}{C_{a,O_2} - C_{\bar{v},O_2}}\right]$$

$$P_{A,O_2} = P_{I,O_2} + \text{Filley}\left[-P_{\bar{v},CO_2} + \frac{(P_{\bar{v},CO_2} - P_{a,CO_2})\ (\alpha P_{A,O_2} + \text{Hb Capac.}\ S_{A,O_2} - C_{\bar{v},O_2})}{C_{a,O_2} - C_{\bar{v},O_2}}\right]$$

$$P_{A,O_2}C_{a,O_2} - P_{A,O_2}C_{\bar{v},O_2} = P_{I,O_2}C_{a,O_2} - P_{I,O_2}C_{\bar{v},O_2} + \text{Filley}(-P_{\bar{v},CO_2}C_{a,O_2} + P_{\bar{v},CO_2}C_{\bar{v},O_2}$$

$$+ P_{\bar{v},CO_2}\alpha P_{A,O_2} + P_{\bar{v},CO_2}\ \text{Hb Capac.}\ S_{A,O_2} - P_{\bar{v},CO_2}C_{\bar{v},O_2} - P_{a,CO_2}\alpha P_{A,O_2}$$

$$- P_{a,CO_2}\ \text{Hb Capac.}\ S_{A,O_2} + P_{a,CO_2}C_{\bar{v},O_2})$$

$$P_{A,O_2}(C_{a,O_2} - C_{\bar{v},O_2} + \alpha\text{Filley } P_{a,CO_2} - \alpha\text{Filley } P_{\bar{v},CO_2}) = P_{I,O_2}C_{a,O_2} - P_{I,O_2}C_{\bar{v},O_2}$$

$$- \text{Filley } P_{\bar{v},CO_2}C_{a,O_2} + \text{Filley } P_{\bar{v},CO_2}\,\text{Hb Capac.}\,S_{A,O_2}$$

$$- \text{Filley } P_{a,CO_2}\,\text{Hb Capac.}\,S_{A,O_2} + \text{Filley } P_{a,CO_2}C_{\bar{v},O_2}$$

so that

$$P_{A,O_2} =$$

$$\frac{P_{I,O_2}(C_{a,O_2} - C_{\bar{v},O_2}) + \text{Filley } S_{A,O_2}\,\text{Hb Capac.}\,(P_{\bar{v},CO_2} - P_{a,CO_2}) + \text{Filley}(C_{\bar{v},O_2}P_{a,CO_2} - P_{\bar{v},CO_2}C_{a,O_2})}{C_{a,O_2} - C_{\bar{v},O_2} + \alpha\text{Filley } (P_{a,CO_2} - P_{\bar{v},CO_2})}$$

In the above equation it has been assumed that the approximate S_{A,O_2} which can be obtained from the approximate P_{A,O_2} in the Nunn (1963) equation:

$$P_{A,O_2}(\text{approx.}) = P_{I,O_2} - \text{Filley } P_{a,CO_2}$$

is close to the true value. Even if this assumption were incorrect the effect on the value of P_{A,O_2} would be negligible in these studies because of the shape of the dissociation curve and the fact that the inspired gas was air. If the F_{I,O_2} were low it would be necessary to introduce an iterative procedure into the solution of this equation to correct for any difference between the true and assumed value of S_{A,O_2}.

A comparison of P_{A,O_2} calculated by this method and the $P_{A,O_2}(approx.)$ calculated from the Nunn (1963) equation is shown in Fig. 3(c):4 and shows strong correlation. This might be expected because this modified form of the Nunn (1963) equation was introduced to correct for the effects of venous admixture on P_{A,O_2}. In the studies described the venous admixture was always low and little difference would be expected between $P_{A,O_2}(approx.)$ and the true $P_{A,O2}$ in such circumstances.

Derivation of $P_{A,CO_2}(approx.)$

Because the end-tidal P_{CO_2} (P_{ET,CO_2}) could not be measured in every study an approximation to the P_{A,CO_2} was attempted. This approximation assumed that the physiological dead space calculated from a modification of the Enghoff (1938) equation which adjusts for the added dead space of the apparatus:

$$V_D = V_T \left(1 - \frac{P_{\bar{E},CO_2}}{P_{a,CO_2}} \right) - V_{D(app.)}$$

was equal to the anatomical dead space. This value was then inserted into the equation derived by Crossman et al. (1970) for the true value of V_D/V_T after allowing for the added apparatus dead space:

$$V_D/V_T = \frac{1 - \dfrac{P_{\bar{E},CO_2}}{P_{a,CO_2} - \dfrac{P_{\bar{E},CO_2}\ V_T\ V_{D(app.)}}{(V_T - V_{D(anat.)} - V_{D(app.)})\ (V_T - V_{D(anat.)})}}}{}$$

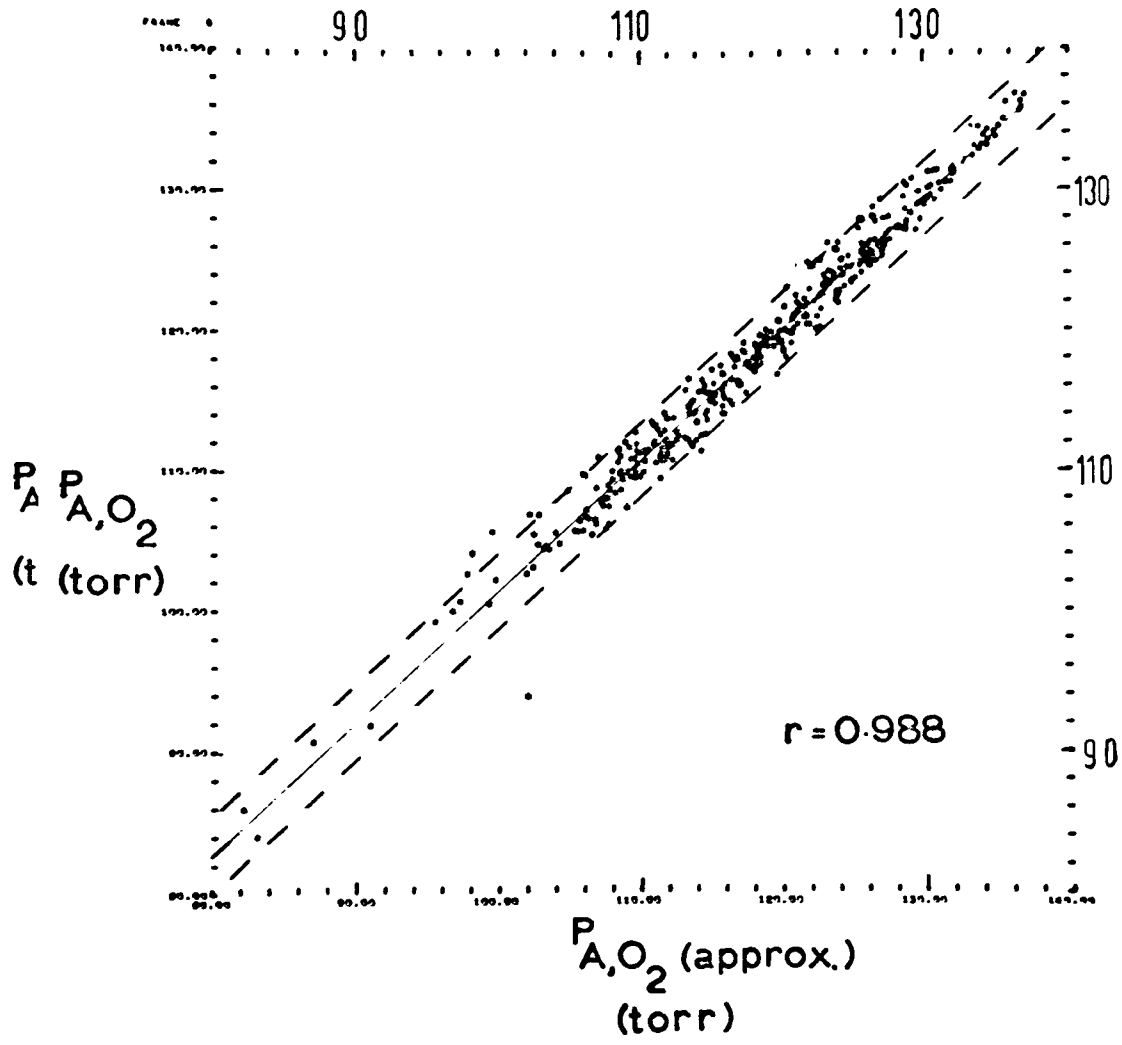


Fig. 3(c):4 Comparison of P_{A,O_2} calculated from the author's equation with P_{A,O_2}(approx) calculated from the Nunn (1963) equation for the same dog data. The line of best fit is drawn together with the 95% confidence limits.

and a new value then derived for the physiological dead space from the first equation. The new value for physiological dead space was again assumed to equal the anatomical dead space and was then inserted into the second equation. This iterative procedure was then continued until a tolerance of 0.005 units had been obtained in both V_D/V_T and V_D. This value was then inserted into a rearranged Bohr (1891) equation to obtain the approximate P_{A,CO_2}.

$$P_{A,CO_2} = \frac{P_{\bar{E},CO_2} V_T}{V_T - V_T(V_D/V_T)}$$

The above equation gives results for $P_{A,CO_2}(approx.)$ which are lower than the true 'ideal' P_{A,CO_2} because of the iterative procedure and the assumptions made to drive it. In fact calculated $P_{A,CO_2}(approx.)$ was less by 12% than the P_{ET,CO_2} measured. There was strong linear correlation between $P_{A,CO_2}(approx.)$ and P_{a,CO_2} ($R = 0.978$) as would be expected because P_{A,CO_2} is a function of P_{a,CO_2} and they are thus autocorrelated. There was also a strong correlation between measured P_{ET,CO_2} and P_{a,CO_2} ($R = 0.914$, slope = 1.04) which compares favourably with the exhaustive study by Ramwell (1958) who obtained a straight line correlation of 0.811. The relationship between measured P_{ET,CO_2} and calculated $P_{A,CO_2}(approx.)$ was linear ($R = 0.848$, slope = 1.01) (Fig.3(c):5) Thus although the calculated $P_{A,CO_2}(approx.)$ does not represent the true P_{A,CO_2} it has been used in this thesis as an index of the manner in which the true P_{A,CO_2} might have behaved had its measurement been possible. No

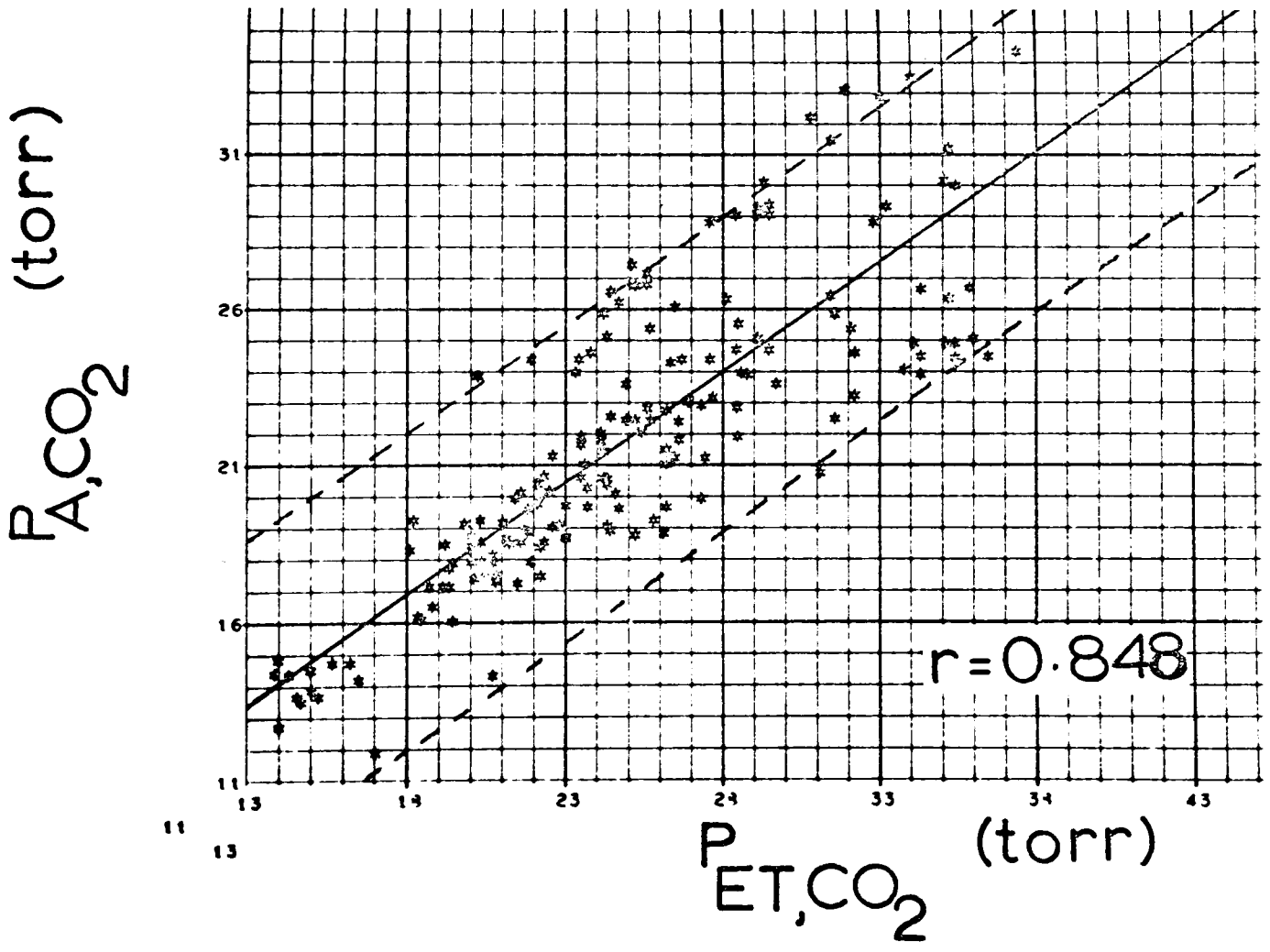


Fig. 3(c):5 Comparison of P_{A,CO_2} calculated by the author's procedure with P_{ET,CO_2} measured at the carina. The line of best fit is drawn together with the 95% confidence limits.

conclusions can be drawn from such an index but it may suggest areas of study which need more positive investigation.

The program printout from the computer is shown in Fig. 3(c):6.

Abbreviations used in the computer program which is written in Atlas Fortran (Hartran).

Q = number of the experimental run within patient or dog.

CO = $\dot{Q}_D$ DG = dog or human. PB = barometric pressure.

ETIME = Experimental time. STIME = Starting time. RMTMP = room temperature.

PTTMP = patient temperature. VCL = measured $V_{\bar{E}}$ HB = haemoglobin.

XNOBR = number of breaths for $V_{\bar{E}}$. TIME = time for $V_{\bar{E}}$ PTWT = patient weight.

VDAPP = apparatus dead space. VC = compressible volume of the airways.

PX = measured end-inspiratory pressure. PEO2 = $P_{\bar{E},O_2}$

XICE = whether or not blood stored on ice. PECO2 = $P_{\bar{E},CO_2}$

PIO2 = P_{I,O_2} RPAO2 = read P_{a,O_2} DTPAO2 = delay time corr. P_{a,O_2}

RPACO = read P_{a,CO_2} DTPAC = delay time corrected P_{a,CO_2}

RPHA = read pH_a DTPHA = delay time corr. pH_a HT = haematocrit.

RPVO2 = read $P_{\bar{v},O_2}$ DTPVO = delay time corrected $P_{\bar{v},O_2}$

RPVCO = read $P_{\bar{v},CO_2}$ DTPVC = delay time corrected $P_{\bar{v},CO_2}$

RPHV = read $pH_{\bar{v}}$ DTPHV = delay time corr. $pH_{\bar{v}}$ T(I) = 1.30, 1.34 or 1.39

CORR = subroutine for correction of P_{CO_2} and pH for delay time and temperature.

POCOR = subroutine for correction of P_{O_2} for delay time and temperature.

SATCO = subroutine for obtaining the oxygen dissociation curve.

CO2CT = subroutine for calculation of CO_2 content - not used in this thesis.

TPAO2 = corrected P_{a,O_2} PAAO2 = corrected P_{A,O_2} QSBQT = $\dot{Q}_s/\dot{Q}$

QSOQT = "$\dot{Q}_s/\dot{Q}$" from CO_2 content. CAO2 = C_{a,O_2} CVO2 = $C_{\bar{v},O_2}$

CCO2 = C_{c',O_2} QT = $\dot{Q}_F$ QTCO2 = "$\dot{Q}_F$" from CO_2 content.

CCCO2 = C_{c',CO_2} TPVO2 = corrected $P_{\bar{v},O_2}$ SAO2 = S_{a,O_2}

SVO2 = $S_{\bar{v},O_2}$ SAAO2 = S_{A,O_2} CACO2 = C_{a,CO_2}

CVCO2 = $C_{\bar{v},CO_2}$ TPACO = corrected P_{a,CO_2} TPVCO = corrected $P_{\bar{v},CO_2}$

CPHA(1) = corrected pH_a by means of the modified Burton equation (1965).

CPHV(1) = corrected $pH_{\bar{v}}$ by means of the modified Burton equation (1965).

PX = measured end-inspiratory pressure. VO2ST = $\dot{V}_{O_2}$ STPD

VCO2S = $\dot{V}_{CO_2}$ STPD VEBTP = $V_{\bar{E}}$ BTPS FILLY = Filley factor.

PTWT = patient weight. IWAVE = inspiratory waveform.

EIRAT = E:I ratio. IBLOK = control or blocked animal.

HRS = hours from start of experiment. NODOG = dog number.

VTBTP = V_T BTPS PAIR = mean airway pressure.

POES = mean oesophageal pressure. VA = $\dot{V}_A$ VDBVT = "V_D/V_T" used for P_{A,CO_2}

VDD = "$V_{D\ (ANAT.)}$" used for P_{A,CO_2} and $\dot{V}_A$ PAACO = a - A P_{CO_2} gradient.

VDVTP = V_D/V_T ratio. PAAOA = A - a P_{O_2} gradient.

```
1           DIMENSION T(3),TITLE(10),CPHA(2),CPHV(2),CPO2(10),SA(19,3),SB(30)
           1,ATEST(7,82),TACK(100)
2           COMMON SO2,ZO2,A,CZO2,B,X,CPO2,K
3           CALL SEARCH(8,185)
4           NA=1
5           LL=0
        C LLIS NO OF RILEYS
6          24 READ(2,21) NODOG,NOQ
7          21 FORMAT(4X,I2,3X,I2)
8             WRITE(1,29) NODOG,NOQ
9          29 FORMAT(9H DOG NO =,I2,2X,6HQ NO =,I2)
        C  DG=1 IF READINGS ARE FROM A DOG, 0 IF FROM A HUMAN
10            READ(2,300) IWAVE,EIRAT,IBLOK,CO,ETIME,STIME,PATR,POES
11         300 FORMAT(I1,F3.1,I1,F4.2,4F5.2)
12            READ(2,1)DG,PB,RMTMP,PTTMP,VOL,XNOBR,TIME,HR,VDAPP,VC
13            READ(2,1)PTWT,PX,XICE,PEO2,PECO2,PIO2,RPAO2,DTPAO,RPACO,DTPAC
14            READ(2,1)RPHA,DTPHA,RPVO2,DTPVO,RPVCO,DTPVC,RPHV,DTPHV,HT
15            MI=INTF(ETIME)
16            NI=INTF(STIME)
17            WA=ETIME-MI
18            WB=STIME-NI
19            IF(WA-WB) 222,301,301
20         222 WA=WA+.6
21            NI=NI+1
22         301 HRS=WA-WB+MI-NI
23            RPAO2=RPAO2*1.04
24            RPVO2=RPVO2*1.04
        C 'CORRECT FOR HEPARIN
25            RPAO2=RPAO2*1.00408-.6118
26            RPVO2=RPVO2*1.00408-.6118
27            IF(PIO2.NE.0.0)801,
28            PIO2=.20946*(PB-47.0)
29            1 FORMAT(10(F7.3))
30         801 PX=PX*.73554
```

Fig. 3(c):6 (i)

```
30        801 PX=PX*.73554
31            T(1)=1.3
32            T(2)=1.34
33            T(3)=1.39
34            VT=VOL/XNOBR
35            VTCOR=VT-VC/1000.0*PX/PB
36            F=60.0*XNOBR/TIME
37            Y=(PB-1.2106*RMTMP+6.7272)/(1+.00367*RMTMP)
38            VEATP=F*VTCOR
39            VESTP=Y*VEATP/760
40            VEBTP=Y*VEATP*(1+.00367*PTTMP)/(PB-2.454*PTTMP+43.43)
41            VTBTP=1000*VEBTP/F
          C CORRECT READ VALUES OF PE02 AND PEC02
42            PE02=PE02*VT/VTCOR
43            PEC02=PEC02*VT/VTCOR
44            FILLY=(PI02-PE02)/PEC02
45            Z=PB-47
46            FE02=PE02/Z
47            FI02=PI02/Z
48            FEC02=PEC02/Z
49            V02ST=1000*VESTP*(FI02*(1-FE02-FEC02)/(1-FI02)-FE02)
50            VC02S=VESTP*FEC02*1000
51            R=VC02S/V02ST
52            IF(PTWT.EQ.0.0)600,
53            VV02S=V02ST/PTWT
54            VVC02=VC02S/PTWT
55        600 DO 11 I=1,3
56            CAPAC=T(I)*HB
57            CALL CORR(DTPAO,ZDTPA,DTPAC,DTPHA,XICE,RPACO,PACO2,RPHA,CPHA,PTTMP
             1,TPACO,PHA)
58            CALL CORR(DTPVO,ZDTPV,DTPVC,DTPHV,XICE,RPVCO,PVCO2,RPHV,CPHV,PTTMP
             1,TPVCO,PHV)
59            CALL POCOR(RPAO2,PAO2,PACO2,PHA,CAPAC,DG,PTTMP,ZDTPA,TPAO2)
60            CALL POCOR(RPVO2,PVO2,PVCO2,PHV,CAPAC,DG,PTTMP,ZDTPV,TPVO2)
```

Fig. 3(c): (contd.)

```
60          CALL POCOR(RPVO2,PVO2,PVCO2,PHV,CAPAC,DG,PTTMP,ZDTPV,TPVO2)
61          CALL SATCO(PAO2,PACO2,PHA,    SAO2,CAC2,CAPAC, DG,PTTMP,1,TPAO2)
62          CALL SATCO(PVO2,PVCO2,PHV,    SVO2,CVC2,CAPAC, DG,PTTMP,1,TPVO2)
63          ALPHA=.0059519-.0001266*PTTMP+.0000013*PTTMP**2
        C CALCULATE PAAO2 APPROXIMATELY TO GET SAAO2 WHICH IS THEN USED TO GET A     BETTER
        C VALUE FOR PAAO2 AND THEN SAAO2
64          PAAO2=PIO2-FILLY*PACO2
65          PAAOA=PAAO2
66          ZP=CAO2-CVO2
67          QT=VO2ST/(10*(CAO2-CVO2))
68        254 TEST=PAAO2
69          CALL SATCO(PAAO2,PACO2,PHA,    SAAO2,CCO2,CAPAC, DG,PTTMP,1,PAAO2)
70          SAAO2=SAAO2/100.0
71          PAAO2=(PIO2*(CAO2-CVO2)+FILLY*SAAO2*CAPAC*(TPVCO-TPACO)+FILLY*(CVO
           12*TPACO-TPVCO*CAO2))/(CAO2-CVO2+ALPHA*FILLY*(TPACO-TPVCO))
72          IF(ABSF(PAAO2-TEST).GT..05) 254,
73          TEST1=0
74          VDD=VTBTP*(1-PECO2/TPACO)-VDAPP
75        251 TEST2=VDD
76          VDBVT=1-1/((TPACO/PECO2)-VTBTP*VDAPP/((VTBTP-VDD)*(VTBTP-VDD-VDAPP
           1)))
77          VDD=VTBTP*VDBVT-VDAPP
78          IF(ABSF(VDBVT-TEST1).LE..0005 .AND. ABSF(VDD-TEST2).LE..05) 250,
79          TEST1=VDBVT
80          GOTO 251
81        250 PAACO=PECO2/(1-VDBVT)
82          SAO2=SAO2/100.0
83          SVO2=SVO2/100.0
84          DO 111 J=1,2
85          CALL SATCO(PAAO2,TPACO,CPHA(J),SAAO2,CCO2,CAPAC, DG,PTTMP,0,PAAO2)
86          SAAO2=SAAO2/100.0
87          QSBQT=(CCO2-CAO2)/(CCO2-CVO2)
88          ZK=PAAO2-TPAO2
89          CALL CO2CT(PTTMP,CPHA(J),TPACO,HT,SAO2,CACO2)
90          CALL CO2CT(PTTMP,CPHV(J),TPVCO,HT,SVO2,CVCO2)
```

Fig. 3(c):6 (...)

```
 91            CALL CO2CT(PTTMP,CPHA(J),PAACO,HT,SAAO2,CCCO2)
 92            XL=CVCO2-CACO2
 93            QSOQT=(CACO2-CCCO2)/(CVCO2-CCCO2)
 94            QTCO2=VCO2S/(10*(CVQO2-CACO2))
 95            QTMN=(QTCO2+QT)/2.0
 96            IF(PTWT.EQ.0.0) 802,
 97            QTX=QT*1000/PTWT
 98            QTXCO=QTCO2*1000/PTWT
 99            QTXMN=(QTX+QTXCO)/2.0
100            COX=CO*1000/PTWT
101        111 CONTINUE
102        802 VDVTP=1-PECO2/TPACO
103            PPCO2=TPACO-PAACO
104            VDBTP=VTBTP*VDBVT
105            VAA=F*(VTBTP-VDBTP)/1000
106            SA(1,I)=TPAO2
107            SA(2,I)=PAAO2
108            SA(3,I)=QSBQT
109            SA(4,I)=QSOQT
110            SA(5,I)=CAO2
111            SA(6,I)=CVO2
112            SA(7,I)=CCO2
113            SA(8,I)=QT
114            SA(9,I)=QTCO2
115            SA(10,I)=CCCO2
116            SA(11,I)=PAO2
117            SA(12,I)=PVO2
118            SA(13,I)=TPVO2
119            SA(14,I)=SAO2
120            SA(15,I)=SVO2
```

Fig. 3(c):6 (iv)

```
121           SA(16,I)=SAAO2
122           SA(17,I)=CACO2
123           SA(18,I)=CVCO2
124        11 CONTINUE
125           SB(1)=TPACO
126           SB(2)=TPVCO
127           SB(3)=CPHA(1)
128           SB(4)=CPHV(1)
129           SB(5)=PX
130           SB(6)=PEO2
131           SB(7)=PECO2
132           SB(8)=PIO2
133           SB(9)=VO2ST
134           SB(10)=VCO2S
135           SB(11)=VEBTP
136           SB(12)=FILLY
137           SB(13)=PTWT
138           SB(14)=IWAVE
139           SB(15)=EIRAT
140           SB(16)=IBLOK
141           SB(17)=CO
142           SB(18)=HRS
143           SB(19)=NODOG
144           SB(20)=PTTMP
145           SB(21)=VTBTP
146           SB(22)=PAIR
147           SB(23)=POES
148           SB(24)=VDBVT
149           SB(25)=VAA
150           SB(26)=VDD
```

Fig. 3(c):6 (v)

```
151           SB(27)=PAACO
152           SB(28)=VDVTP
153           SB(29)=PAAOA
154           IM=0
155           DO 4 II=1,18
156           DO 4 I=1,3
157           IM=IM+1
158         4 TACK(IM)=SA(II,I)
159           DO 5 I=1,29
160           IM=IM+1
161         5 TACK(IM)=SB(I)
162           WRITE(8) (TACK(I),I=1,83)
163           LL=LL+1
164           READ(2,3)J
165         3 FORMAT(I1)
      C IF J=0 THERE IS MORE DATA ELSE THERE IS NOT
166           IF(J.EQ.0) 24,
167           CALL SEARCH(8,185)
168           DO 7 I=1,7
169         7 READ (8) (ATEST(I,J),J=1,83)
170           WRITE(1,6) ((ATEST(I,J),J=82,83),I=1,7)
171         6 FORMAT(14F9.3)
172           CALL EXIT
173           END
```

Fig. 3(c):6 (vi)

```
LINE                                    ATLAS  FORTRAN                    29/06/71          VERSION 7
NUMBER                                  SOURCE ROUTINE LISTING            19.27.29     COUNTER=     1035
                                                                                      LABEL FIELD
    1           SUBROUTINE CORR(DTPO2,ZDTPO,DTPCO,DTPH,XICE,RPCO2,PCO2,RPH,CPH,
               1PTTMP,TPCO,PH)
          C CORRECTS DELAY TIMES AND PH AND PCO2 FOR DELAY TIME AND PATIENTS TEMP
    2           DIMENSION CPH(2)
    3           ZDTPO=DTPO2
    4           ZDTPC=DTPCO
    5           ZDTPH=DTPH
    6           IF(XICE.EQ.0.0) 1,
    7           ZDTPO=ZDTPO/10.0
    8           ZDTPC=ZDTPC/10.0
    9           ZDTPH=ZDTPH/10.0
          C CORRECT FOR DELAY TIMES
   10         1 PCO2=RPCO2-.1*ZDTPC
   11           PH=RPH+.00094*ZDTPH
          C CORRECT FOR PATIENTS TEMP
   12           TPCO=PCO2*10**(.021*(PTTMP-37.0))
   13           PGPRO=ALOG10(PCO2*10**.021)
   14           CPH(1)=PH-(.01963-.003038*PGPRO)*(PTTMP-37.0)
   15           CPH(2)=PH-.0147*(PTTMP-37.0)
   16           RETURN
   17           END
```

Fig. 3(c):6 (vii)

```
LINE                                    ATLAS  FORTRAN                          29/06/71        VERSION 7
NUMBER                                SOURCE ROUTINE LISTING                    19.27.32    COUNTER=     1130
                                                                                          LABEL FIELD
    1          SUBROUTINE SATCO(PO2,PCO2,PH,SO2,CO2,CAPAC,NG,PTTMP,IA,TPO2)
    2          IF(DG.EQ.1.0) 2,
    3          XDASH=PO2/10*10**(.4*(PH-7.4)+.06*(ALOG10(40.0)-ALOG10(PCO2)))
    4          IF(IA.GT.0) 680,
    5          XDASH=XDASH*10**(.024*(37.0-PTTMP))
    6      680 SO2=100*XDASH*(XDASH*(XDASH*(XDASH-6.7074)+21.214)-8.53223)  /(XDA
              1SH*(XDASH*(XDASH*(XDASH-6.71044)+23.9617)-31.3463)+93.5961)
    7          GOTO 3
    8        2 PT=PTTMP
    9          IF(IA.EQ.0) 1,
   10          PT=37
   11        1 ZZ=10.0**(2.5198*ALOG10(PO2)+1.1804*(PH-7.0)-2.3621-.047234*PT)
   12          SO2=100.0*ZZ/(1.0+ZZ)
   13        3 ALPHA=.0059519-.0001266*PTTMP+.0000013*PTTMP**2
   14          CO2=ALPHA*TPO2+CAPAC*SO2/100.0
   15          RETURN
   16          END
```

Fig. 3(c):6 (viii)

```
      SUBROUTINEPOCOR(RPO2,PO2,PCO2,PH,   CAPAC,DG,PTTMP,ZDTPO,TPO2)
      COMMON SO2,ZO2,A,CZO2,B,X,CPO2,K
C :CORRECTS PO2 FOR DELAY TIME, HEPARIN AND PATIENTS TEMP
C :CORRECT FOR DELAY TIME
      CALL SATCO(RPO2,PCO2,PH,    SO2,ZO2,CAPAC,DG,PTTMP,1,RPO2)
      ZO2=ZO2+.00794*ZDTPO
      DO 400 I=1,761,20
      A=I
      CALL SATCO(A,PCO2,PH,    SO2,CZO2,CAPAC,DG,PTTMP,1,A)
      IF(ZO2.LE.CZO2)402,
  400 CONTINUE
  402 K=I-20
      DO403 JJ=K,I
      B=JJ
      CALL SATCO(B,PCO2,PH,    SO2,CZO2,CAPAC,DG,PTTMP,1,B)
      IF(ZO2.LE.CZO2)404,
  403 CONTINUE
  404 DO 406 I=1,11
      X=B-1.0+(I-1)/10.0
      CALL SATCO(X,PCO2,PH,    SO2,CZO2,CAPAC,DG,PTTMP,1,X)
      IF(ZO2.LE.CZO2)405,
  406 CONTINUE
  405 PO2=X
C :CORRECT FOR PATIENTS TEMP
      CALL SATCO(PO2,PCO2,PH,    SO2,ZO2,CAPAC,DG,PTTMP,1,PO2)
      SO2=SO2/100.0
      TPO2   =PO2*10**((PTTMP-37.0)*(.0052+.0268*(1-EXP(-30*(1-SO2)))))
      RETURN
      END
```

Fig. 3(c):6 (ix)

CHAPTER

3(d)

EXPERIMENTAL DESIGN AND STATISTICS

CHAPTER 3(d)

EXPERIMENTAL DESIGN AND STATISTICS

Examination of previous studies in this field made it clear that, although there have been studies of different flow waveforms and studies of changing I;E ratios, with one exception (Watson 1961) there has been no attempt to assess the synergistic* effect of different flow patterns and I:E ratios on respiratory and cardio-vascular physiology. Watson's work (1961) was not, however, analysed with this synergism* in mind. The series of observations described was arranged so that factorial design analysis (Snedecor and Cochran 1967, p.339 and Cooper 1969, p.144) could be applied to the results.

The factorial design was usually of an m x n type where m is 3 or 4 waveforms and n is 3, 4 or 5 I:E ratios depending on the particular experiment. On one occasion an m x n x o type was used where m is 5 I:E ratios, n is 2 wave patterns and o is 2 different drug states. Factorial design analysis should:-

1. smooth out the effects of background variables which are not important in the experiment, such as dog type, weight, state of health, susceptibility to drugs, etc.

2. use a wide range of factor combinations to provide a more reliable basis for making practical recommendations.

3. obtain as much information about each factor from a single experiment as if the whole experiment were devoted only to that factor.

4. collect information about the nature of interactions between different factors.

5. allow for missing factors without invalidating

* Statistical synergism may be defined as the additional effect of one factor upon another factor at different levels of the second factor. (Snedecor and Cochran 1967, p. 341)

the statistical tests. In this series of experiments there were certain missing factors, approximately one in each experiment. For this reason a "missing plot" factorial design analysis was used (Cooper 1969, p.149). This type of factorial design analysis applies a detailed analysis of variance to all the groups of results under study as well as to their interactions. The value of each missing plot was estimated by minimising the residual sum of squares, and was then incorporated in the design with one less degree of freedom.

Other statistical tests were performed on the experimental data when appropriate. The data were tested for normality of distribution by the chi-squared method (Cooper, p.78) and by display on normal probability paper as a first approximation (Fig 3(c):1). These tests confirmed that the data processed were from a normal population distribution and that the statistical tests were valid. Paired t-tests (Snedecor and Cochran 1967, p.102) were performed during the factorial analysis and on sections of the data, particularly on the series of replicates and on those where a straight line of best fit was involved (Snedecor and Cochran 1967, p.147). Where applicable, the F-test was used to confirm that the "best fit" for the data tested was linear (Snedecor and Cochran 1967, p.147). Where one group of data was compared with another, the fact that the variances were similar was established by means of another F-test (Snedecor and Cochran 1967, p.116).

Most of the statistical analysis was performed on the S.R.C. Atlas Computer at Harwell, England, either with statistical programs in use at the establishment or by programs prepared by Mrs. A. Kosniowska of the Nuffield Department of Anaesthetics, University of Oxford.

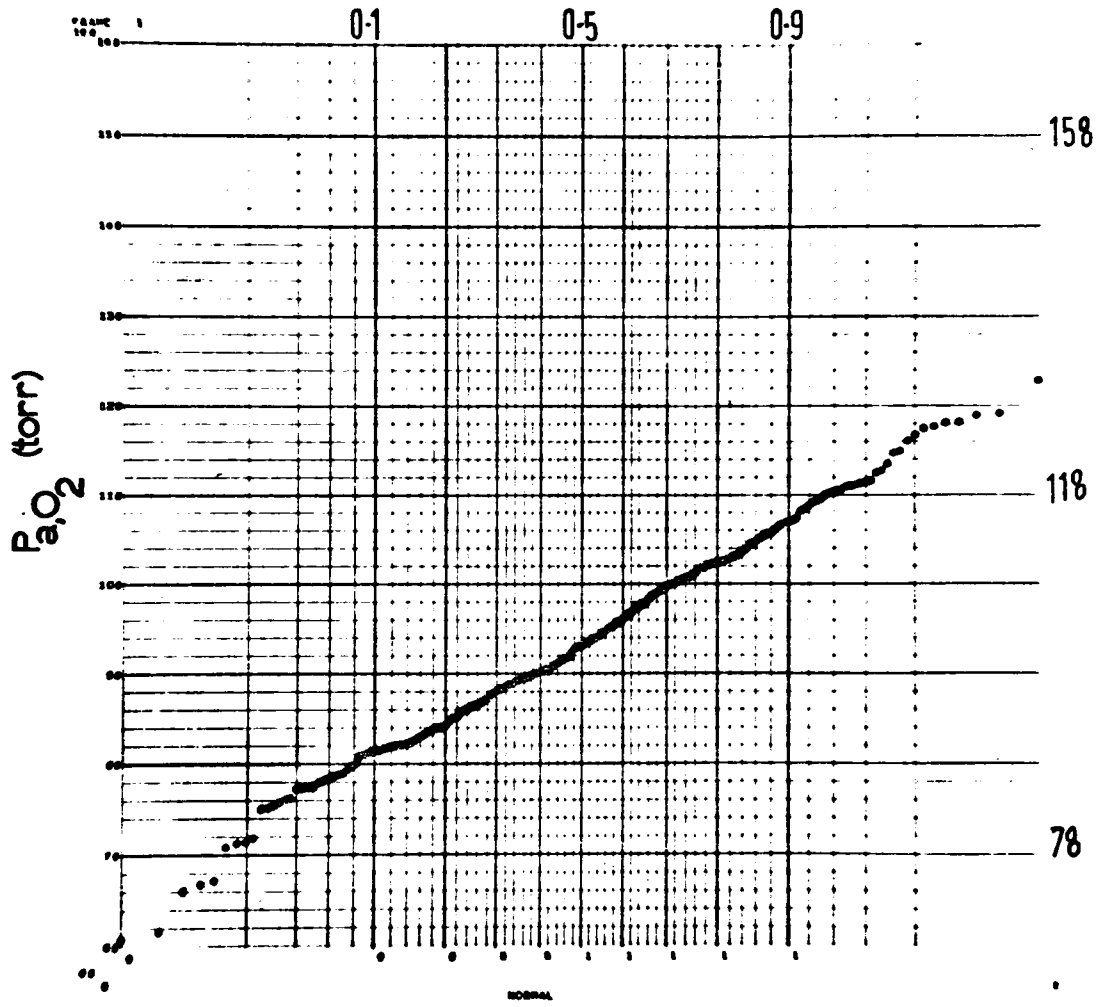


Fig. 3(d):1 Example of a normality plot as a quick check for the normal distribution of the experimental data.

The factorial design analysis was calculated on an Orion Computer at Rothampstead Agricultural Station, Harpenden, England, by Mr. H. Simpson who originally described this particular form of analysis.

The design of the physiological experiments fulfilled the criteria for factorial analysis, and consisted of at least one reading of each measured variable at each flow waveform and I:E ratio. The waveforms were selected randomly and the I:E ratios were systematically increased for that waveform from 0.5 - 2.2 sec inspiratory time in a cycle time of 4.0 sec. Three types of experiment were undertaken - a small series to evaluate the techniques, a series to investigate the effects of inspiratory flow characteristics in the normal animal, and a series to investigate the effects where the animal's autonomic system was pharmacologically blocked. The results were then analysed as follows:-

Series 1. Dogs 5, 6, 8: a 3 x 3 factorial design with replicates. The waveforms were ramp, sine and tophat with inspiratory times of 0.67, 1.33 and 2.0 sec duration.

Series 2. Dogs 9, 10: a 3 x 3 factorial design with replicates. The waveforms were ramp, sine and tophat with inspiratory times of 0.67, 1.0 and 2.0 sec duration.

These two experiments were performed to test the validity of the techniques used in the physiological conditions of an experiment. The linear correlations of the replicates of measured variables are shown in Table 3(d):1.

Series 3. Dogs 11, 12; a 3 x 4 factorial design. The waveforms were ramp, sine and tophat with inspiratory times of 0.67, 1.0, 2.0 and 2.2 sec duration.

Series 4. Dogs 11, 12, 13, 14, 15, 18, 19, 20: a 4 x 4

TABLE 3 (d) : 1

Variable	Linear Correlation Coefficient
P_{a,O_2}	0.890
$P_{\bar{v},O_2}$	0.927
P_{a,CO_2}	0.930
$P_{\bar{v},CO_2}$	0.922
pH_a	0.946
$pH_{\bar{v}}$	0.908
$\dot{Q}_F$	0.900
$\dot{Q}_D$	0.952
P_{air}	0.867
P_{oes}	0.977
C_T	0.981
C_{C-W}	0.949
Heart rate	0.921

Table: Linear correlation coefficients for the measured physiological variables in the replicate experiments. Cardiac output calculated by the direct Fick method has also been included though this is not a directly measured variable.

factorial design. The waveforms were reversed ramp, ramp, sine and tophat with inspiratory times of 0.67, 1.0, 2.0 and 2.2 sec duration.

Series 5. Dogs 11, 12, 13, 14, 15, 18, 19, 20: a 4 x 5 factorial design. The waveforms were reversed ramp, ramp, sine and tophat with inspiratory times of 0.5, 0.67, 1.0, 2.0 and 2.2 sec duration.

Series 6. Dogs 13, 14, 15, 18, 19, 20: a 4 x 5 factorial design. The waveforms were reversed ramp, ramp, sine and tophat with inspiratory times of 0.5, 0.67, 1.0, 2.0 and 2.2 sec duration.

Series 3, 4, 5 and 6 were used to assess the accuracy of missing plot factorial analysis, and to investigate the basic physiological changes occurring with different inspiratory flow patterns.

Series 7. Dogs 24, 27, 28, 29, 30, 31, 32: a 5 x 2 x 2 factorial design. The waveforms were sine and tophat with inspiratory times of 0.5, 0.67, 1.0, 2.0 and 2.2 sec duration. Observations were made before and after pharmacological blockade of the autonomic nervous system, and the experiment was designed to assess the physiological effects of the variation in inspiratory flow when the animal's autonomic nervous system was depressed.

CHAPTER

4

AN ANALOGUE STUDY OF CONTROLLED VENTILATION

CHAPTER

4

AN ANALOGUE STUDY OF CONTROLLED VENTILATION

Many electrical analogues of the process of respiration have been described (Clements et al. 1959; van den Berg 1960; Campbell and Brown 1963; Mead and Milic-Emili 1964; Rattenborg and Holaday 1966; Wald et al, 1968) since Otis et al. (1956) and Dubois et al. (1956) first used electrical models to simulate normal thoracic mechanics. The most comprehensive of these is that described by Mead and Milic-Emili (1964). There are, however, only three descriptions of the application of electrical analogues to the study of artificial ventilation (Campbell and Brown 1963; Wald et al, 1968; Jain and Guha 1970) These authors used very simple analogues and each study has certain deficiencies.

The present study is of the effects of artificial ventilation on respiratory mechanics and there has been no attempt to include a cardiovascular component in the analogue. The cardiovascular system is, however, probably affected in two ways by artificial ventilation. The subatmospheric phase of the intrathoracic pressure in normal spontaneous inspiration is believed to assist venous return to the heart (Werkö 1947) and this effect is absent in artificial ventilation if the patient expires to atmosphere. In certain circumstances this can lead to a reduction in cardiac output of sufficient proportions to require a subatmospheric pressure to be applied during the expiratory phase of ventilation (Maloney et al. 1953). The peak alveolar pressures reached may cause lung capillary closure because the alveolar pressure exceeds the pulmonary artery pressure (West et al. 1964). Thus the mean intrathoracic pressure, and peak and mean alveolar

pressures may have important effects on cardiovascular function during I.P.P.V.

The Electrical Analogue.

The lung analogue shown in Fig. 4:1 was used in this study. It represents the tracheal and bronchial airways resistances together with lung and chest wall compliances and chest wall resistance using values which were obtained from Mead and Milic-Emili (1964).

The validity of results from an electrical circuit used as a lung/thorax analogue may be questioned on several grounds. The analogue is linear, but Rohrer (1915 and 1916), Otis et al. (1950), Jaeger and Matthys (1968) and Pedley et al. (1970 a and b) have all shown that the lung/thorax system is not linear. This alinearity would be very difficult to represent electrically as it would be necessary to include a resistance which altered with current in a very complex fashion. The analogue is lumped but gas is compressible and bronchial walls are elastic so the system is distributed. The analogue is determined but all respiratory characteristics alter continuously during a single breath. The analogue is time invariant; hysteresis in a single breath may be simulated (Baker 1971), but the long-term effects of hysteresis are more difficult to represent. These imperfections have, however, been accepted by Mead and Milic-Emili (1964) as reasonable in an analogue study of the lung. Other sources of error include the inertance of a patient subjected to I.P.P.V., but this is less than that of a spontaneously breathing normal subject because an endotracheal tube reduces the turbulence caused by flow over the larynx, and has been ignored. The gas compression effect, not encountered in spontaneous respiration, and the effect of expansion of the inspired gas, due to an increase in temperature, are not simulated by the analogue

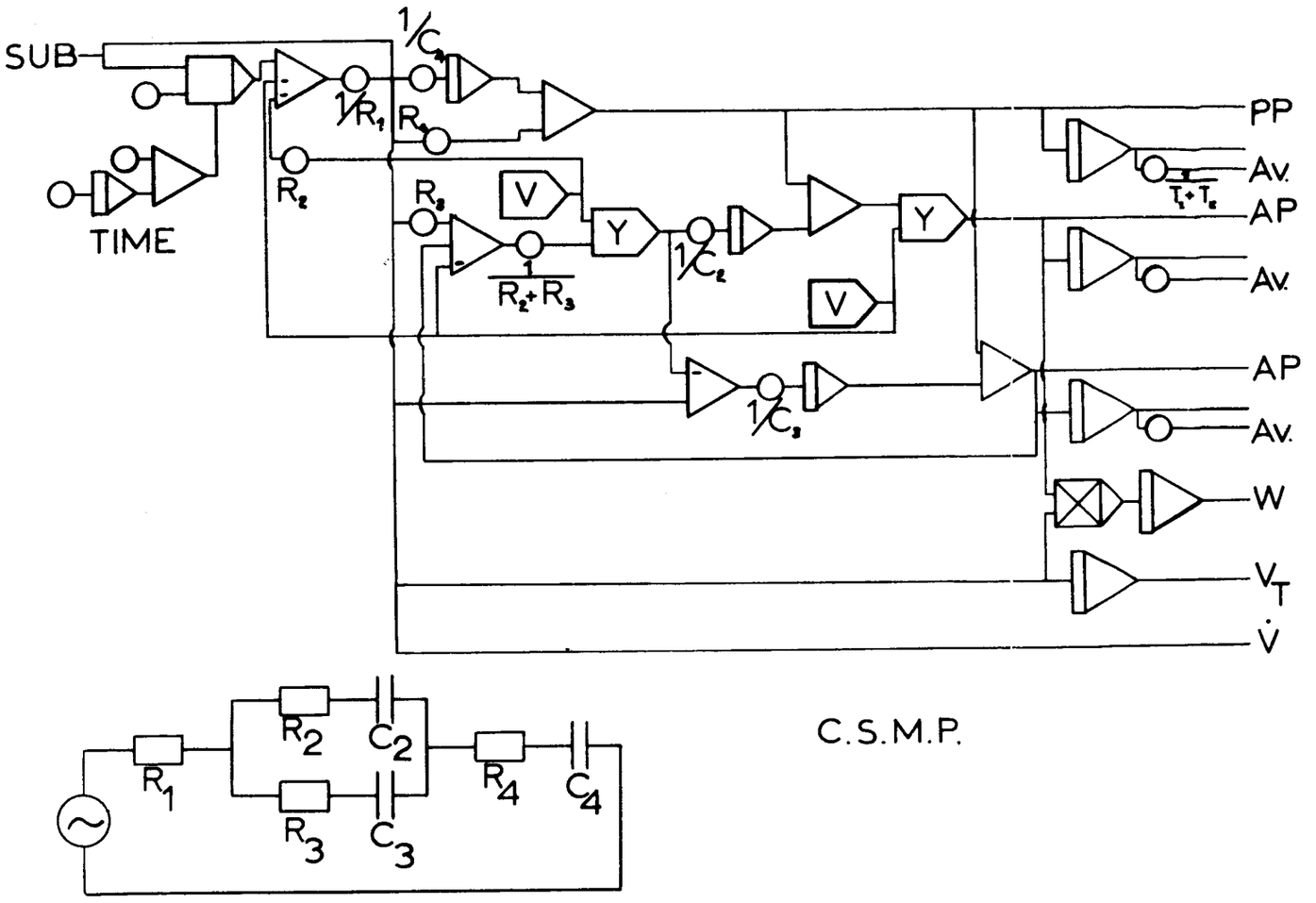


Fig. 4:1 Electrical analogue of the lung/thorax system. R_1 = 1.5 cm H_2O l^{-1} sec^{-1}; R_2 and R_3 = 0.4 cm H_2O l^{-1} sec^{-1}; C_2 and C_3 = 100 ml/cm H_2O; R_4 = 1.0 cm H_2O l^{-1} sec^{-1}; C_4 = 200 ml/cm H_2O. Alveolar pressure is measured at a point between R_2 and C_2 or R_3 and C_3, and pleural pressure is measured at a point between C_2 and R_4 or C_3 and R_4. Also shown is a block diagram of the C.S.M.P. program where sub = special input waveform; time = time control; PP = pleural pressure; AP = alveolar pressure; Av. = average pleural or alveolar pressure as the case may be; W = work; V_T = tidal volume; V = flow.

but the effects are small. The true inspired volume is 1.056 to 0.992 of the apparent volume for inspiratory pressures of 1 - 50 torr and changes of temperature from 17°C to 37°C.

The model was tested by passing an electrical signal across the analogue from a variable waveform signal generator (Servomex Waveform Generator LF141, Crowborough, Sussex, U.K.) and by recording voltages from selected points in the circuit. In addition a mathematical analysis of the analogue was performed by Mr. C.E.W. Hahn using the Laplace transform method (Jaeger and Newstead 1969). This analysis was embodied in a program for a KDF 9 computer so that results could be expressed in analogue form by a graph plotter. A further hybrid program was written by the author using C.S.M.P. (Continuous System Modeling Program) and an IBM 1130 digital computer. Results obtained from the three methods were compared and agreed well (Fig. 4:2) and it seemed important to compare the methods to exclude errors as far as possible. A true analogue computer was not available to the author so experiments with the electrical analogue were analysed by means of the hybrid program referred to above. This system was used to assess the effects of various inspiratory flow waveforms on some indices of respiratory mechanics. The waveforms chosen are illustrated in Fig. 4:3 and the indices measured were peak alveolar and pleural pressures, mean alveolar and pleural pressures and inspiratory work. Peak alveolar pressure was used as an indication of the degree of obstruction to lung capillary blood flow, and mean alveolar and pleural pressures as an indication ofthe forces acting on the venous return to the heart. The frequency of respiration was held constant at 15 breaths/min in all the experiments, and within a respiratory cycle I:E ratios were varied from 1:7 through 1:5, 1:3, 1:1 to 1:0.8.

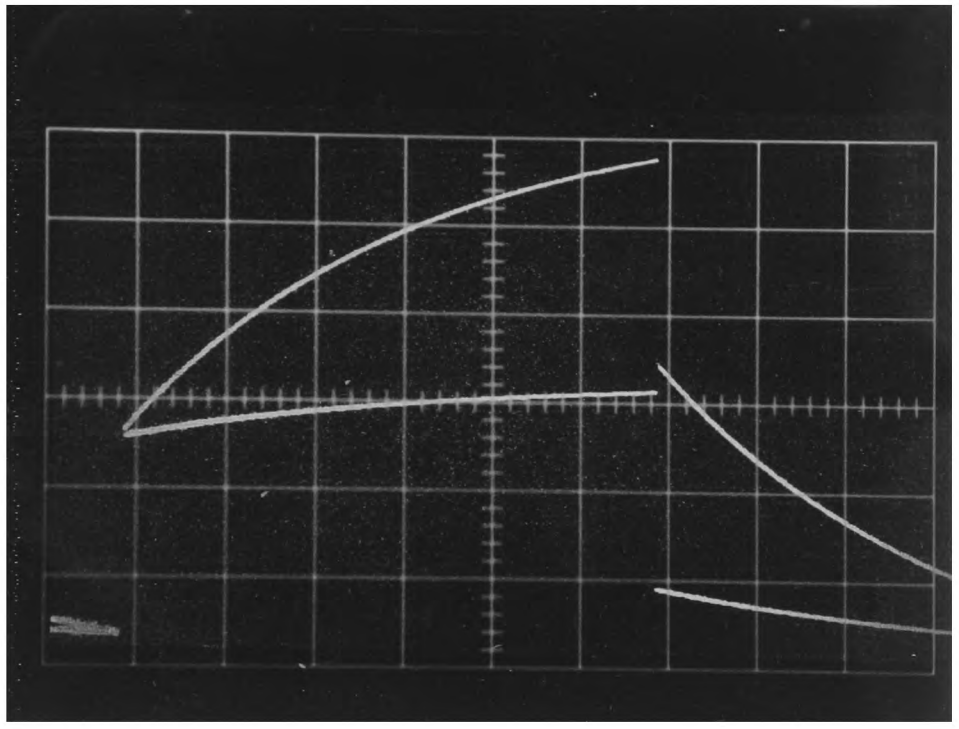


Fig. 4:2(i) Alveolar and pleural pressure responses to a decreasing negative exponential flow, or tophat pressure, wave input on the electrical analogue.

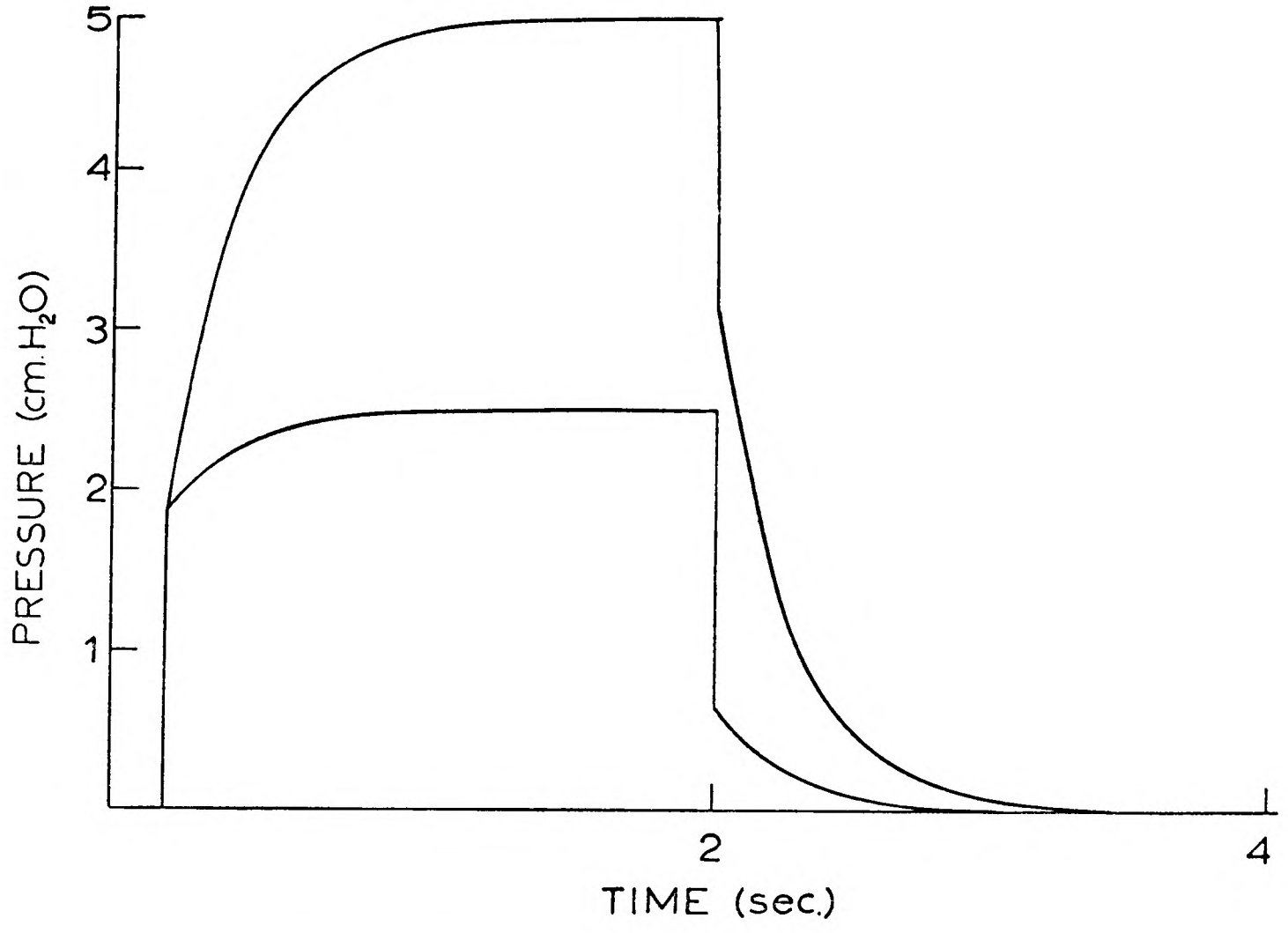


Fig. 4:1(ii) Alveolar and pleural pressure responses to a tophat pressure wave input on the C.S.M.P. computer program of the electrical analogue.

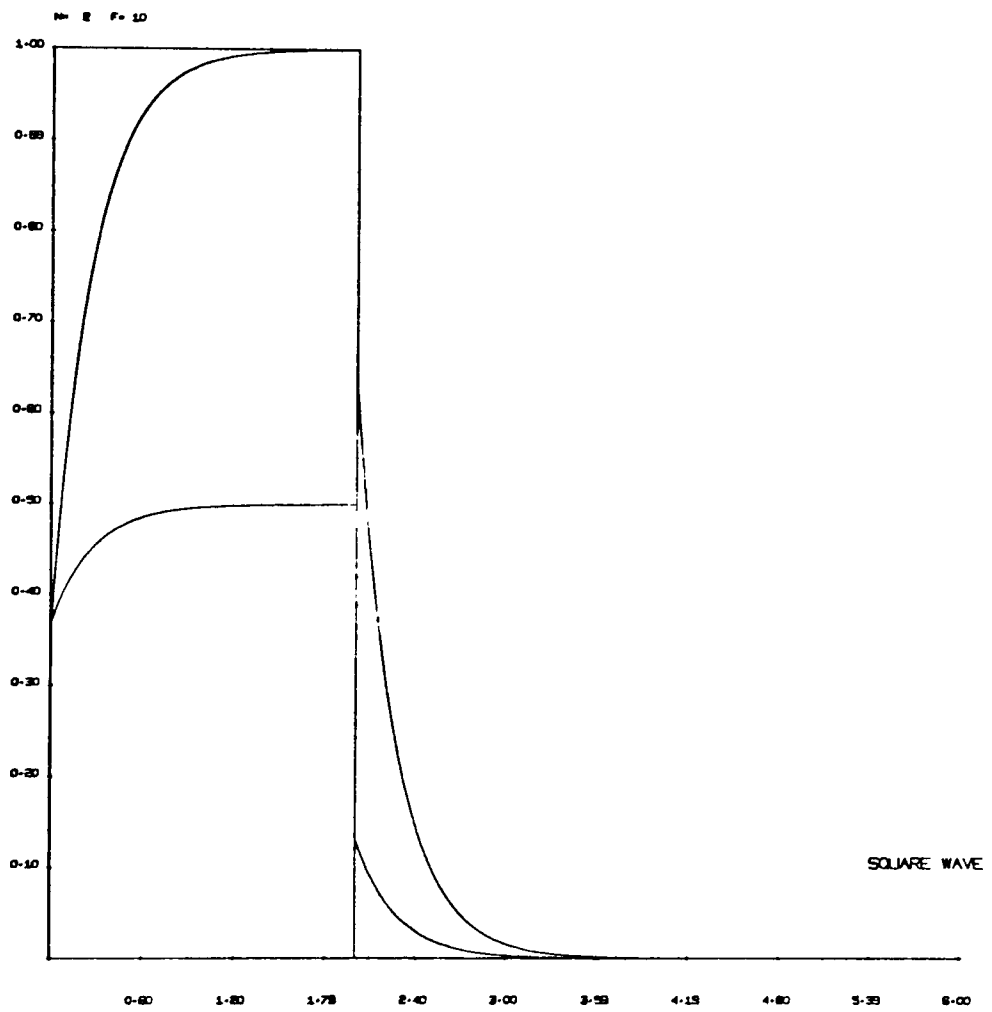
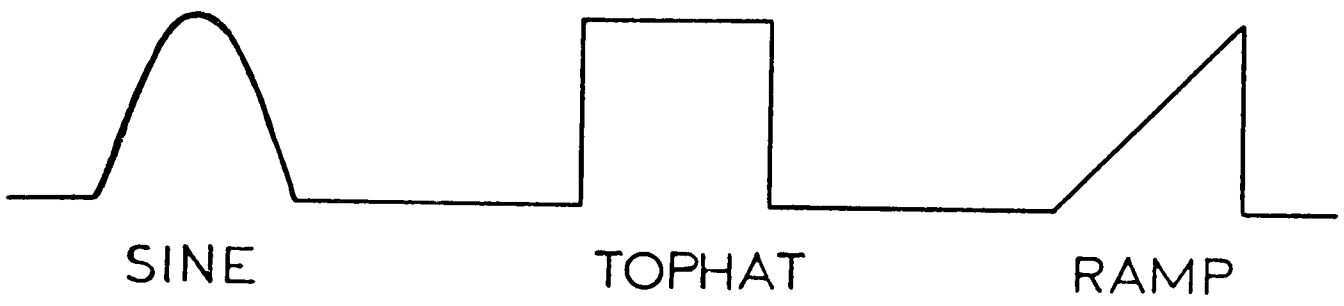


Fig. 4:2(iii) Alveolar and pleural pressure responses to a tophat pressure wave input on the mathematical analogue after processing by a digital computer.



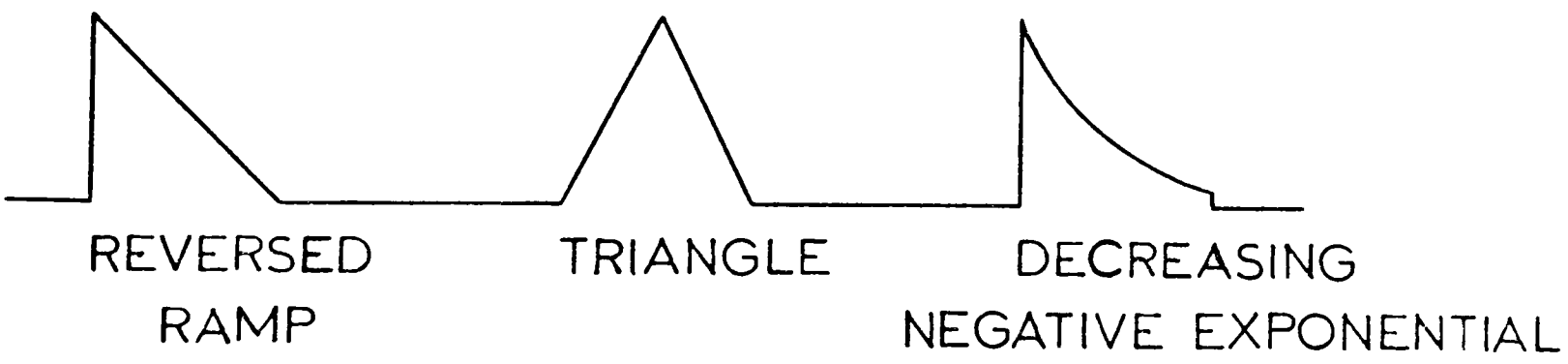


Fig. 4:3 Diagram of the flow waveforms used in the analogue experiments. The flow shapes were the same for the physiological studies where only the reversed ramp, ramp, sine and tophat waveforms were used.

Alveolar Pressure.

Fig. 4:4 shows two electrical circuits which follow Thévenin's theorem (1883). If the voltage at X is taken to represent the alveolar pressure and a constant current is suddenly applied to the circuit the voltage (or alveolar pressure) will rise smoothly from the baseline and no instantaneous step in voltage will occur. I_n the second circuit which includes a second resistance distal to point Y, a current suddenly applied to the circuit will result in an instantaneous step rise in voltage and a similar step in theopposite direction when current stops. These step changes are due to the second resistance and are explained by electrical circuit theory applied to the reactance (or resistance) of a capacitor to a rapidly changing input, according to the equation

$$X_C = \frac{1}{2\pi fC} \text{ ohms} \qquad \text{(Leach 1969)}$$

where X_C = reactance of capacitor, C = capacitance, and f = frequency.

The electrical analogue described includes a resistance distal to the point A at which alveolar pressure is measured and which represents the chest wall resistance. The analogue displayed a step in the voltage representing alveolar pressure followed by a smooth rise to peak pressure when a constant current was suddenly applied. This bears a close relationship to the pressure changes in trachea, oesophagus and pleura in the human patient during I.P.P.V. (Chapter 5 and Baker et al. 1971). This finding may be of importance as it suggests that the true values of peak and mean alveolar pressures are higher than those obtained by body plethysmography (Dubois et al. 1956b). The effect of chest wall resistance on alveolar pressure does not appear in the analogue study by Campbell and Brown (1963) and has been overlooked by Wald et al. (1968). Baker and Hahn (1971) have drawn attention to the fact that Wald et al. (1968) do not give sufficient information

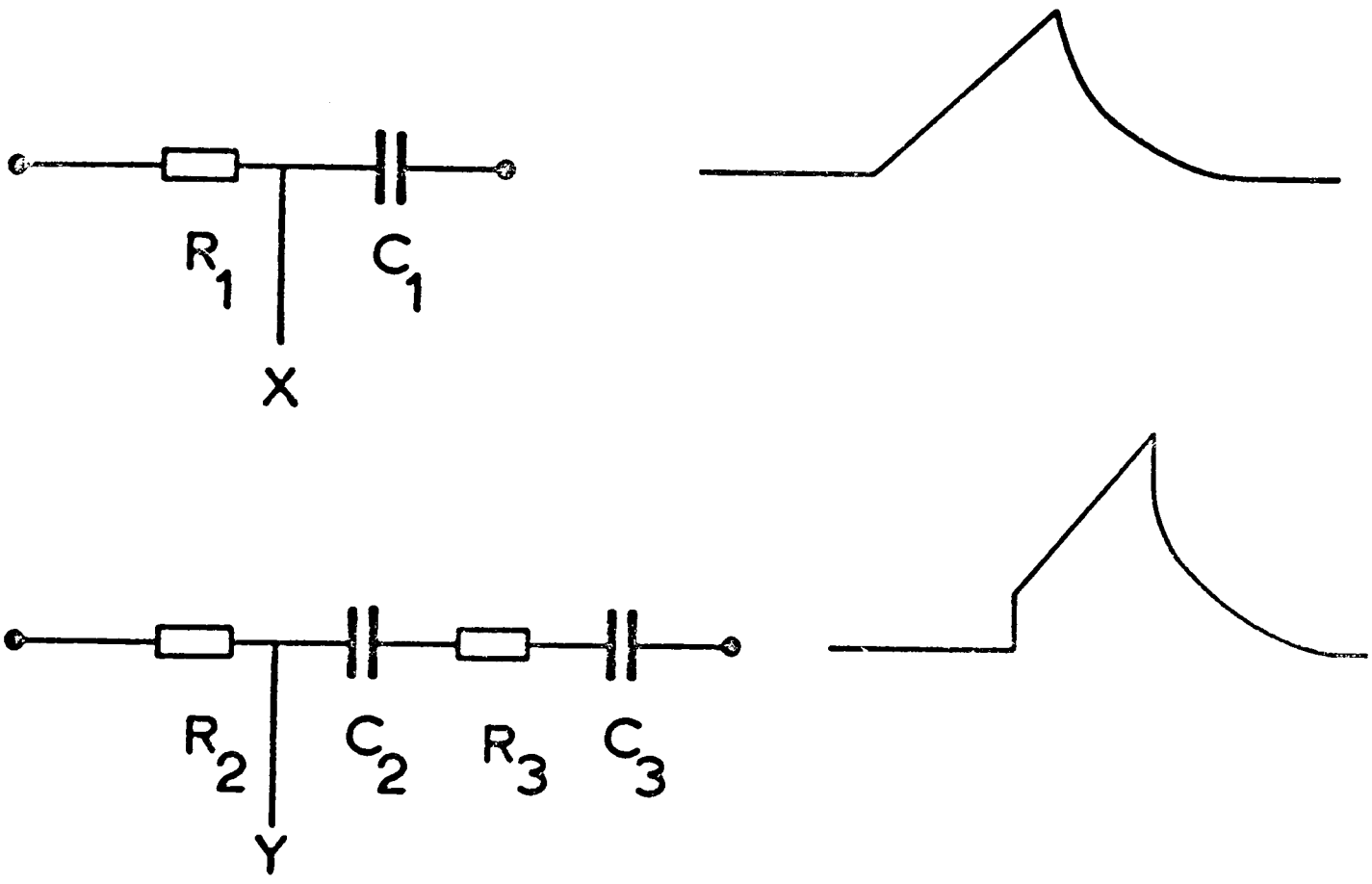


Fig. 4:4 On the left-hand side of the figure are shown two electrical circuits following Thevenin's theorem so that the sum of the resistances and compliances in each circuit is the same. X represents a point at which alveolar pressure might be measured, Y represents a similar point in the other circuit. On the right-hand side of the figure are shown the voltage or "pressure" recordings at X and Y which would be obtained when a constant current or "flow" was passed to the circuits.

in their article to assess the accuracy of their calculation.

The peak alveolar pressure may affect lung capillary closure (see above) and consequently cardiac output and gas transfer across the alveolar capillary membrane. Fig. 4:5 shows the effect on the peak alveolar pressure of shortening inspiratory time with different inspiratory flow waveforms when respiratory frequency and V_D/V_T ratio are held constant. Rather surprisingly, the peak alveolar pressure is not affected by triangular, sine or reversed ramp waveforms when inspiratory time is shortened. The values obtained for peak alveolar pressure from the analogue in circumstances simulating normality are, however, low in comparison to physiological pulmonary artery driving pressures, and may have no effect on lung capillaries.

The mean alveolar and pleural pressures reflect intrathoracic pressure which in turn may obstruct the return of blood to the right heart. Fig. 4:6 shows that the ramp waveform has least effect on mean pressures. Fig. 4:7 shows the relative effects of peak versus $\bar{A}_{mean}$ alveolar pressures. From these relationships it would seem that triangle and sine inspiratory flow waveforms were least upsetting to the cardiovascular system when mean and peak alveolar pressures are used as a critical index.

Work.

Otis et al. (1950), Christie (1953) and Mead (1960) in observations on human subjects found that the work of respiration was least at the frequency of normal resting breathing and this finding was supported by mathematical analysis (Otis et al. 1950; Mead 1960). Proctor and Hardy (1949) and Silverman et al. (1951) have shown that flow patterns become rectangular during exercise and Proctor and Hardy (1949) and Cain and Otis (1949) have reported rectangular flow waveforms following the addition of external

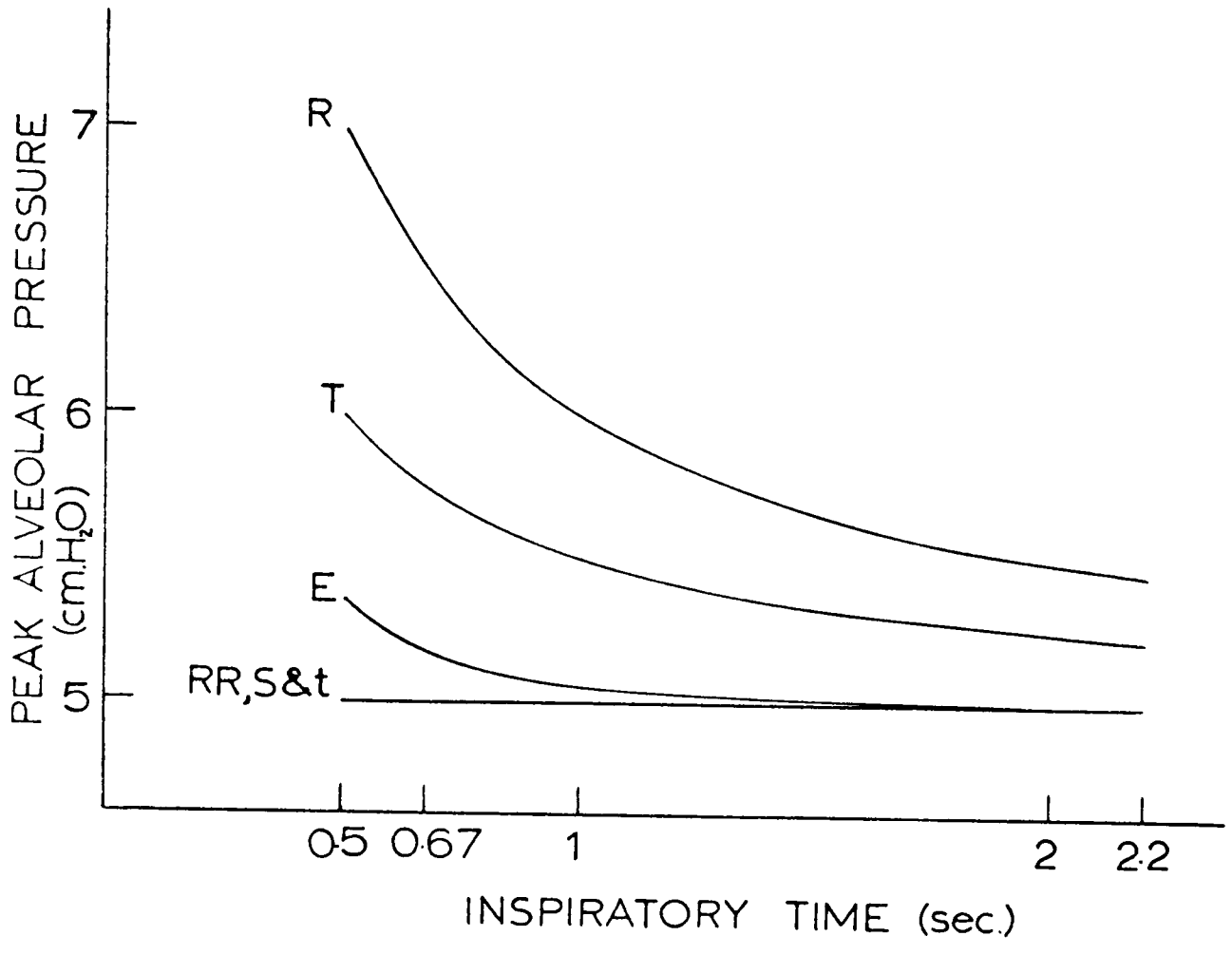


Fig. 4:5 Peak alveolar pressure versus inspiratory time for different inspiratory flow waveforms. RR = reversed ramp; R = ramp; S = sine; T = tophat; t = triangular; E = decreasing negative exponential.

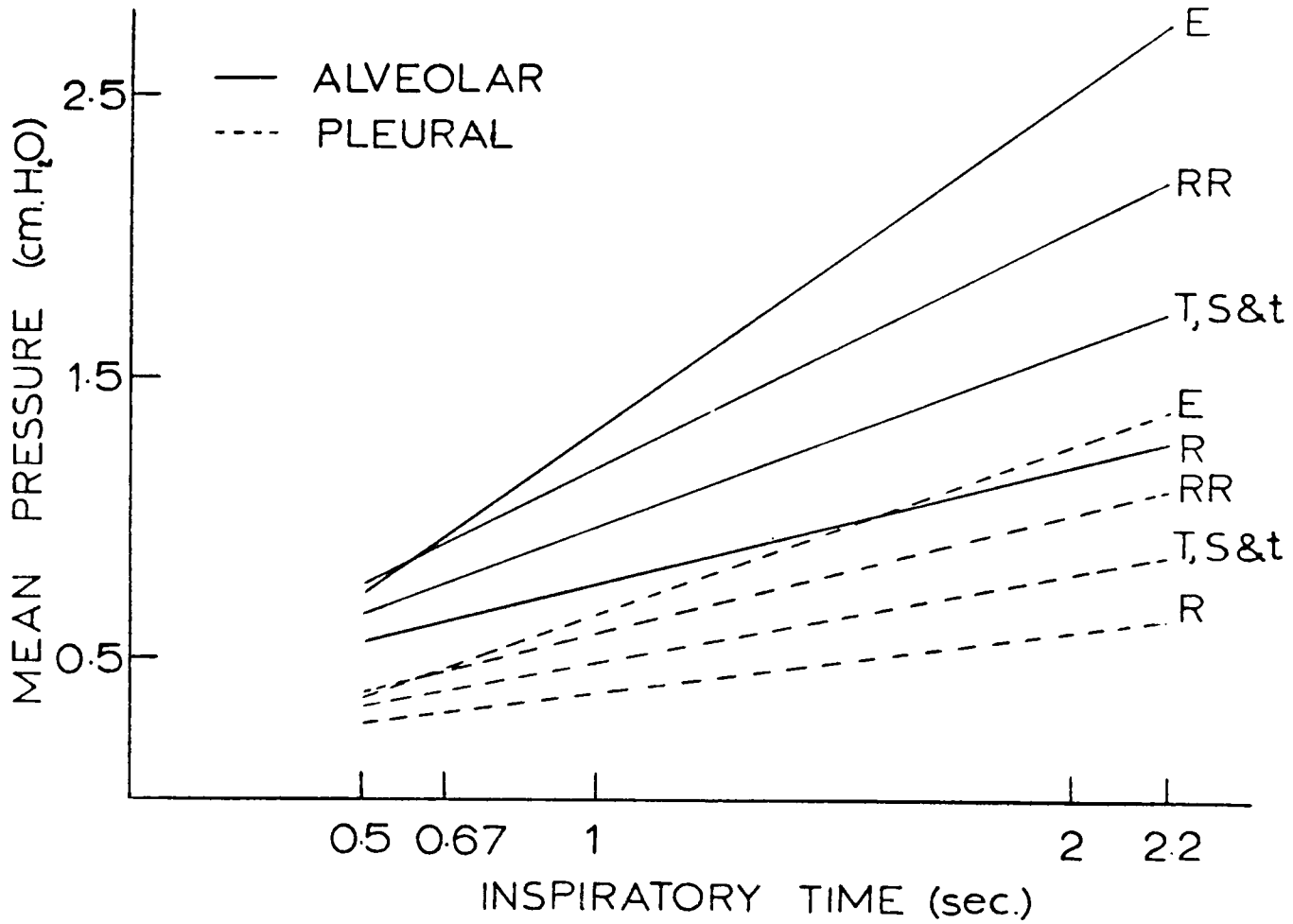


Fig. 4:6 Mean alveolar and pleural pressures versus inspiratory time for different inspiratory flow waveforms. Symbols as for Fig. 4:5.

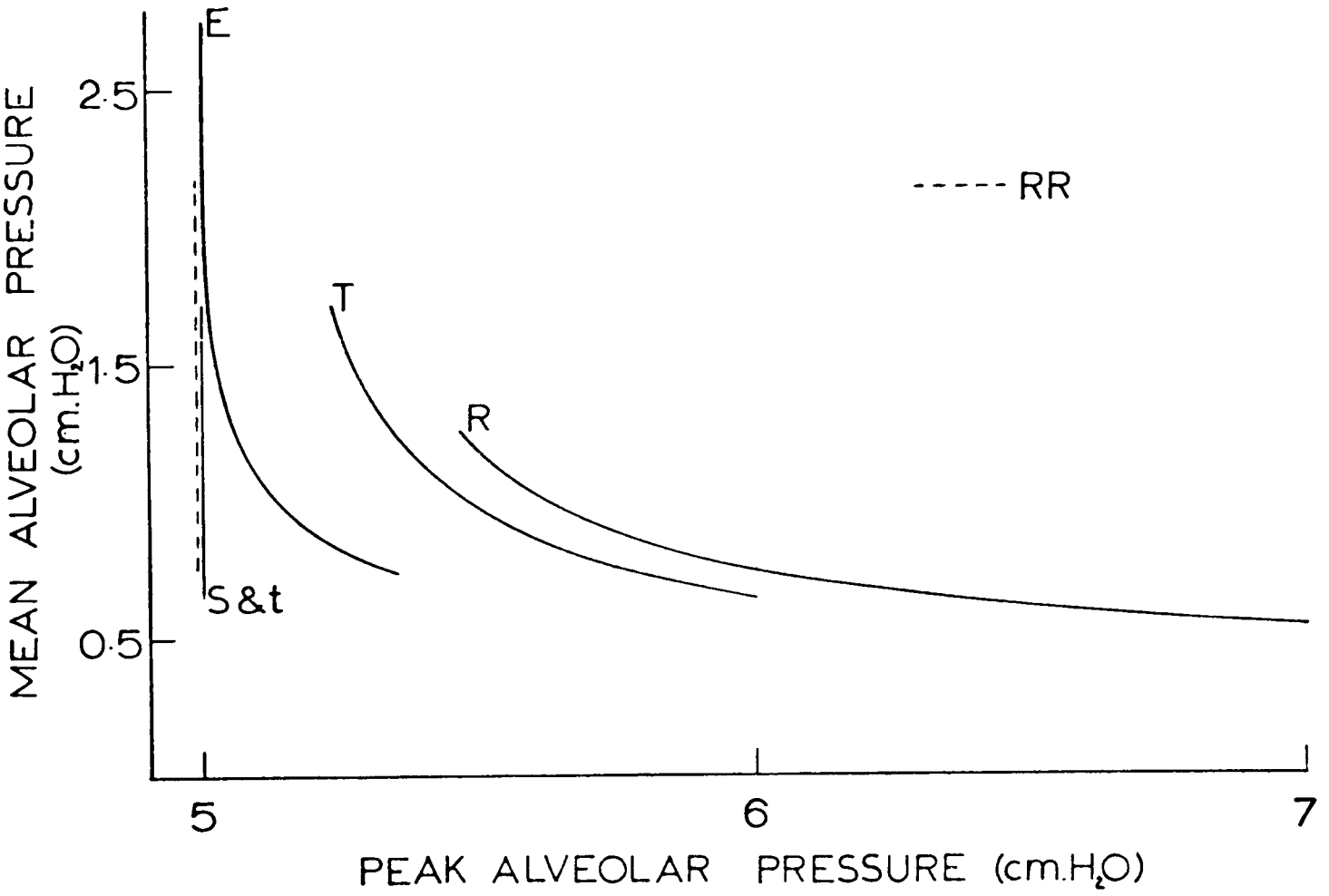


Fig. 4:7 Peak alveolar pressure versus mean alveolar pressure for different inspiratory flow waveforms. Symbols as for Fig. 4:5.

resistances to breathing. Yamashiro and Grodins (1971) have confirmed by mathematical analysis that least work is required by a 'tophat' flow in inspiration and a reversed tophat flow in expiration.

The flow pattern requiring least work in spontaneous respiration may not be relevant to I.P.P.V. but it would seem to be a justifiable assumption that the flow pattern requiring least work to achieve a given respiratory minute volume will cause leastphysiological disturbance. This assumption was used by Wald et al. (1968) and by Jain and Guha (1970) as one of the factors involved in the prediction of an ideal inspiratory waveform. Wald et al. (1968) applied an input simulating a pressure generator to their electrical analogue and found that a ramp pressure waveform, which resembles the pressure waveform produced by a tophat flow waveform, required the least inspiratory work of the waveforms studied. Fig. 4:8 shows that in the present analogue study a tophat flow waveform requires least inspiratory work. This finding thus agrees with Wald et al. (1968), and also with the work of Yamashiro and Grodins (1971) who used an infinite Fourier series to predict their ideal flow waveform. Fig. 4:9 shows the result of observing the interaction between inspiratory work and peak and mean alveolar pressures on the lung/thorax model. The 'best' waveform by this interaction is not obvious, but sine and triangle waveforms achieve a reasonable compromise.

Electrical lung/thorax models can only represent linear functions and consequently ignore the effects of changes in viscous and turbulent resistance, non-elastic tissue shear, acceleration forces and kinetic energy of the respired gas. Fig. 4:10 from Otis et al. (1950) shows that the summation of linear and non-linear components of inspiratory work is least at 15 breaths/min, and therefore

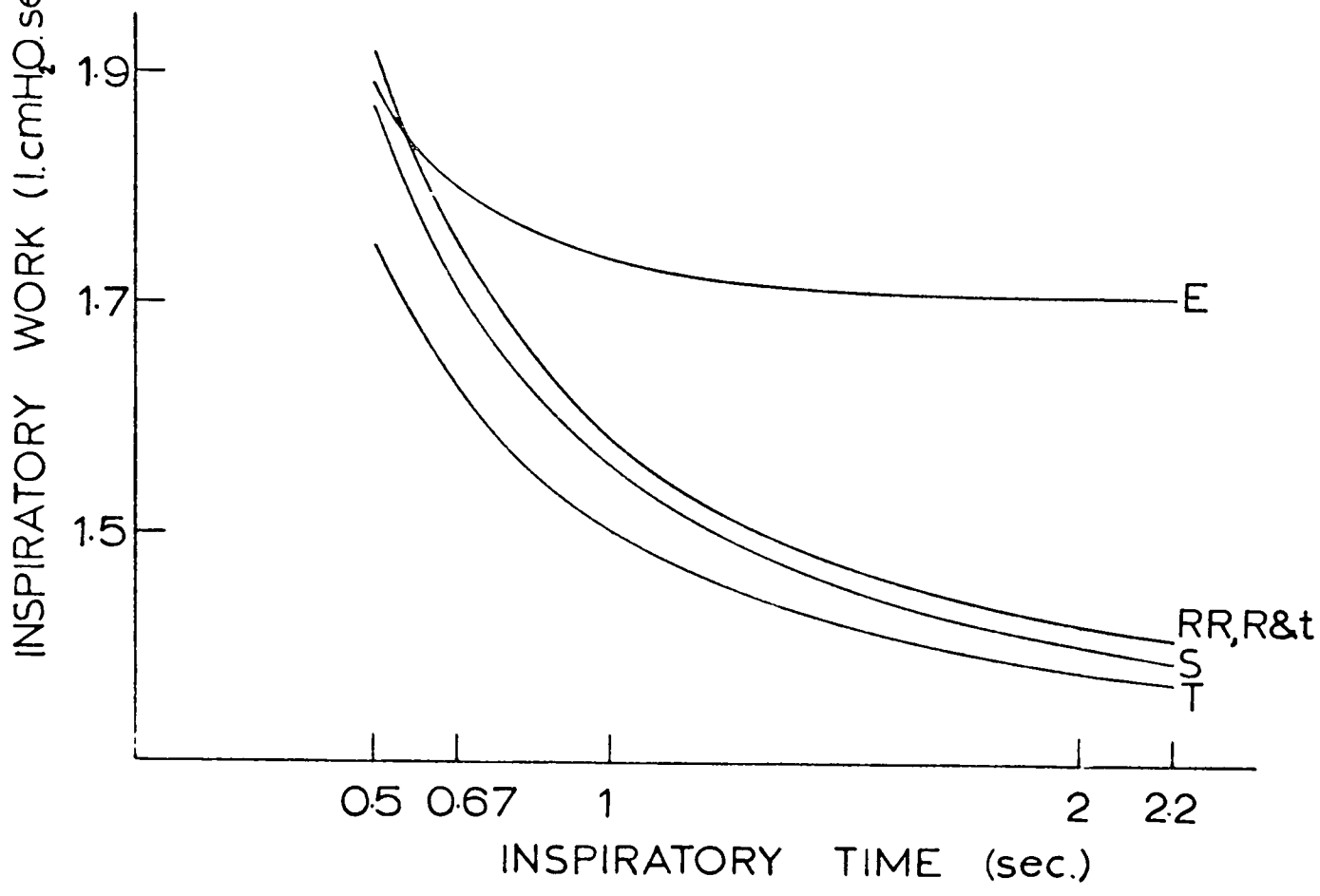


Fig. 4:8 Inspiratory elastic work versus inspiratory time for different inspiratory flow waveforms. Symbols as for Fig. 4:5.

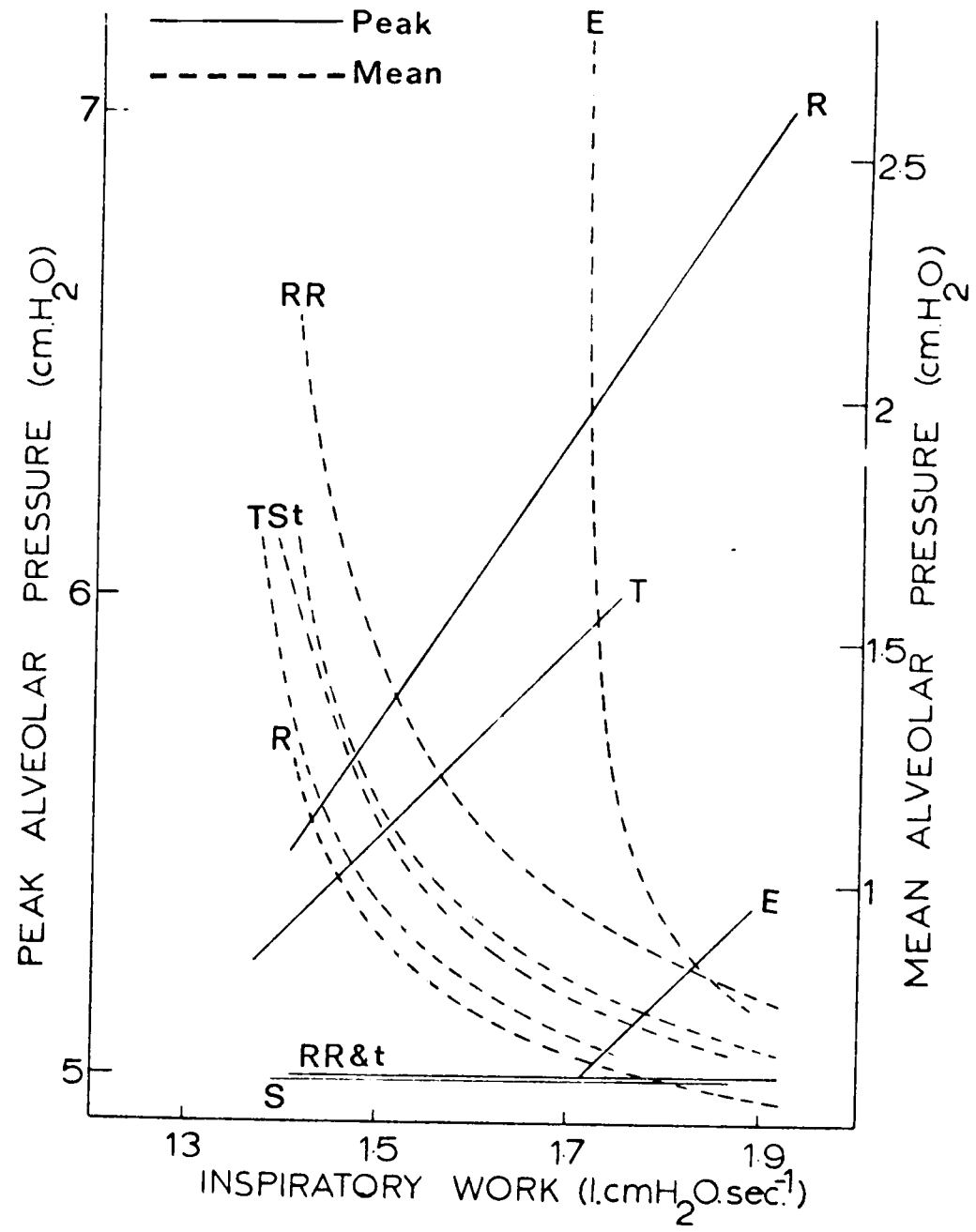


Fig. 4:9 Peak and mean alveolar pressures versus inspiratory elastic work for different inspiratory flow waveforms. Symbols as for Fig. 4:5.

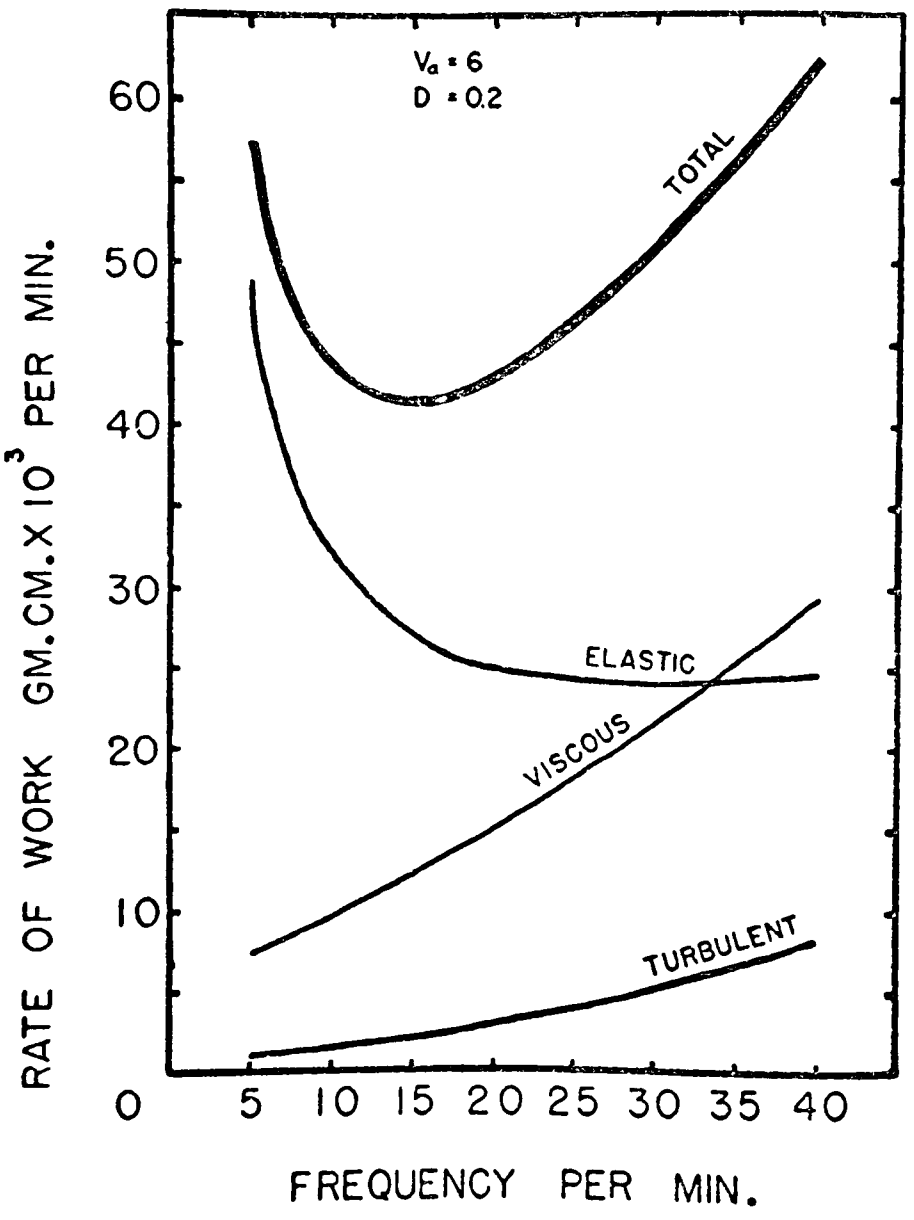


Fig. 4:10 Diagram from Otis et al. (1950) to demonstrate the relationships of total work, and elastic and non-elastic work, to an increasing frequency of respiration.

the effect of ignoring non-linear factors will not markedly compromise the results of the present study. These non-linear factors, however, exert a disproportionate effect on the total work of inspiration compared to compliance and resistance when inspiratory time is short or the frequency of respiration is high. The analogue studies of Wald et al. (1968) and Jain and Guha (1970) assumed that if inspiratory work was minimised the inspiratory waveform would be ideal, but neither study took account of the effect of the non-linear factors mentioned above. This author believes that the very short inspiratory times used by Wald et al. (1968) and Jain and Guha (1970) would grossly increase inspiratory work if non-linear factors were taken into account.

Dead Space and Ventilation.

Physiological dead space is not directly represented in this electrical analogue but the ratio of dead space to tidal volume was assumed to be 1/3 and this, with a tidal volume of 500 ml, gave an alveolar ventilation of 5 l/min.

The frequency and ventilation volume chosen for artificial ventilation may be too great and cause a reduction in the level of arterial P_{CO_2} which may lead to adverse physiological effects (Kety and Schmidt 1948; Suskind and Rahn 1954; Prys-Roberts et al. 1967). Suwa et al. (1968) have developed a formula for correcting P_{CO_2} to normal levels by means of an additional dead space volume added to the apparatus, but this increases the V_D/V_T ratio and decreases the alveolar ventilation. Such a change precludes the use of this compensatory mechanism in the present study which assumes a constant alveolar ventilation. Jain and Guha (1970) investigated the effects of added dead

space on ventilatory requirements. They, however, changed tidal volume and frequency while adding dead space whereas the work of Suwa et al. (1968) was based on constant tidal volume and frequency. Jain and Guha's (1970) results are consequently very likely to be invalid.

CONCLUSIONS

In two previous articles (Wald et al. 1968 and Jain and Guha 1970) the authors chose what they consider to be the best pressure waveform and I:E ratio and then suggest ventilator design characteristics to achieve this. Both groups suggest very short inspiratory times, Wald et al. (1968) recommending 0.16 sec and Jain and Guha (1970) 0.126 - 0.339 sec. Neither group, however, used an analogue which incorporated non-linear factors. These factors become important at short inspiratory times, and their omission must cast doubt on the inspiratory times chosen. Jain and Guha (1970) accepted the waveform chosen by Wald et al. (1968) in theory although rejecting it on practical grounds. Unfortunately insufficient evidence is provided by Wald et al. (1968) to enable a critical analysis of their experiments to be made but one at least of their results (that for alveolar pressure) is not borne out either by the present analogue studies (Baker and Hahn 1971) or by physiological observations (Baker et al. 1971). Apart from these objections the author's experience in designing ventilators would suggest that inspiratory times of such short duration are impractical.

The present analogue study, which was conducted at respiratory frequencies at which non-linear forces are unlikely to have a significant effect suggest that the aspects of respiratory mechanics investigated by the analogue are least affected by triangular, sine or reversed ramp flow waveforms. These waveforms have been chosen on the

basis of a compromise between all the factors considered. If only one factor was considered, one of these waveforms or a different waveform might be selected. No attempt can be made to choose the best frequency from the present study because non-linear factors have been ignored, but other studies (Otis et al. 1950; Mead 1960) suggest that a frequency in the 12 - 20 range will be least harmful. Some attempt can be made to chose a best inspiratory time within the constrictions applied by the design of the analogue. On the basis that the best inspiratory time is that which will minimise peak and mean alveolar pressure, data from the analogue suggests that an inspiratory time of 1.0 - 1.5 sec will be least harmful. In a respiratory cycle time of 4 sec an inspiratory time of this duration will not introduce significant errors de to the omission of non-linear factors.

CHAPTER

5

ALVEOLAR PRESSURE RESPONSE TO 'TOPHAT' GAS FLOW OR PRESSURE WAVES IN INSPIRATION

CHAPTER 5

ALVEOLAR PRESSURE RESPONSE TO 'TOPHAT' GAS FLOW OR PRESSURE WAVES IN INSPIRATION

INTRODUCTION

Previous studies of artificial ventilation in humans and animals have suggested that alveolar pressure[1]. invariably rises smoothly from the end-expiratory alveolar pressure, irrespective of the shape of the gas pressure wave applied to the patient by the ventilator (Mushin et al., 1969; Nunn, 1970). These studies have reported observations from mechanical test-lungs (Herzog and Norlander, 1968; Mapleson, 1969) and electrical lung analogues (Campbell and Brown, 1963; Wald et al., 1968). This chapter presents evidence which suggests that in certain circumstances the alveolar pressure does not rise smoothly.

METHODS

Experiments were undertaken on dogs, and on patients anaesthetised and paralysed prior to thoracotomy. A high pressure air source (2,000 p.s.i.) was passed through a needle valve to the trachea of the patient or dog. This system delivered a flow rate of 1 litre/sec., and the trachea was exposed to this gas flow by the anaesthetist manually operating a four-way tap (Fig. 5:1). Tidal volume depended upon the anaesthetist's clinical impression of adequate ventilation and varied between 610 and 3820 ml., Gas flow to the patient was measured by means of a Godart

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1. Alveolar pressure is assumed to mean the pressure at a point between the end of the respiratory bronchiole and the pleura.

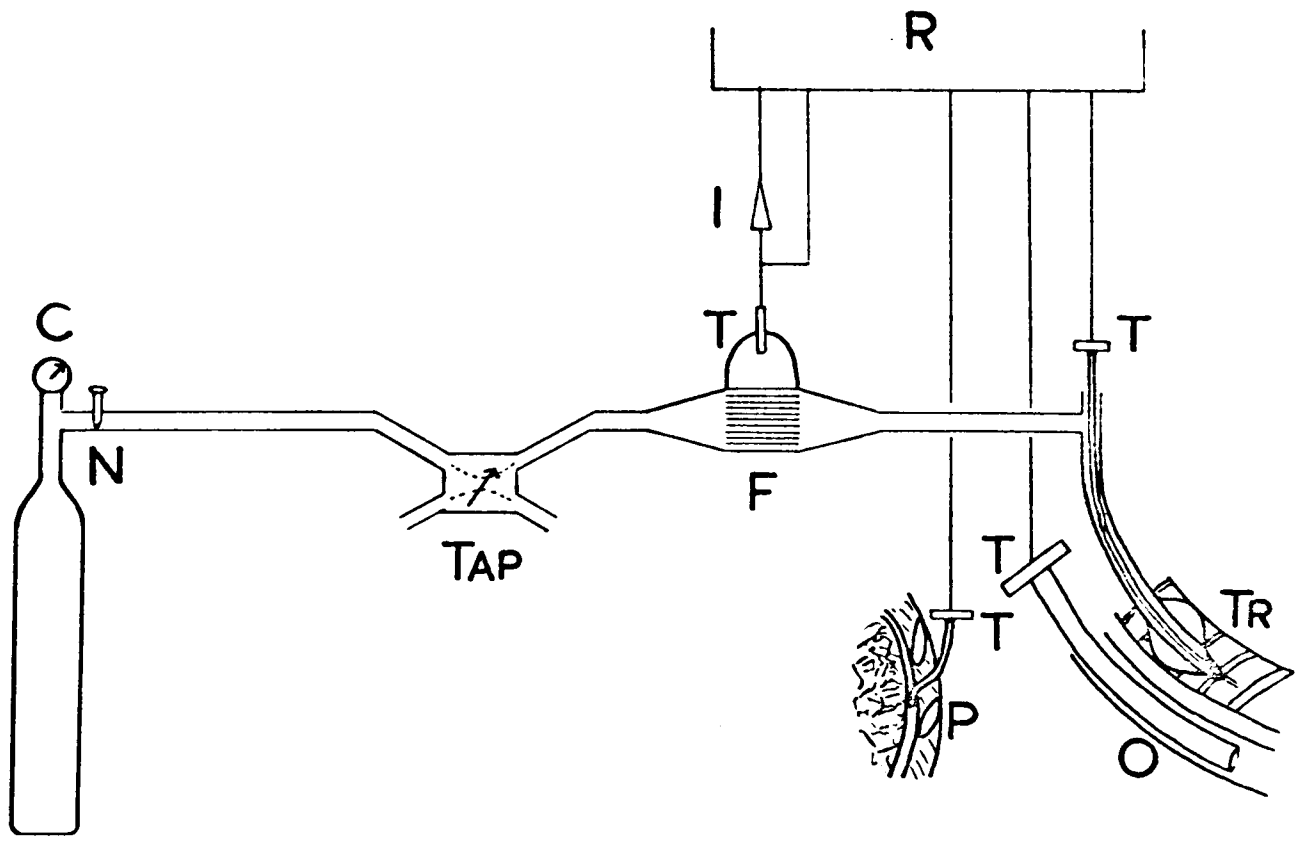


Fig. 5:1 Flow diagram of experimental arrangement. C = compressed air cylinder; N = needle valve: TAP = 4-way gas tap; F = Fleisch pneumotachograph head; T = pressure transducer; I = integrator: R = recorder; P = pleural area; O = oesophageal area; TR = tracheal area.

pneumotachograph and Fleisch head (Fleisch, 1925) with the pneumotachograph head placed between the four-way tap and the patient. Tidal volume was measured by electrical integration of the flow signal (Godart integrator), and by planimetry. Strain guage manometer measurements were made from the trachea near the carina and from as far as possible into the endobronchial lumen. Pressure measurements were also made from the oesophagus. The pressure in the pleural space was measured and in patients the pleural catheter was inserted through the intercostal space later to be used for a thoracotomy incision. No significant pneumothorax was demonstrated at thoracotomy in any patient.

The initial pressure steps and the maximum pressure were obtained from the tracheal and oesophageal pressure recordings. Where cardiac artifacts masked the pressure step in the oesophageal pressure recordings the average slope of increasing pressure was drawn by eye and the initial discontinuity then became obvious (Fig. 5:2). Compliance and resistance were calculated as shown in Fig. 5:3; tracheal pressure recordings were used for calculating whole chest resistance and compliance whilst oesophageal recordings were used for calculating chest wall resistance and compliance. Lung resistance and compliance were calculated using the formulae:-

$$1/C_L = 1/C_T - 1/C_{C-W}$$

$$R_L = R_T - R_{C-W}$$

RESULTS

(i) Endobronchial Study.

A catheter was passed as far as possible down a

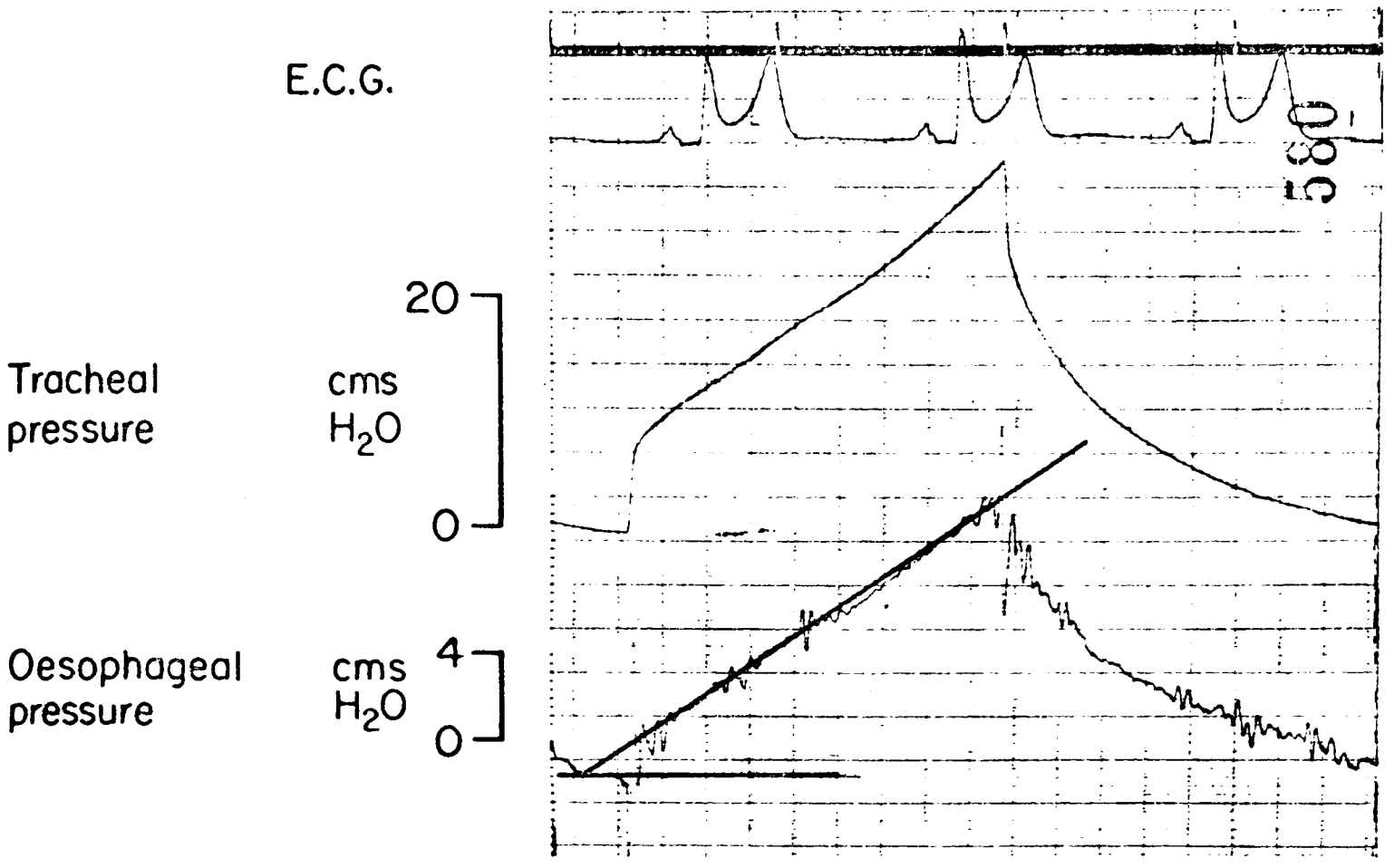
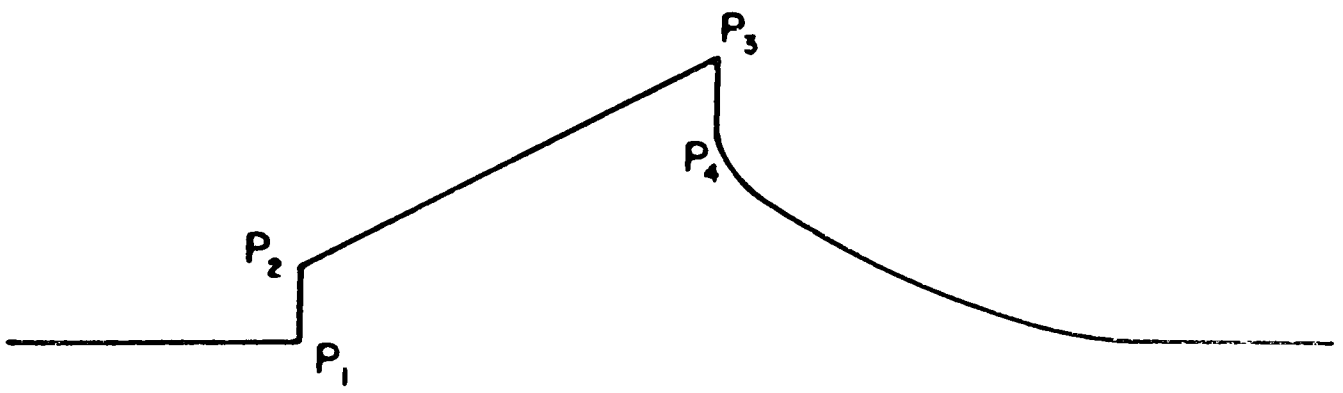


Fig. 5:2 Demonstration of oesophageal pressure discontinuity by superimposing straight lines on the oesophageal trace.



$$\text{Compliance} = \frac{V_T}{P_4 - P_1} \text{ or } \frac{V_T}{P_3 - P_2}$$

$$\text{Resistance} = \frac{P_2 - P_1}{\text{Constant flow}} \text{ or } \frac{P_3 - P_4}{\text{Constant flow}}$$

Fig. 5:3 Schematic drawing to demonstrate calculation of airways compliance and resistance. The results used for each trace were the means of the two compliance and resistance measurements for that trace.

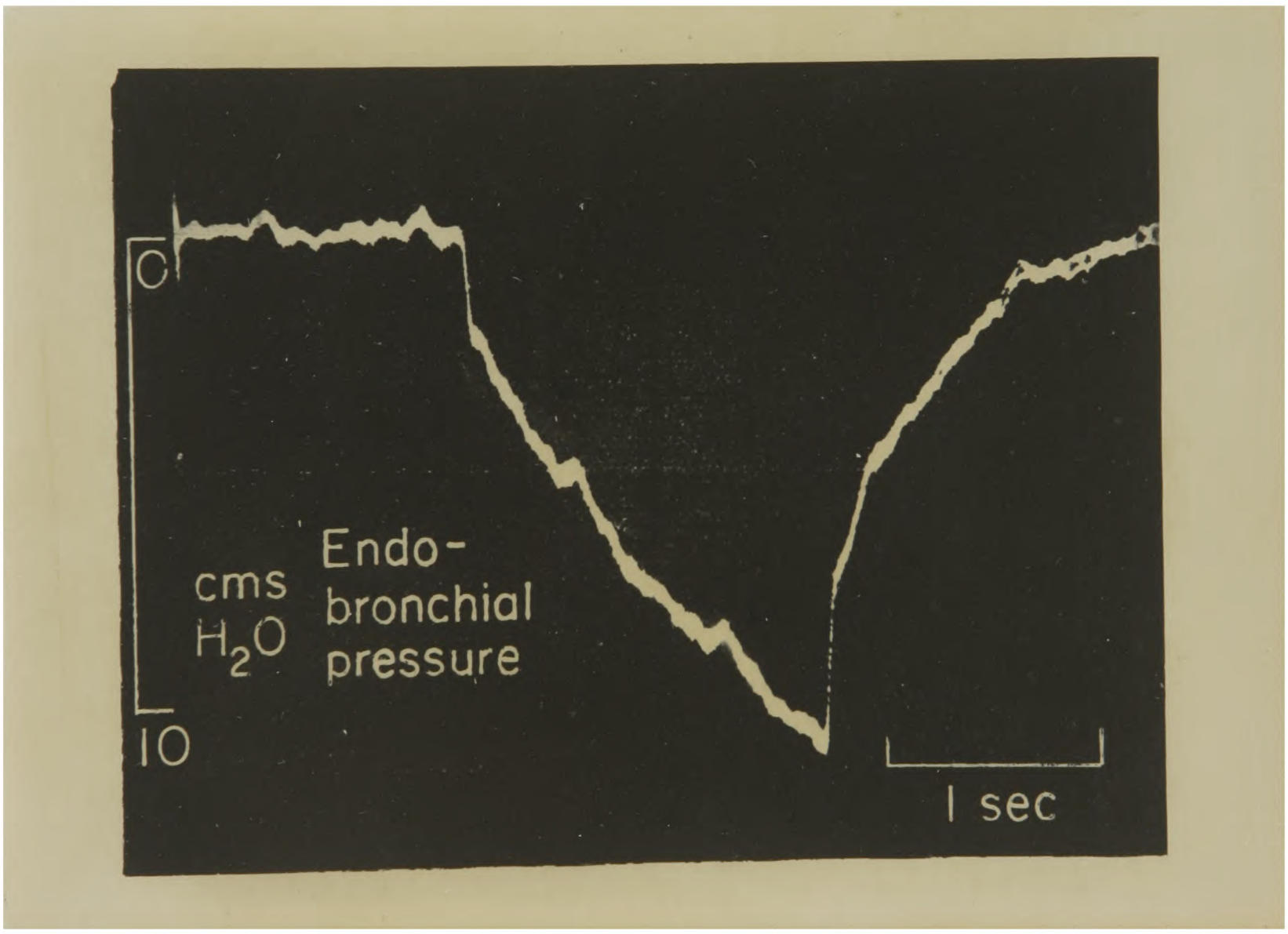


Fig. 5:4 Oscillograph of the human endobronchial pressure trace for a sudden constant flow inflation, showing the pressure discontinuity at beginning and end of inspiration.

main bronchus and an instantaneous pressure step was recorded when a constant flow was suddenly applied to the patient. Fig. 5:4 shows this pressure step occurring at the beginning and end of inspiration.

(ii) Intrapleural Study.

Oesophageal, tracheal and intrapleural pressures in dogs and humans all showed an instantaneous pressure step when a constant flow was applied to the trachea (Fig. 5:5). Because the patients concerned were to be submitted to thoracic surgery and some had pleural adhesions, seven subjects were studied before uncomplicated pleural pressure tracings were obtained in two patients. The compliance and resistance measurements of all patients are shown in Table 5:1.

DISCUSSION

The supposition that the alveolar pressure response to artificial ventilation is always sufficiently damped to rise smoothly from the end-expiratory pressure irrespective of the air flow presented to the trachea, derives from studies on incomplete lung analogues. The mechanical 'test-lung' is a lung analogue without a chest wall component so that no instantaneous pressure difference builds up in the 'alveolus' (Mapleson, 1969). Simple electrical lung analogues (Campbell and Brown, 1963; Wald et al., 1968; Jain and Guha,1970) built to study the effects of variously shaped electrical pulses also failed to show an alveolar pressure step because the chest wall resistance was not represented adequately. More elaborate electrical analogues such as those of van den Berg (1960) and Mead and Milic-Emili (1964) included adequate chest wall representation, but, as they were used only to study sine wave impulses simulating

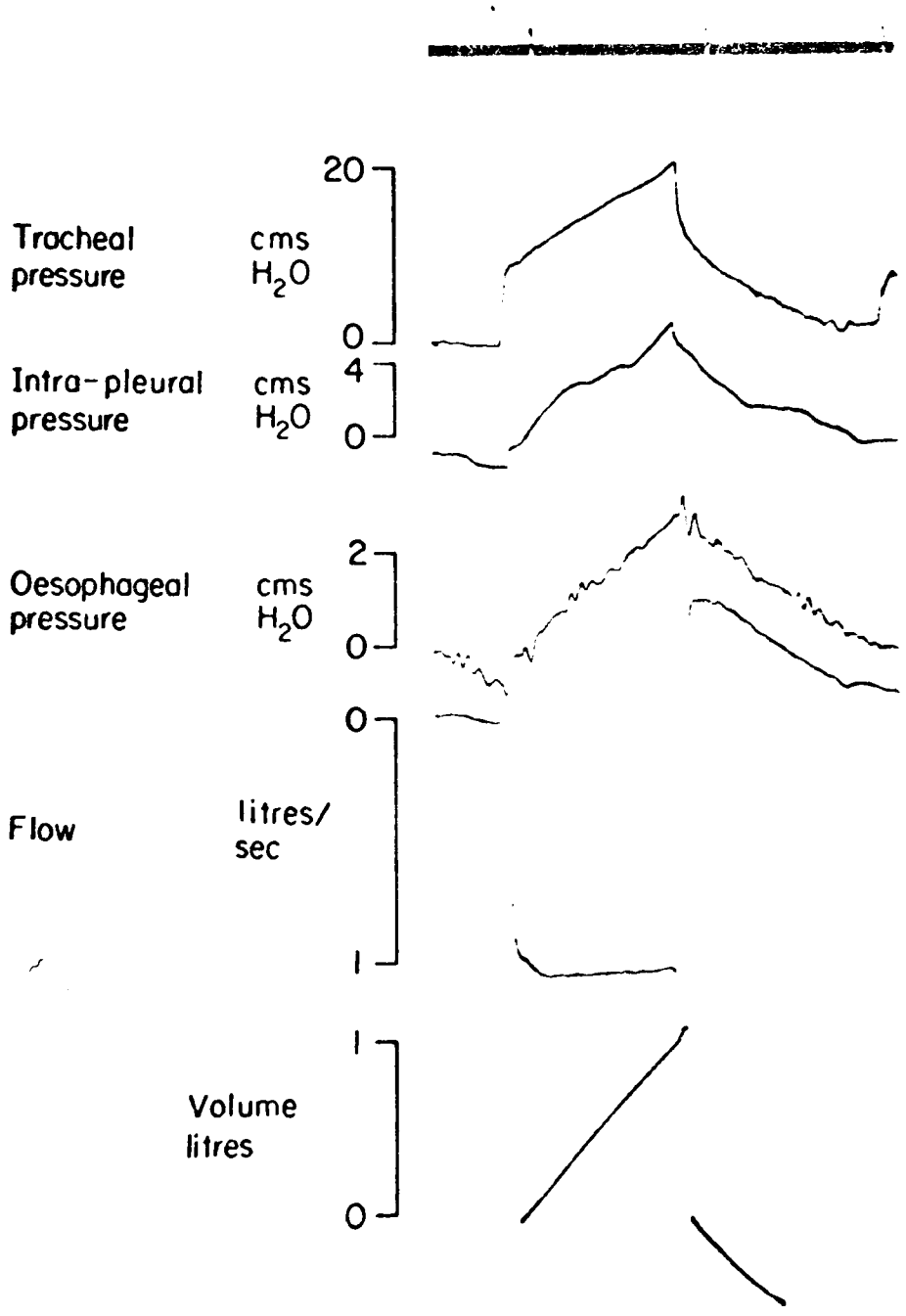


Fig. 5:5 Recording showing human tracheal, intrapleural and oesophageal pressure responses to a sudden constant flow inflation of 1 1/sec. The pressure discontinuity is particularly evident at the commencement of inspiration.

TABLE 5 : 1

PATIENT	Pathology	V_T	Total		Chest Wall		Lung	
			C	R	C	R	C	R
J.C. 53 F.	Lung Ca. and Bronchiectasis	1780	85.1	10.90	211.9	1.76	143.7	9.16
		(180)	(6.5)	(0.90)	(10.9)	(0.60)	(19.9)	(1.10)
J.W. 62 F.	Lung Ca.	3820	222.9	11.70	394.7	1.70	532.9	9.92
		(630)	(21.3)	(4.60)	(82.5)	(1.00)	(70.9)	(4.21)
G.C. 49 M.	Lung Ca.+ drained pleural effusion.	610	44.6	2.59	89.5	1.70	104.8	0.99
		(40)	(0.9)	(0.29)	(4.4)	(0.40)	(62.2)	(0.44)
G.H. 64 M.	Lung Ca.	1580	107.6	5.49	215.4	1.30	216.3	4.25
		(340)	(4.3)	(0.94)	(12.3)	(0.40)	(18.0)	(0.90)
W.W. 69 M.	Old fibrosed empyema.	1450	89.9	2.40	308.5	0.83	131.2	1.57
		(130)	(1.0)	(0.70)	(79.1)	(0.13)	(16.9)	(0.58)
B.G. 55 M.	Lung Ca.	1260	60.4	5.85	122.2	1.80	122.0	4.05
		(220)	(7.0)	(0.90)	(18.8)	(0.40)	(19.5)	(1.11)
F.T. 40 F.	Bronchiectasis.	1350	90.9	8.10	281.5	0.74	135.4	7.39
		(240)	(5.9)	(2.00)	(32.4)	(0.19)	(13.0)	(1.95)

Table: Human respiratory resistance and compliance showing patients' age and sex together with the pathology defined at thoracotomy. Calculations were carried out as described in Fig. 5:3 and in the equations in the text. Means are given with their standard deviation in brackets. V_T = tidal volume in ml; C = compliance in ml/cm H_2O; R = resistance in cm H_2O/1/sec all measurements having been taken at a gas flow of 1 1/sec.

spontaneous ventilation, also failed to show an instantaneous alveolar pressure step.

In the course of studies on an electrical lung analogue (Fig. 5:6), supported by mathematical calculations and described in Chapter 4, a constant voltage was suddenly applied across the analogue. The analogue of the alveolar pressure did not rise smoothly but by an instantaneous step followed by a smooth rise and Fig. 5:7. shows the effect in the mathematical analogue when plotted by a digital computer. Physiological measurements to confirm this theory have been made on either side of the alveolus and the instantaneous pressure step is present when pressures are measured in a distal bronchus and when measured in the pleural space.

If this observation is to be used to calculate chest wall resistance and compliance, a pressure step must also be measurable in pressure recordings made from the oesophagus. The firm wide-bore catheter system described has a better frequency response than narrow catheter systems which may be too damped to show an instantaneous step function. Responses due to cardiac artifacts in such a system may be easily distinguished with E.C.G. control (Fig. 5:8). Don and Robson (1965) used a pressure step in tracheal pressures to measure whole chest resistance and compliance. The results presented extend this method to enable chest wall and hence lung resistance and compliance to be calculated in addition. These results are compatible with other published figures. It is realised, however, that the airways and tissue resistance measured by such a technique include impedance elements which most workers consider to be very small indeed (Mead and Milic-Emili, 1964).

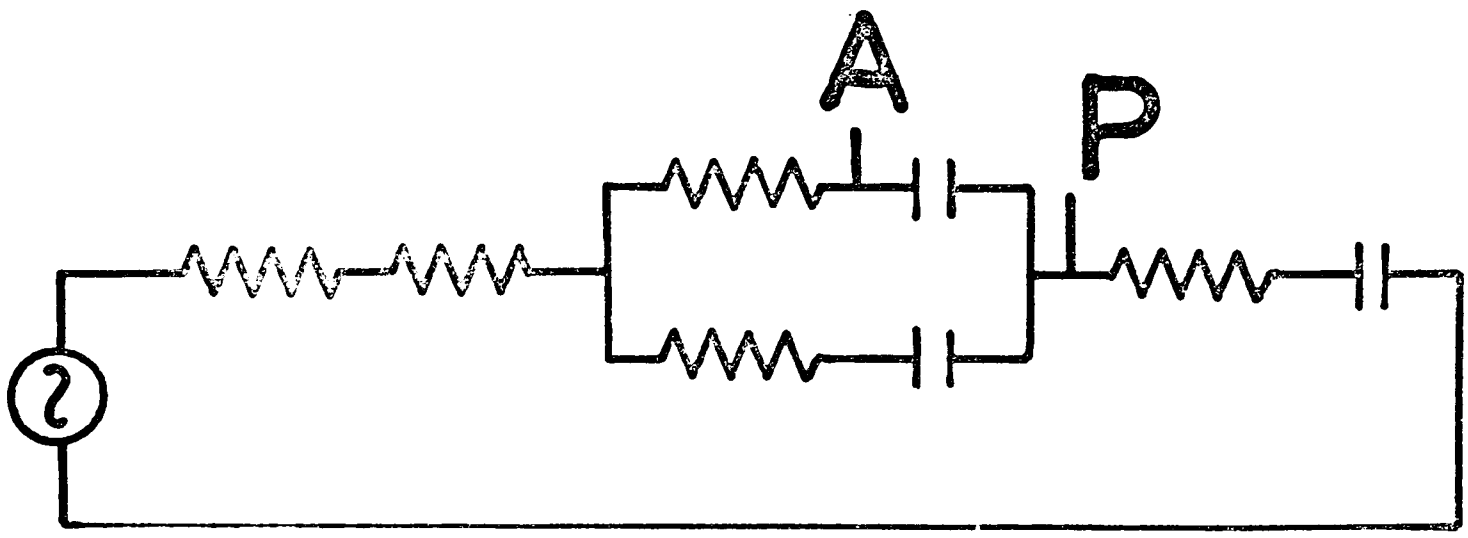


Fig. 5:6 Electrical lung analogue. A = position of voltage measuring "alveolar pressure"; P = position of voltage measuring "pleural pressure".

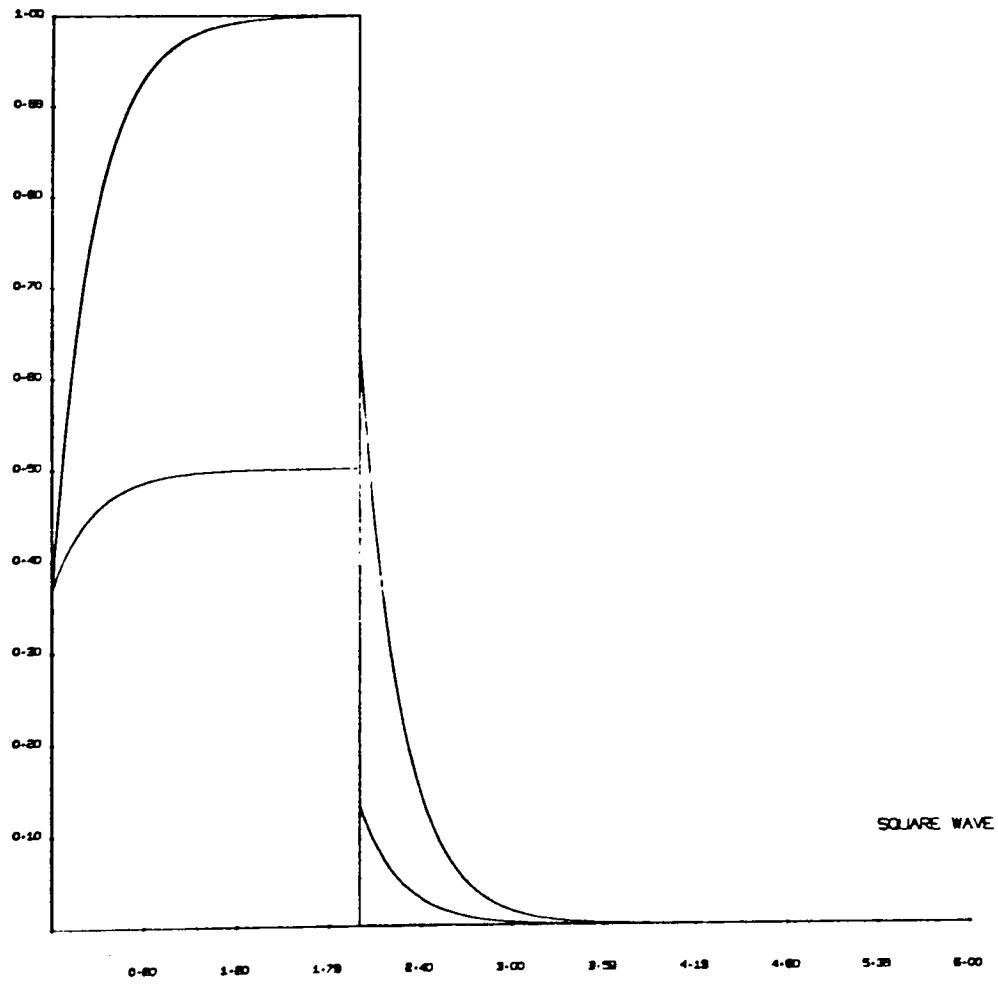


Fig.5:7 Digital computer plot of the response to a top-hat pressure signal in a mathematical analogue of the electrical lung analogue shown in Fig. 6. The upper trace is of alveolar pressure and the lower trace of pleural pressure. The discontinuity is obvious at the beginning and end of the inspiratory period.

Fig. 5:8 Human oesophageal pressure recording for a constant flow inflation of 1 1/sec demonstrating the relationship of cardiac artifacts, timed by the E.C.G., to the pressure discontinuity.

CHAPTER

6

PHYSIOLOGICAL EFFECTS OF VARYING INSPIRATORY GAS FLOW AND INSPIRATORY TO EXPIRATORY TIME RATIO

CHAPTER 6

PHYSIOLOGICAL EFFECTS OF VARYING INSPIRATORY GAS FLOW AND INSPIRATORY TO EXPIRATORY TIME RATIO

Chapter 2 briefly sketches previous knowledge concerning the physiological effects of alteration of gas flow waveform and time during inspiration in artificial ventilation. The studies are summarised in Table 6:1.

METHODS

Acute experiments on mongrel dogs* were performed using the ventilator described in Chapter 3(a). The animals were intubated with a Magill endotracheal tube and gas leaks were tested for by means of 'Valsalva's manoeuvre' carried out using the ventilator hold device (Fig.6:1). The frequency of respiration used was 15 breaths/min so that the respiratory cycle time was 4 seconds. This frequency was chosen as representative of frequencies used in human artificial ventilation, and because it approximates the normal human respiratory frequency (Mead 1960). The normal respiratory frequency for dogs is 11 - 15 breaths/min (Hamlin and Smith 1967). The inspiratory flow waveforms used are shown in Figs. 6:2-5 and the inspiratory times varied between 0.5 - 2.2 sec. The flow waveforms were selected in a random manner but the inspiratory times were applied to a particular waveform sequentially beginning with a short inspiratory time and progressing to a long inspiratory time. A tidal volume was selected which gave an end-tidal CO_2 concentration of approximately 4% and a P_{ET,CO_2} of about 30 torr. The tidal volume selected was

* The mongrel dogs were all healthy, well fed and hydrated animals when the experiments were undertaken on them.

TABLE 6 : 1

Author	V_D/V_T	Compliance T	Compliance C-W	Compliance L	P_{a,O_2}	$A\text{-}aP_{O_2}$	P_{a,CO_2}	$a\text{-}AP_{CO_2}$	$\dot{Q}$	Airways Pressure	$\dot{Q}_s/\dot{Q}$
Watson (1962)	+		-								
Bergman (1963)						?+		+		-	
Fairley & Blenkarn (1966)	+				0	0	0			-	0
Bergman (1967)	+				0	0	?+			-	
Lumley et al. (1968)	0				0	0					
Lumley et al. (1969)	0				0	0	0				
Sykes & Lumley (1969)	0&+	-				0					0
Knelson et al. (1969)	+				-		+				
Finlay et al. (1970)	0	0			0&-				+	0	- 0&+
Knelson et al. (1970)	+				-		+				
Lyager (1970)	+	0			0	0	+			0	-

Table: Short summary of the reported physiological effects following a reduction in the duration of inspiration. + represents an increase, - a decrease and 0 no change. doubt concerning the statistical significance is represented by ?

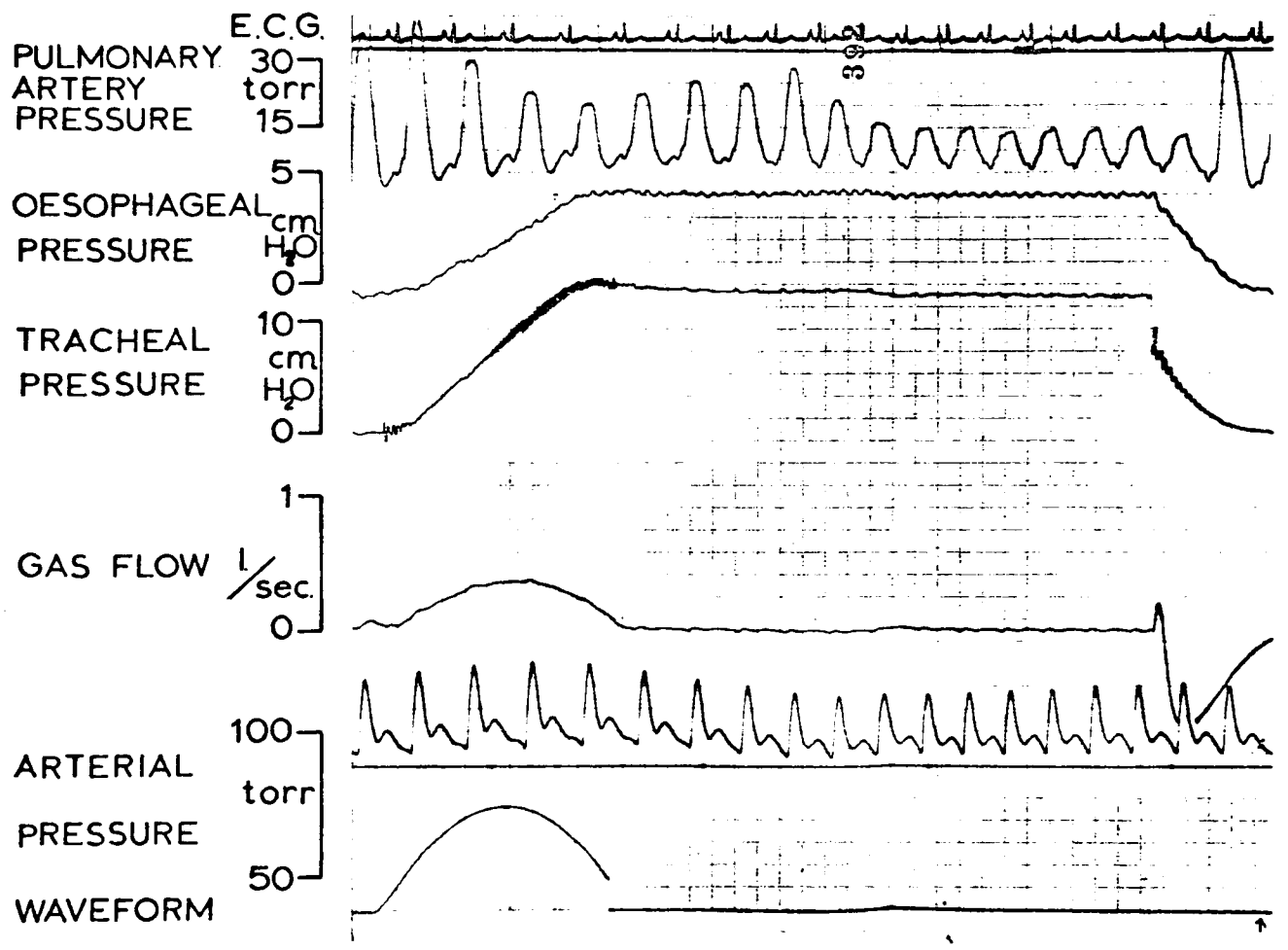


Fig. 6:1 Experimental recording, from Dog 14, of the 'Valsalva manoeuvre' carried out to ensure that there was no gas leak from the lungs. This manoeuvre was repeated between all changes of I:E ratio and waveform.

The pulmonary artery pressure characteristics in this recording are thought to be due to the resonance characteristics of the system, the catheter was definitely located in the pulmonary artery.

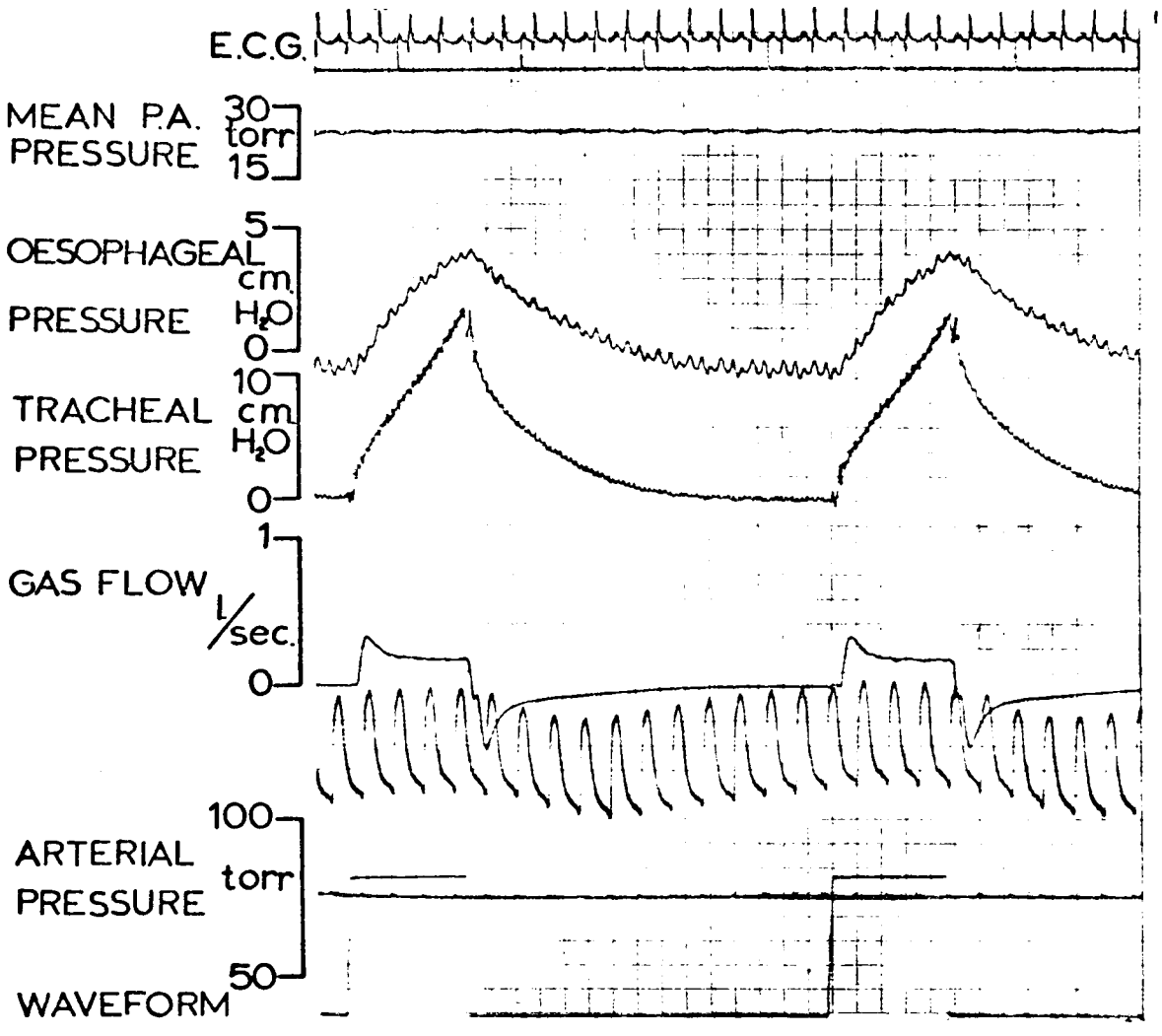


Fig. 6:2 Experimental recording, from Dog 12, of the tophat inspiratory flow waveform produced by the ventilator.

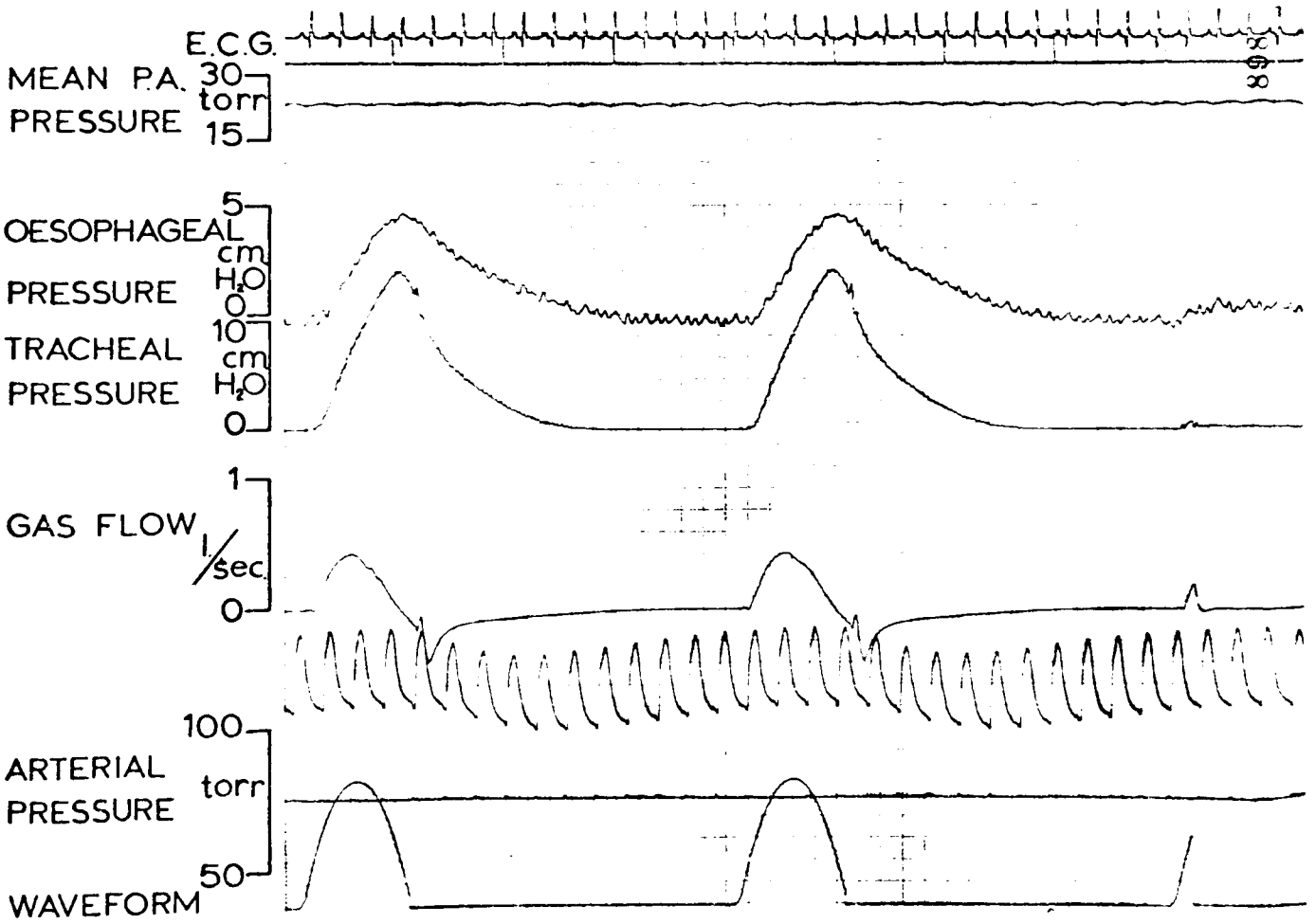


Fig. 6:3 Experimental recording, from Dog 19, of the sine inspiratory flow waveform produced by the ventilator.

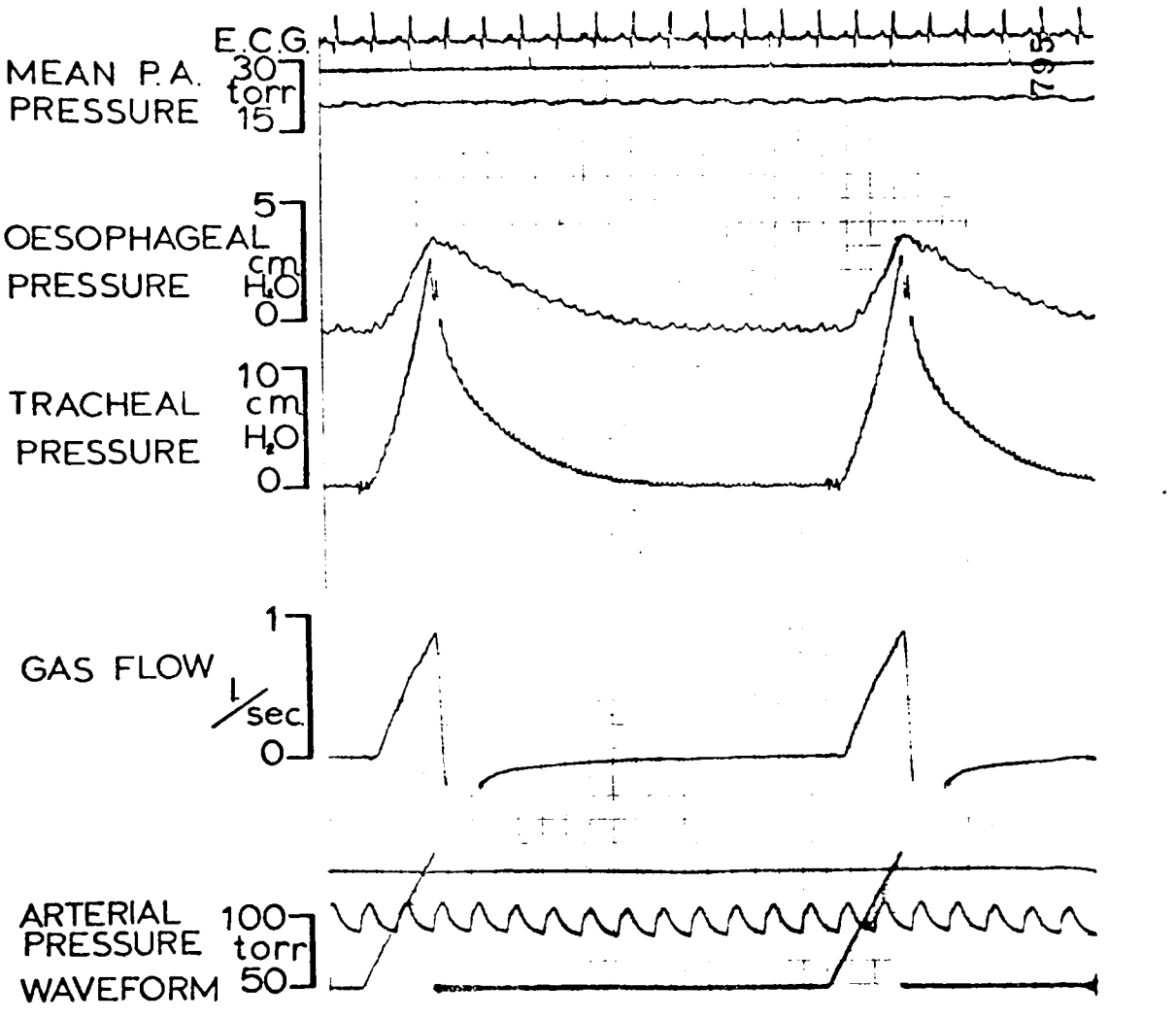


Fig. 6:4 Experimental recording, from Dog 18, of the ramp inspiratory flow waveform produced by the ventilator.

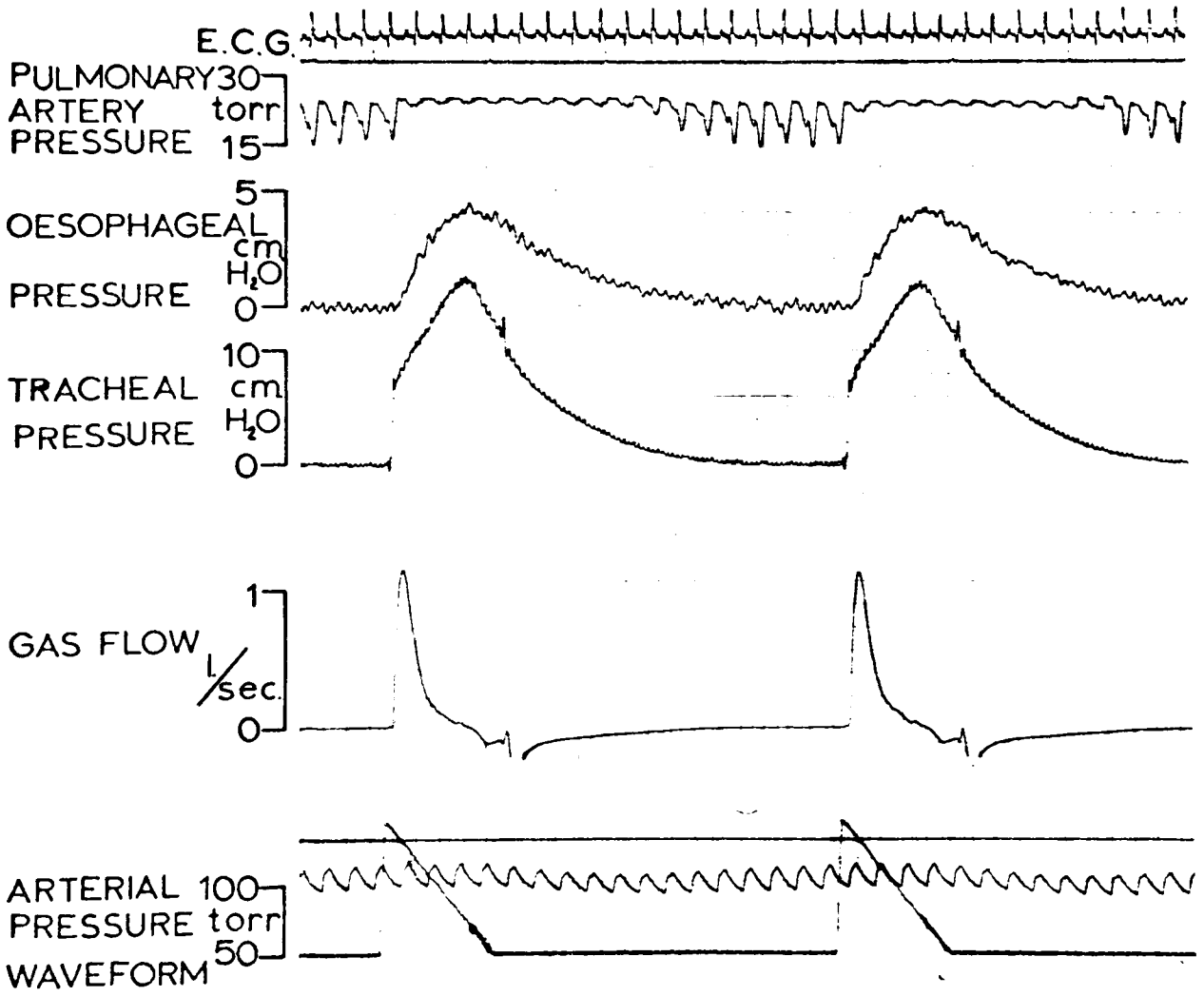


Fig. 6:5 Experimental recording, from Dog 15, of the reversed ramp flow waveform produced by the ventilator.

kept constant throughout an experiment, and expiration was always passive to atmosphere. After measurements had been made in the control state in Series 7, pharmacological blockade of the animals' autonomic nervous system was performed.

The laboratory methods described in Chapter 3(b) were used to measure cardiac output, blood pressures, airway and oesophageal pressures, blood gas partial pressures, gas flow and tidal volume, end-tidal CO_2, E.C.G., Hb., barometric pressure and temperatures. Chapter 3(c) describes the calculations used to derive other physiological variables. Total dynamic compliance was measured by taking the average airway pressure difference between the points of no flow at the beginning and end of inspiration over a period of two minutes.This value was divided into the average tidal volume calculated by collection of expired gas over the same period. The calculation of the dynamic chest wall compliance assumed that the oesophageal pressure difference between points of no flow was representative of the intrapleural pressure change (Milic-Emili et al. 1964). Lung compliance was calculated as in Chapter 5. All compliance figures for dogs were related to body weight (Agostoni et al. 1959; Cook et al. 1959). Mean airway and oseophageal pressures were calculated for the whole respiratory cycle using the trapezoid rule for the area under a curve (Thomas 1968). Series of experiments were performed as detailed in Chapter 3(d). The results of these experiments have been statistically analysed by factorial design analysis, and also by unpaired t-tests. Factorial design analysis enables synergism between the effect of changes in waveform and changes in I:E ratio to be recognised when it occurs (Chapter 3(d)). Discussion of a particular physiological variable is given after the results of that variable to

facilitate reference.

The results are presented in graphical and tabular format. Series 5 is truely representative of Series 3,4,5 and 6 and thus has been presented alone of these particular Series to simplify the graphical presentation. The results of all the Series, however, are tabulated, and this format reemphasises the inspiratory times and waveforms used in the various Series of experiments.

RESULTS AND DISCUSSION

V_D/V_T Ratio.

Results

Fig. 6:6 shows the relationship obtained between the V_D/V_T ratio and duration of inspiration, and between the V_D/V_T ratio and the waveform. Table 6:2 shows the means and standard deviations (S.D.) of the results together with their statistical significance. The V_D/V_T ratio increases when the inspiratory time is decreased. When the inspiratory gas flow waveform is changed the results show a marked difference between waveforms, and the waveforms, in order, which produced the least disturbance in V_D/V_T ratio were reversed ramp, sine, tophat and ramp gas flow waveforms. Statistically significant synergism was found between the waveforms and duration of inspiration in Series 1, 4, 5, 6 and 7.

Discussion

The pneumotachograph head and solenoid valve added 120 ml of apparatus dead space to the normal anatomical dead space of the dogs, and this additional dead space is the cause of the high V_D/V_T ratio obtained. The results of the study of V_D/V_T ratio against duration of inspiration confirm previous studies by Watson (1962b), Bergman (1967), Fairley and Blenkarn (1966) and Sykes and Lumley (1969) all of whom showed an increase in V_D/V_T ratio with shortening of inspiration. The recent studies of Knelsen et al. (1969 and 1970) and Lyager (1970) may also be interpreted as confirmatory evidence, although these authors were studying phenomena due to an end-inspiratory pause. As mentioned in Chapter 2, other studies have disagreed with this finding (Lumley et al. 1968 and 1969; Finlay etal. 1970). The

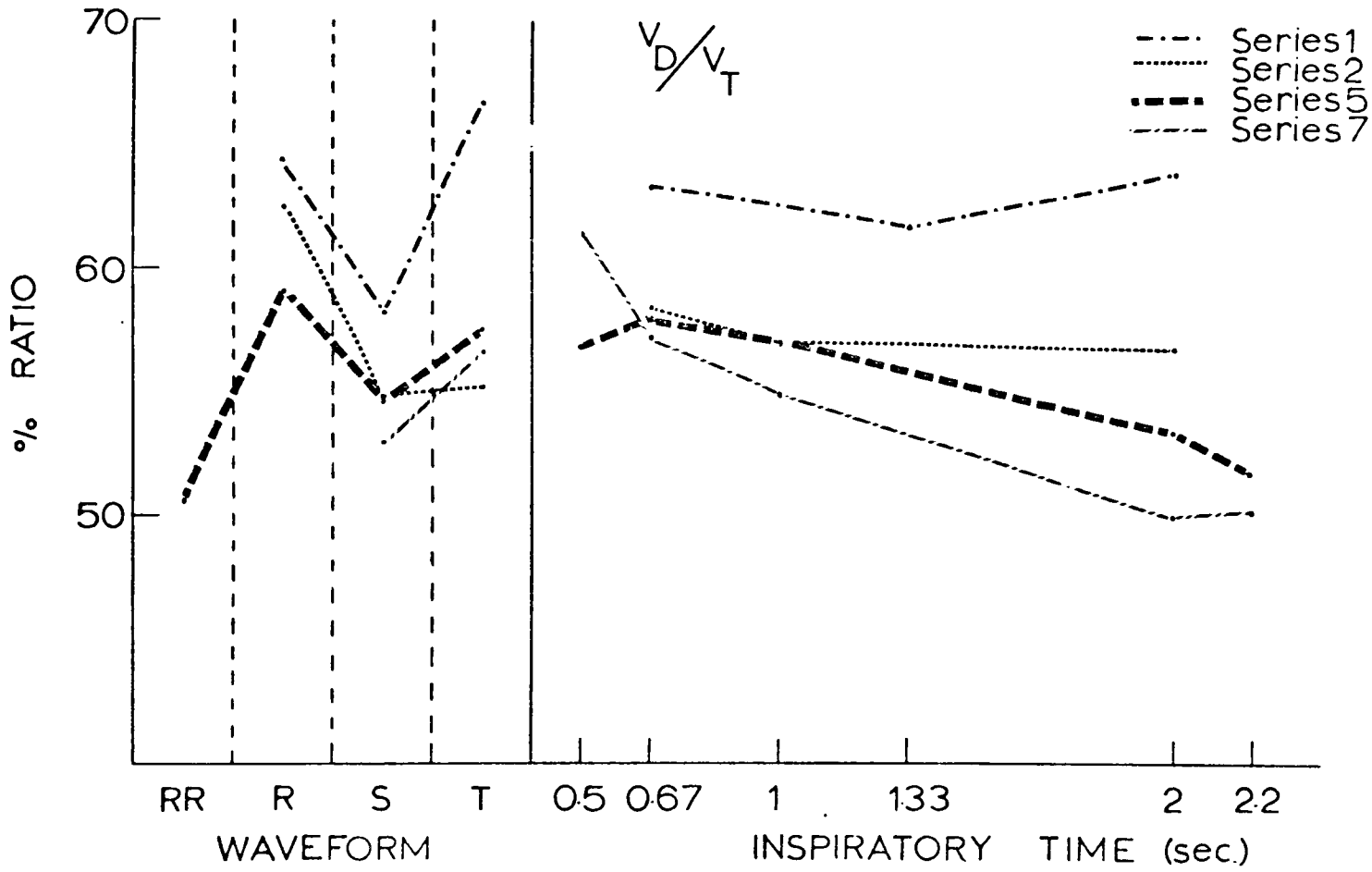


Fig. 6:6 Changes in mean V_D/V_T with different inspiratory waveforms and times. RR = reversed ramp waveform; R = ramp waveform; S = sine waveform; T = tophat waveform.

TABLE 6: 2

Inspiratory variable	Series1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
			Means				
2.2			0.543±0.098	0.519±0.071	0.519±0.071	0.519±0.064	0.503±0.086
2.0	0.640±0.090	0.569±0.055	0.583±0.065	0.535±0.066	0.535±0.066	0.529±0.063	0.501±0.097
1.33	0.619±0.058						
1.0		0.571±0.055	0.591±0.030	0.572±0.042	0.572±0.042	0.567±0.042	0.550±0.068
0.67	0.634±0.063	0.585±0.090	0.594±0.045	0.580±0.050	0.580±0.050	0.576±0.051	0.573±0.075
0.5					0.569±0.054	0.565±0.056	0.615±0.084
* S.E.D.	0.013	0.024	0.024	0.010	0.010	0.011	0.010
R.R.				0.503±0.067	0.506±0.067	0.502±0.067	
R.	0.643±0.053	0.625±0.036	0.622±0.031	0.592±0.049	0.591±0.049	0.583±0.050	
S.	0.583±0.060	0.549±0.072	0.548±0.084	0.541±0.056	0.547±0.056	0.544±0.048	0.530±0.103
T.	0.667±0.073	0.552±0.061	0.563±0.048	0.571±0.045	0.576±0.045	0.576±0.045	0.567±0.075
* S.E.D.	0.013	0.024	0.021	0.010	0.009	0.010	0.006

* S.E.D. refers to the standard error of the difference between any of the means of the Series tabulated above the particular S.E.D. in question.

Table continued on following page

Continuation of table from previous page

Inspiratory variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
				Statistical Probability			
2.2/2.0							
2.0/1.33							
1.33/0.67							
2.2/1.0				.001	.001	.001	.001
2.0/1.0				.001	.001	.001	.001
2.0/0.67				.001	.001	.001	.001
1.0/0.67							.025
0.67/0.5							.001
1.0/0.5							.001
2.2/0.67				.001	.001	.001	.001
2.2/0.5					.001	.001	.001
2.0/0.5					.001	.005	.001
R.R/R				.001	.001	.001	
R./S.	.001	.005	.01	.001	.001	.001	
R.R./S.				.001	.001	.001	
S./T.	.001			.005	.005	.005	.001
R.R./T.				.001	.001	.001	
R./T.		.01	.02	.05			
Synergism	+			+	+	+	+

Table: Means ± S.D. of V_D/V_T for different series of experiments. 2.2, 2.0, 1.33, 1.0, 0.67 and 0.5 represent inspiratory time in seconds R.R. = reversed ramp, R = ramp, S = sine, T = tophat inspiratory flow waveforms; S.E.D. = standard error of the difference. The statistical probability that the differences observed are due to chance are less than the values quoted in the table.

+ indicates that synergism occurred between inspiratory time and waveform.

responses observed in this study to different inspiratory gas flow waveforms have not been demonstrated either by Watson (1962b) or Adams et al. (1970). These are the only previous studies which can definitely be said to have investigated different inspiratory flow waveforms. As neither study monitored gas flow to the patient or animal during the study, the flow waveforms used may have been subject to alteration by the state of the subjects' lungs. This criticism particularly applies to Watson's (1961) work as he used a "pressure generator" (Mapleson 1962) to produce the inspiratory waveform. The flow waveforms used in the study of Adams et al. (1970) may have been insufficiently different to produce an effect, bearing in mind that in the present study the distinction between sine, tophat and ramp waveforms were sometimes not statistically significant.

Previous studies have not been designed to show synergism. The results of this study indicate that synergism is probably important in the consideration of V_D/V_T ratio. The absence of statistically significant synergism in Series 2 and 3 does not necessarily mean that this was completely absent. Synergism may have been present with certain combinations of waveforms and inspiratory times but did not occur with the majority.

Investigation of the underlying mechanism increasing the V_D/V_T ratio was not carried out in these experiments. Two mechanisms have been suggested to account for this increase (Watson 1962b; Lumley et al. 1969). The anatomical dead space may be increased by the higher end-inspiratory pressures necessary to apply a constant tidal volume with short inspiratory times, or the alveolar dead space may be increased by impaired gas distribution.

It would seem probable that both mechanisms play a part.

COMPLIANCE

Results

Total Dynamic Compliance.

Fig.6: 7 shows the relationship obtained between total dynamic compliance and inspiratory time and waveform. Table6: 3 shows the statistical significance and the means and S.D. of the results. The results show a decrease in total dynamic compliance as the inspiratory time is shortened and statistically significant differences between the inspiratory waveforms tested. The greatest compliance was found with the reversed ramp flow waveform and the lowest with ramp flow. Sine flow and tophat flow were not statistically significantly different except in Series 7, and synergism was only found in this Series.

Chest Wall Dynamic Compliance.

Fig. 6:8 and Table 6:4 show the results obtained. There was no statistically significant difference between the effects of different inspiratory times or waveforms except between reversed ramp and tophat flow in Series 4, 5 and 6. Because the other results in the Series of experiments are conflicting this significance is probably not important. Synergism was not found.

Dynamic Lung Compliance.

As can be seen from Fig. 6: 9 and Table 6: 5 these results were similar to those obtained for total compliance.

Discussion

The results for total dynamic compliance and lung compliance confirm Watson's (1962a) studies and the study by Sykes and Lumley (1969). Finlay et al. (1970) and

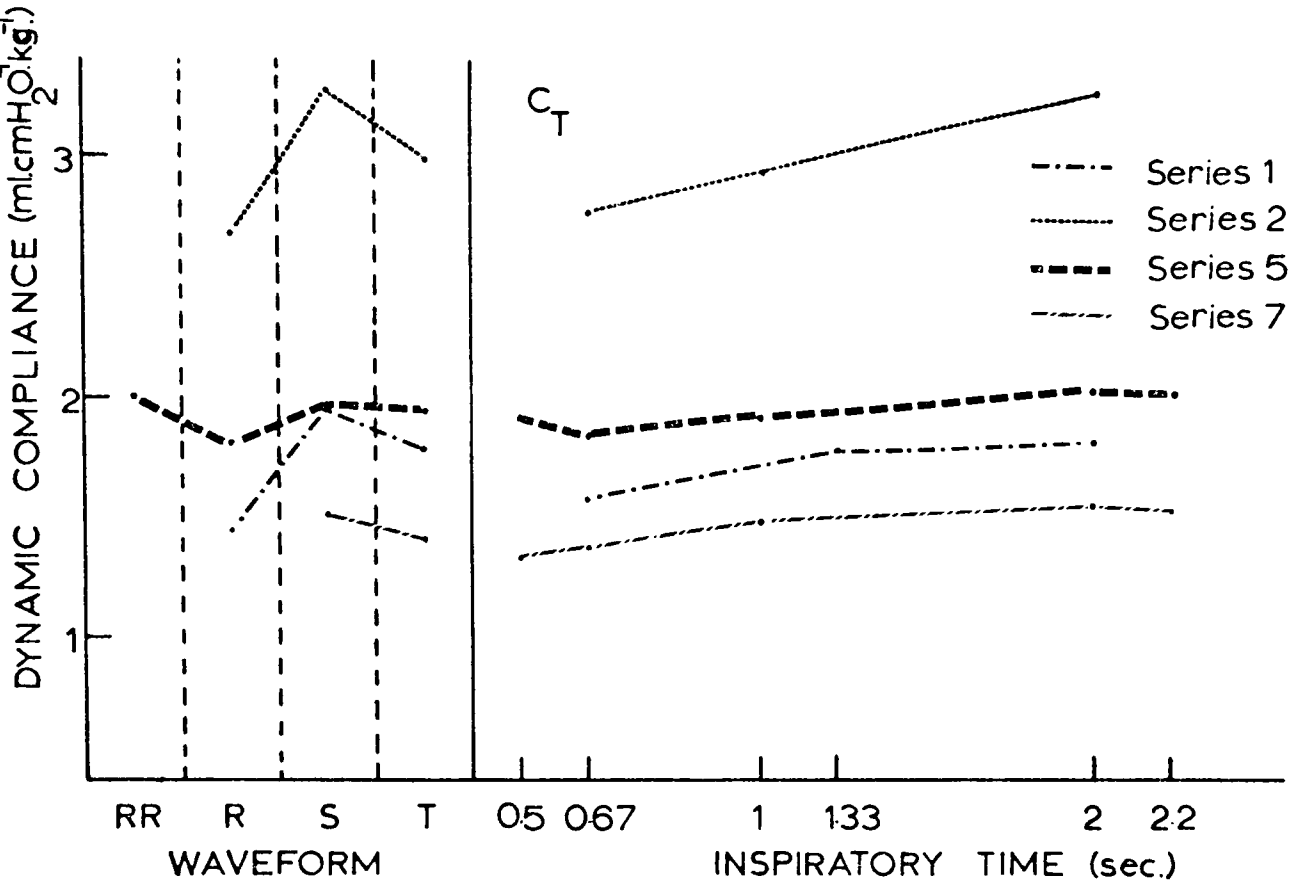


Fig. 6:7 Changes in mean total dynamic compliance with different inspiratory waveforms and times. Waveform symbols as for Fig. 6:6.

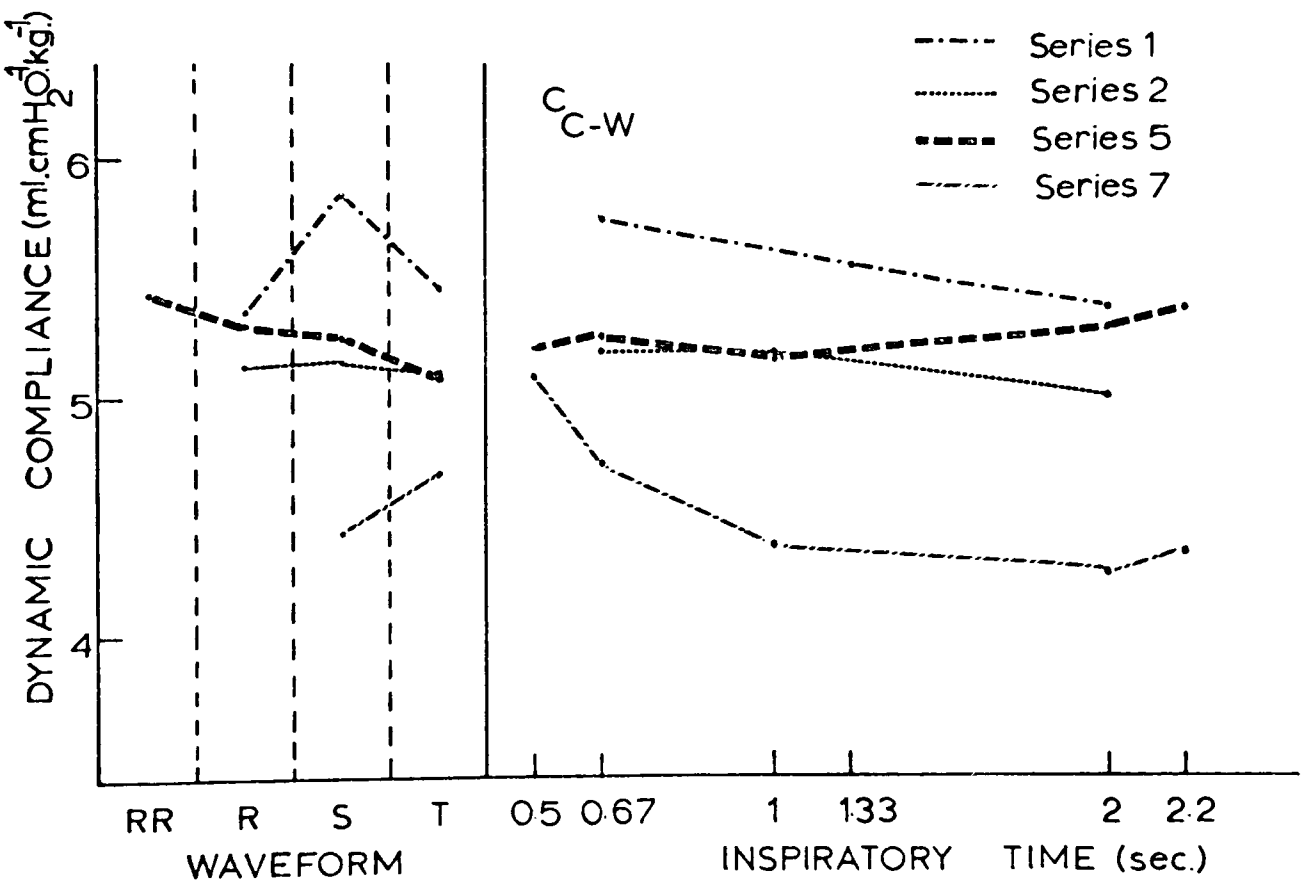


Fig. 6:8 Changes in mean dynamic chest wall compliance with different inspiratory waveforms and times. Waveform symbols as for Fig. 6:6.

TABLE 6: 3

Inspiratory variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
			Means (ml. cm. $H_2O^{-1}.kg^{-1}$.)				
2.2			2.28±0.48	2.02±0.52	2.02±0.52	1.92±0.51	1.53±0.21
2.0	1.81±0.40	3.26±1.36	2.38±0.65	2.04±0.53	2.04±0.53	1.91±0.47	1.56±0.20
1.33	1.79±0.46						
1.0		2.94±1.11	2.13±0.43	1.92±0.50	1.92±0.50	1.83±0.52	1.49±0.24
0.67	1.58±0.36	2.77±1.04	2.05±0.40	1.85±0.49	1.85±0.49	1.79±0.51	1.38±0.17
0.5					1.91±0.59	1.82±0.58	1.34±0.16
S.E.D.	0.069	0.14	0.113	0.046	0.047	0.053	0.018
R.R.				2.07±0.52	2.06±0.52	1.96±0.52	
R.	1.45±0.23	2.69±1.00	2.03±0.33	1.80±0.48	1.82±0.48	1.74±0.51	
S.	1.94±0.48	3.28±1.44	2.29±0.53	2.00±0.51	1.97±0.51	1.88±0.47	1.51±0.22
T.	1.79±0.35	2.99±1.01	2.32±0.59	1.95±0.55	1.95±0.55	1.84±0.51	1.41±0.21
S.E.D.	0.069	0.14	0.098	0.046	0.042	0.048	0.011

Table continued on following page

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Inspiratory variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
				Statistical Probability			
2.2/2.0							
2.0/1.33							
1.33/0.67	.005						
2.2/1.0				.025	.025		.025
2.0/1.0		.05		.02	.02		.001
2.0/0.67	.005	.005		.001	.001	.025	.001
1.0/0.67							.001
0.67/0.5							.05
1.0/0.5							.001
2.2/0.67				.001	.001	.02	.001
2.2/0.5					.02		.001
2.0/0.5					.01		.001
R.R/R				.001	.001	.001	
R./S.	.001	.001	.05	.001	.001	.01	
R.R./S.					.05		
S./T.		.05					.001
R.R./T.				.02	.02	.01	
R./T.	.001	.05	.02	.001	.005		
Synergism							+

Table: Statistical results and significance for total dynamic compliance. Abbreviations are as shown in Table 6: 2

TABLE 6: 4

Inspiratory variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
			Means (ml. cm. $H_2O^{-1}.kg^{-1}$.)				
2.2			4.78±2.03	5.37±1.26	5.37±1.26	5.51±0.99	4.34±1.81
2.0	5.38±0.80	5.00±1.97	4.84±2.18	5.29±1.39	5.29±1.39	5.39±1.15	4.27±1.56
1.33	5.55±0.82						
1.0		5.19±2.06	4.80±2.22	5.17±1.14	5.17±1.14	5.30±0.81	4.38±1.95
0.67	5.74±1.00	5.19±2.06	4.89±2.50	5.25±1.41	5.26±1.41	5.43±0.76	4.72±3.01
0.5					5.21±0.88	5.31±0.78	5.08±3.37
S.E.D.	0.21	0.24	0.140	0.102	0.101	0.127	0.45
R.R.				5.44±1.28	5.44±1.28	5.56±1.28	
R.	5.36±0.79	5.13±1.95	4.86±2.09	5.30±1.29	5.31±1.29	5.46±0.80	
S.	5.85±0.49	5.15±2.14	4.91±2.16	5.27±1.14	5.21±1.14	5.33±0.68	4.44±2.26
T.	5.46±1.19	5.10±2.01	4.72±2.07	5.07±1.19	5.09±1.19	5.20±0.84	4.67±3.05
S.E.D.	0.21	0.24	0.122	0.102	0.090	0.113	0.28

Table continued on following page

Continuation of table from previous page

Inspiratory variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
			Statistical Probability				
2.2/2.0							
2.0/1.33							
1.33/0.67							
2.2/1.0							
2.0/1.0							
2.0/0.67							
1.0/0.67							
0.67/0.5							
1.0/0.5							
2.2/0.67							
2.2/0.5							
2.0/0.5							
R.R/R							
R./S.							
R.R./S.							
S./T.				.02	.05		
R.R./T.			.05				
R./T.			.001	.001	.005		
			.025	.025	.05		
Synergism							

Table: Statistical results and significance for dynamic chest wall compliance. Abbreviations are as shown in Table 6:2

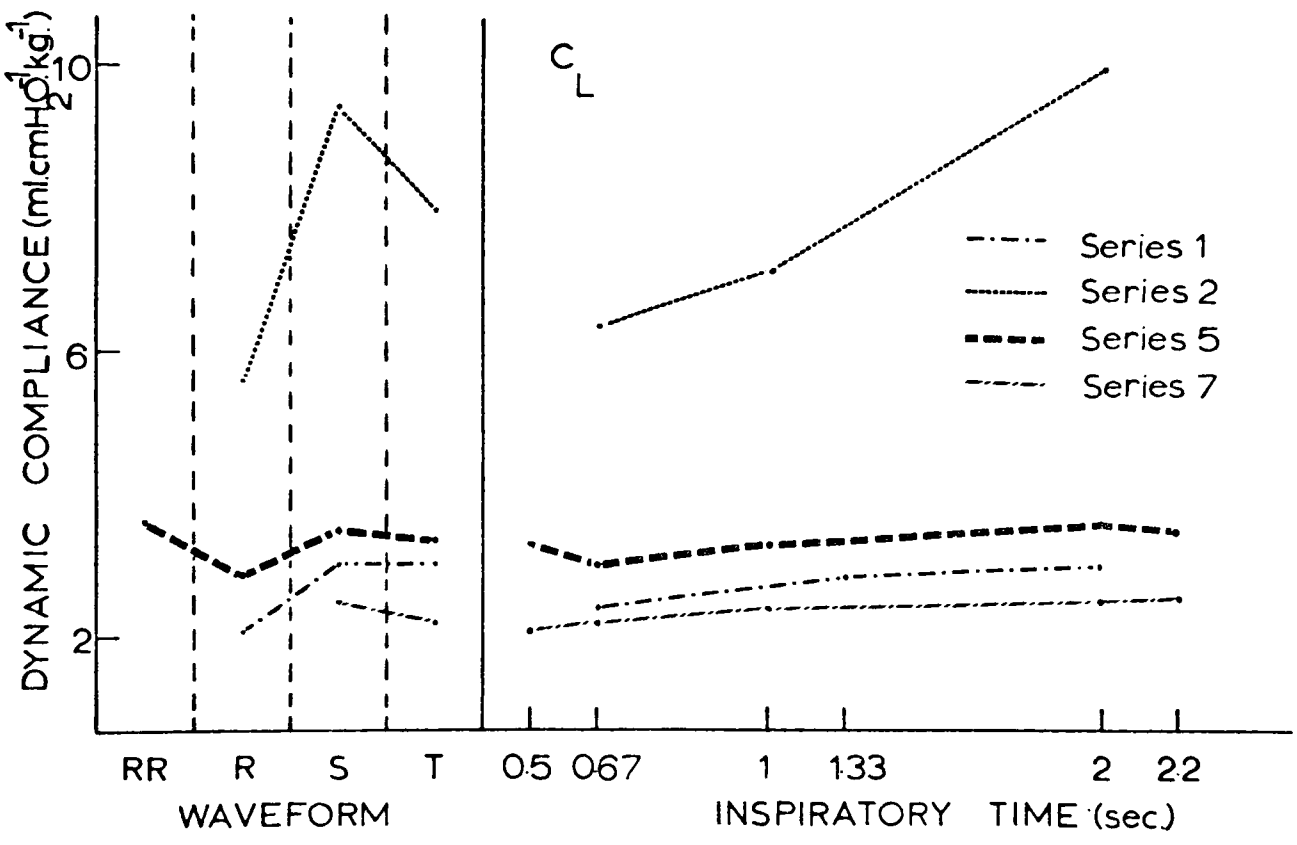

Fig. 6:9 Changes in mean dynamic lung compliance with different inspiratory waveforms and times. Waveform symbols as for Fig. 6:6.

TABLE 6: 5

Inspiratory variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
			Means (ml. cm. H_2O^{-1}.kg $^{-1}$.)				
2.2			4.87±0.67	3.53±1.28	3.53±1.28	3.08±1.14	2.55±0.56
2.0	3.00±1.39	10.03±5.65	5.28±1.07	3.63±1.36	3.63±1.36	3.09±1.04	2.55±0.53
1.33	2.83±1.14						
1.0		6.84±2.41	4.47±0.90	3.29±1.34	3.29±1.34	2.91±1.32	2.43±0.44
0.67	2.30±0.81	6.40±3.10	3.89±0.42	3.04±1.11	3.05±1.11	2.74±1.16	2.16±0.44
0.5					3.27±1.36	2.89±1.39	2.07±0.42
S.E.D.	0.22	0.96	0.38	0.127	0.134	0.138	0.088
R.R.				3.59±1.28	3.57±1.28	3.16±1.28	
R.	2.06±0.54	5.90±2.33	3.93±0.64	2.92±1.09	2.95±1.09	2.62±1.05	
S.	3.04±1.06	9.40±5.19	4.84±0.88	3.53±1.30	3.47±1.30	3.03±1.10	2.47±0.56
T.	3.03±1.45	7.98±4.15	5.10±0.92	3.45±1.43	3.43±1.43	2.96±1.25	2.23±0.42
S.E.D.	0.22	0.96	0.33	0.127	0.120	0.124	0.055

Table continued on following page

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Inspiratory variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
			Statistical Probability				
2.2/2.0							
2.0/1.33							
1.33/0.67	.025						
2.2/1.0							
2.0/1.0		.005		.01			
2.0/0.67	.005	.001	.005	.001	.001	.02	.001
1.0/0.67				.05			.005
0.67/0.5							
1.0/0.5							.001
2.2/0.67			.05	.001	.001	.02	.001
2.2/0.5							.001
2.0/0.5					.01		.001
R.R/R				.001	.001	.001	
R./S.	.001	.005	.025	.001	.001	.005	
R.R./S.							
S./T.							.001
R.R./T.							
R./T.	.001	.05	.01	.001	.001	.01	

Synergism

Table: Statistical results and significance for dynamic lung compliance.
Abbreviations are as shown in Table 6: 2

Lyager (1970) did not agree with this finding. Sykes and Lumley (1969) and Finlay et al. (1970) both used indirect methods to assess compliance and Lyager's (1970) study is difficult to interpret. Watson (1962a) and Adams et al. (1970) did not obtain statistically significant differences with different inspiratory flow waveforms and the explanation may be the same as for V_D/V_T ratio. The difference in Series 7 between sine and tophat flow may be explained by the fact that the autonomic nervous system was blocked in these experiments and it is possible that the blood flow through the lung varied more with one inspiratory flow pattern than with another. The means of the control/blocked states (1.48/1.44 $ml.cmH_2O^{-1}.kg^{-1}$) were statistically significant at the 0.005 level but there was no drug/wave synergism. The best inspiratory flow patterns in order are, once again, reversed ramp, sine, tophat and ramp flow. No other studies have been reported on chest wall dynamic compliance with variations of inspiratory flow patterns, though Watson (1962c) stated that he had results indicating a decrease in chest wall compliance with decrease in the duration of inspiration. The consistent results for chest wall dynamic compliance obtained in the present study suggests that the reduction of total dynamic compliance is due at least in part to maldistribution of inspired gas to alveolar units with different time constants.

P_{a,O_2}

Results

Fig. 6: 10 shows the relationship obtained between P_{a,O_2} and inspiratory time and waveform. Table 6: 6 shows the means and S.D. together with their statistical significance. Changes with I:E ratio are not statistically significant except in Series 7 where there is a marked

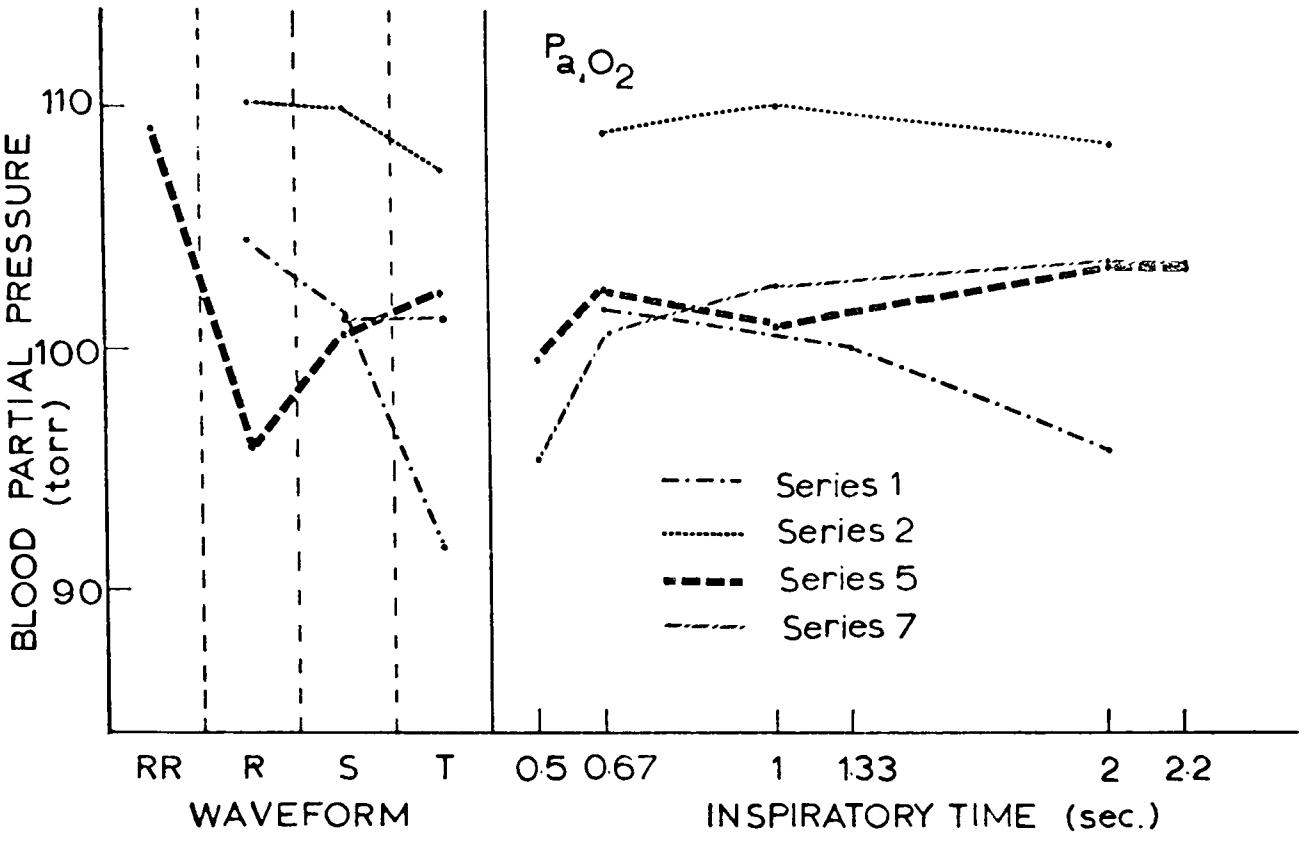

Fig. 6:10 Changes in mean P_{a,O_2} with different inspiratory waveforms and times. Waveform symbols as for Fig. 6:6.

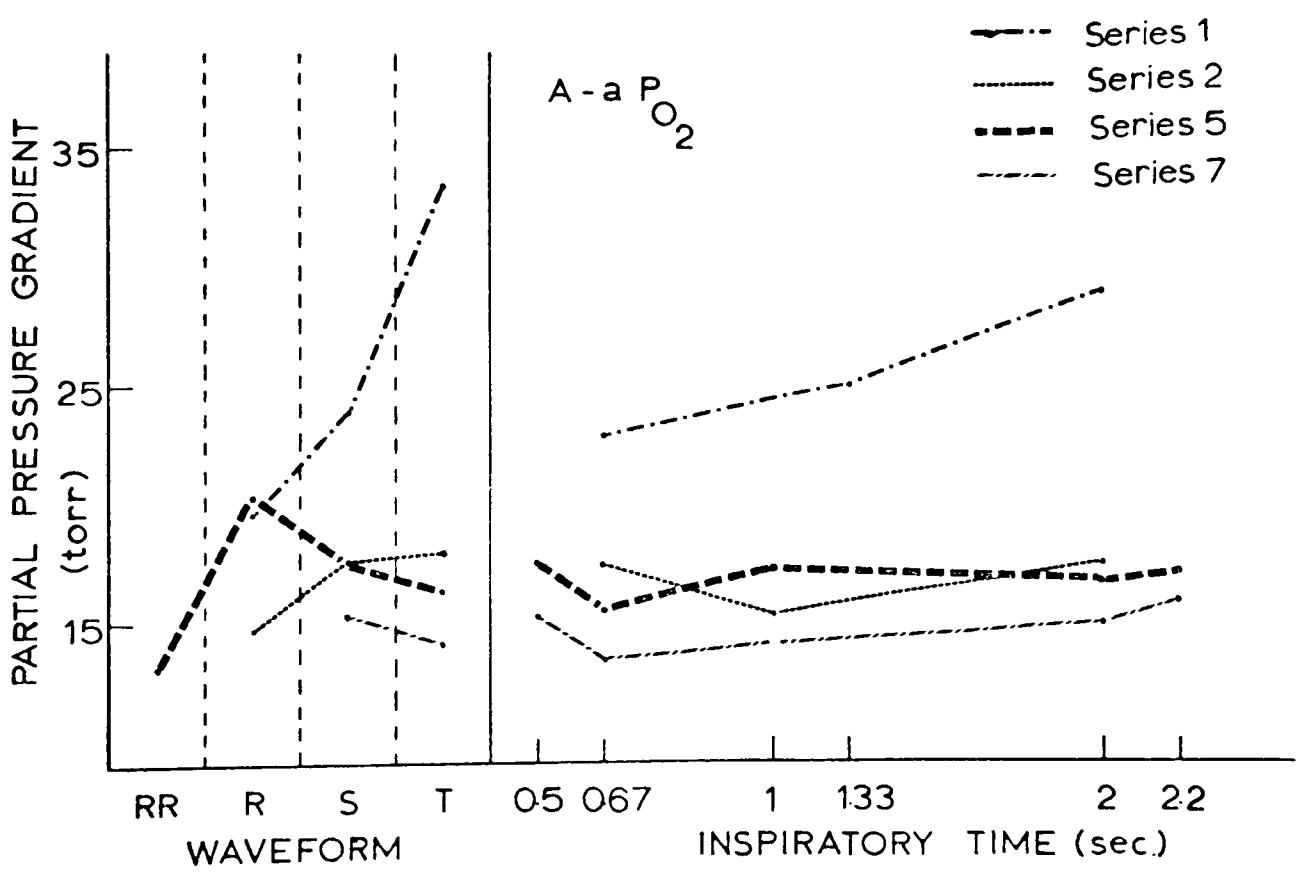

Fig. 6:11 Changes in mean A - a P_{O_2} gradient with different inspiratory waveforms and times. Waveform symbols as for Fig. 6:6.

TABLE 6:6

Inspiratory Variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
			Means (torr)				
2.2			114.3±7.7	103.4±11.9	103.4±11.9	98.8±10.8	103.6±10.5
2.0	95.9±11.7	108.6±2.8	112.3±8.5	103.5±11.2	103.5±11.2	99.3±10.3	103.8±9.3
1.33	100.1±12.2						
1.0		110.1±3.0	116.7±6.8	101.0±11.2	101.0±11.2	95.9±9.1	102.7±9.7
0.67	101.7±11.7	109.0±4.7	113.8±3.4	102.4±10.3	102.5±10.3	97.8±9.1	100.7±8.5
0.5					99.6±8.8	95.1±8.1	95.4±10.9
S.E.D.	3.39	1.43	3.45	1.37	1.36	1.61	1.67
R.R				109.6±10.7	109.1±10.7	104.6±10.7	
R.	104.5±13.1	110.2±2.4	110.2±4.2	96.6±10.4	95.9±10.4	91.2±7.3	
S.	101.5±9.1	110.0±3.8	115.5±5.2	101.3±11.5	100.6±11.5	95.9±8.9	101.2±12.2
T.	91.7±9.9	107.4±4.0	117.1±8.2	102.7±10.3	102.3±10.3	97.8±7.0	101.3±7.9
S.E.D.	3.39	1.43	2.99	1.37	1.21	1.44	1.06

Table continued on following page

Table continued from previous page

Inspiratory variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
			Statistical Probability				
2.2/2.0							
2.0/1.33							
1.33/0.67							
2.2/1.0							.05
2.0/1.0							
2.0/0.67							
1.0/0.67							
0.67/0.5					.05		.005
1.0/0.5							.001
2.2/0.67							
2.2/0.5							.001
2.0/0.5					.01	.02	.001
R.R/R			.001		.001	.001	
R./S.			.001		.001	.005	
.R.R./S			.001		.001	.001	
S./T.	.01						.001
R.R./T.			.001		.001	.001	
R./T.	.001		.001		.001	.001	
Synergism							+

Table: Means $\pm$ S.D. of P_{a,O_2} for different series of experiments.

Abbreviations are as shown in Table 6:2.

decrease of P_{a,O_2} with very short inspiratory times. Differences with different waveforms are, however, statistically significant with reversed ramp flow giving the highest P_{a,O_2} values, followed by tophat and sine flows which were not significantly different statistically. Ramp flow produced the lowest P_{a,O_2} values except in Series 1 and 2. Synergism for waveform and inspiratory time was found in Series 7.

Discussion

Other studies of P_{a,O_2} have been reported by Fairley and Blenkarn (1966), Bergman (1967), Finlay et al. (1970) and Lyager (1970) none of whom found any significant difference when the inspiratory time was shortened. Lyager's (1970) results are again rather difficult to interpret but seem to indicate an increase in P_{a,O_2} with a ramp or sine flow waveform. The I:E ratio, however, is also altered in his studies so that little reliability can be placed on this finding. Knelson et al. (1969 and 1970) showed an increase in P_{a,O_2} when an end-inspiratory pause was introduced but as previously indicated this manoeuvre increased inspiratory time so that their results may be confirmatory evidence for the results obtained in Series 7 and evident as a trend in certain other Series (Fig. 6:10 and Table 6:6). The synergism found in Series 7 also suggest that this trend is genuine. Series 7 admittedly includes animals with blocked autonomic nervous systems, but there was no significant difference in P_{a,O_2} between control and blocked animals.

A - a P_{O_2} Gradient.

Results

The relationships between A - a P_{O_2} gradient and

inspiratory time and waveform are shown in Fig. 6:11. The means and S.D. of these results are shown in Table 6:7 with their statistical significance. Changes in I:E ratio did not significantly alter the A - a P_{O_2} gradient. The series of experiments performed with variation of the inspiratory waveform were contradictory, but probably the lowest A - a P_{O_2} gradient would be obtained with a reversed ramp flow waveform. Synergism was found only in Series 7.

Discussion

The results of changes in the I:E ratio on A - a P_{O_2} gradient confirm most other studies, except the study reported by Bergman (1963). Bergman found an increase in A - a P_{O_2} gradient with shortening of inspiration, but his results were not statistically significant. Bergman's (1963) experiments were the only previous ones in which air was used as the ventilatory gas, and it has been suggested (Finlay etal. 1970) that all other studies obsured the gradient changes by using more than 30% oxygen in the inspired mixture. The present study also used air as the ventilating gas but no significant alteration of A - a P_{O_2} gradient with I:E ratio was shown. No other study has found changes in A - a P_{O_2} gradient with inspiratory gas flow waveforms, and as stated the present study is inconclusive.

P_{a,CO_2}

Results

Fig. 6:12 and Table 6:8 demonstrate the relationships obtained for P_{a,CO_2} and inspiratory time and waveform. Changes in I:E ratio did not produce statistically significant changes in P_{a,CO_2} except in Series 7 when the P_{a,CO_2}

TABLE 6: 7

Inspiratory Variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
			Means (torr)				
2.2			14.1±5.4	17.1±7.1	17.1±7.1	18.5±7.3	15.9±9.7
2.0	29.0±12.6	17.5±4.6	14.9±5.2	16.7±7.3	16.7±7.3	18.0±7.7	14.9±8.6
1.33	25.0±11.0						
1.0		15.3±2.8	11.2±3.6	17.2±6.7	17.2±6.7	19.0±6.7	14.0±8.9
0.67	22.9±9.4	17.4±5.9	12.6±3.8	15.5±7.7	15.5±7.7	17.1±8.4	13.4±6.2
0.5					17.5±7.1	19.1±7.2	15.3±8.0
S.E.D.	3.11	1.81	2.77	1.35	1.31	1.58	1.45
R.R.				12.9±6.0	13.1±6.0	14.6±6.0	
R.	19.6±11.8	14.7±4.2	13.2±4.8	19.8±8.3	20.3±8.3	22.5±8.1	
S.	23.8±6.0	17.6±4.9	14.0±3.7	17.6±7.6	17.5±7.6	18.8±8.1	15.3±8.7
T.	33.4±10.4	17.9±4.8	12.3±4.9	16.1±6.1	16.2±6.1	17.4±6.1	14.1±7.9
S.E.D.	3.11	1.81	2.40	1.35	1.18	1.41	0.92

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Continuation of table from previous page

Inspiratory Variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
				Statistical Probability			
2.2/2.0							
2.0/1.33							
1.33/0.67							
2.2/1.0				.01			
2.0/1.0				.02			
2.0/0.67				.01			
1.0/0.67							
0.67/0.5							
1.0/0.5							
2.2/0.67				.005			
2.2/0.5							
2.0/0.5							
R.R/R.				.001	.001	.001	
R./S.				.005	.025	.01	
R.R./S.				.001	.001	.005	
S./T.							
R.R./T.				.001	.01	.05	
R./T.				.01	.001	.001	
Synergism							

Table: Statistical results and significance for A-a PO_2. Abbreviations are as shown in Table 6: 2

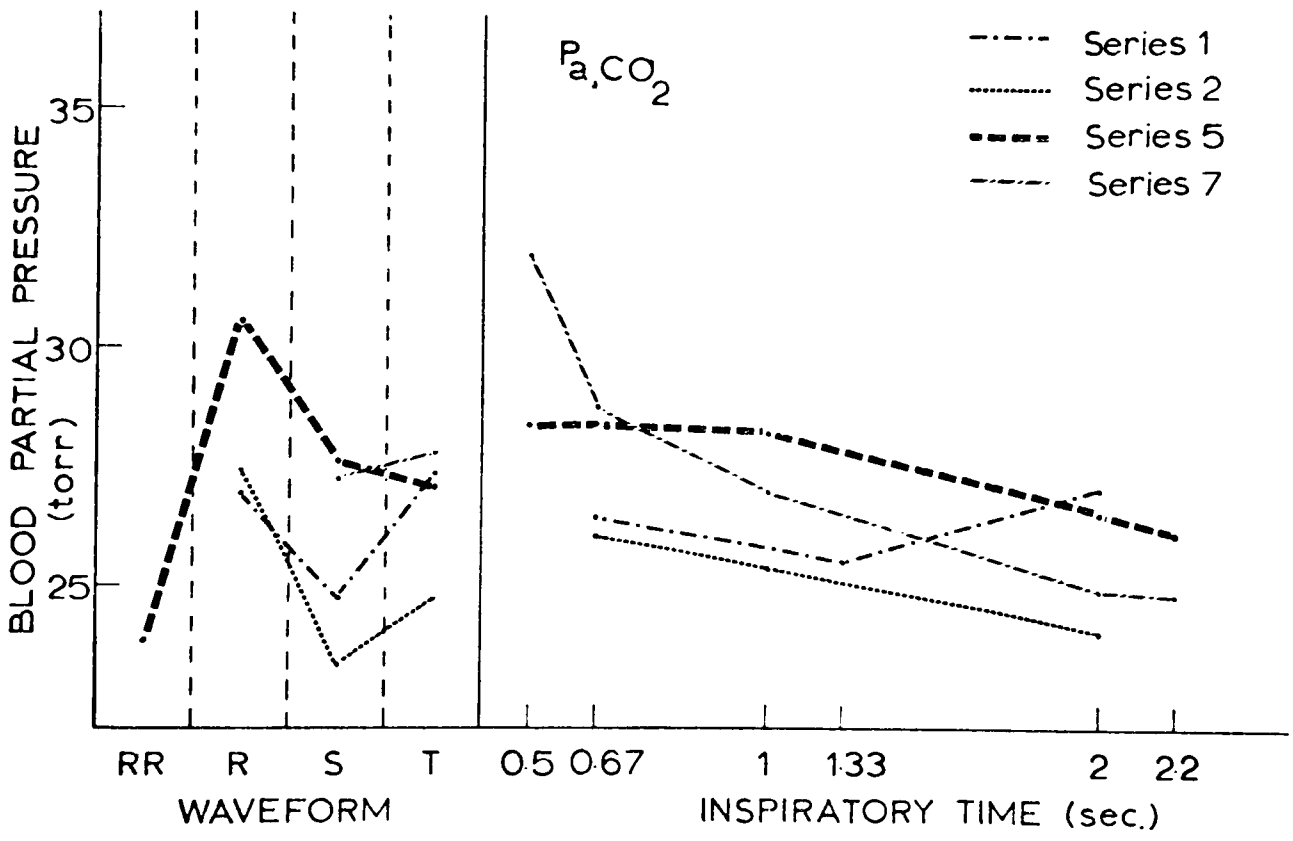

Fig. 6:12 Changes in mean P_{a,CO_2} with different inspiratory waveforms and times. Waveform symbols as for Fig. 6:6.

TABLE 6: 8

Inspiratory Variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
			Means (torr)				
2.2			20.0±3.9	26.1±8.1	26.2±8.1	28.6±8.0	24.9±5.4
2.0	27.1±4.8	24.1±1.8	21.3±3.4	26.6±7.8	26.6±7.8	28.8±7.9	24.9±5.6
1.33	25.5±4.4						
1.0		25.4±2.6	21.2±3.0	28.3±8.5	28.3±8.5	30.7±8.5	27.0±5.6
0.67	26.5±5.6	26.1±4.0	22.1±3.1	28.5±7.4	28.5±7.4	30.6±7.7	28.8±6.2
0.5					28.4±8.9	30.7±9.0	32.0±8.4
S.E.D.	0.49	1.06	0.96	0.73	0.73	0.91	0.86
R.R				24.6±6.0	24.8±6.0	27.1±6.0	
R.	27.0±5.1	27.4±3.4	24.9±1.6	30.8±9.0	30.6±9.0	32.6±9.9	
S.	24.8±4.5	23.4±1.7	19.4±2.3	27.0±8.6	27.7±8.6	30.2±8.2	27.2±7.6
T.	27.4±5.0	24.8±2.4	19.1±1.6	27.0±7.3	27.2±7.5	29.7±6.7	27.8±5.9
S.E.D.	0.49	1.06	0.83	0.73	0.65	0.81	0.54

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Inspiratory Variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
			Statistical Probability				
2.2/2.0							
2.0/1.33	.005						
1.33/0.67							
2.2/1.0				.005	.005	.05	.02
2.0/1.0				.025		.05	.02
2.0/0.67				.01	.02	.05	.001
1.0/0.67					.05		.05
0.67/0.5							.001
1.0/0.5							.001
2.2/0.67				.005	.005	.05	.001
2.2/0.5					.005	.05	.001
2.0/0.5					.02	.05	.001
R.R/R.				.001	.001	.001	
R./S.	.001	.001	.001	.001	.001	.005	
R.R./S.				.005	.001	.001	
S./T.	.001						
R.R./T.				.005	.001	.005	
R./T.		.025	.001	.001	.001	.001	
Synergism	+	+					+

Table: Statistical results and significance for P_{a,CO_2}. Abbreviations are as shown in Table 6:[2]

was significantly raised with the shortest inspiratory time. There was, however, in Series 7 a difference of 30 ml in mean tidal volume between the two I:E ratios used. The inspiratory waveform was important, results showing that the lowest P_{a,CO_2} was obtained with the reversed ramp flow and the highest with the ramp flow. Synergism for waveform and inspiratory time was found in Series 1, 2 and 7.

Discussion

These results confirm previous studies. Bergman (1967) found a non-statistically significant increase in P_{a,CO_2} with shortening of inspiration but Fairley and Blenkarn (1966) did not, whereas Lyager (1970) shows an increase in some of his experiments and not in others. Knelson et al. (1969 and 1970) found a rise in P_{a,CO_2} in both their studies with their shorter inspiratory time. The significant differences of P_{a,CO_2} and P_{a,O_2} in Series 7 with the shortest inspiratory time might have been due to the tidal volume difference referred to above. Adams et al. (1970) did not find that inspiratory flow waveform influenced P_{a,CO_2}. The results of the present study suggest that there is an increase in the P_{a,CO_2} with shortening of inspiration although this is not statistically significant. This trend together with the statistically significant influence of flow waveform and the synergism exhibited in Series 1, 2 and 7 would suggest that the results for V_D/V_T and P_{a,CO_2} are consistent.

a - A P_{CO_2} Gradient and P_{A,CO_2}

Results

The results of calculations of P_{A,CO_2} and a - A P_{CO_2} .

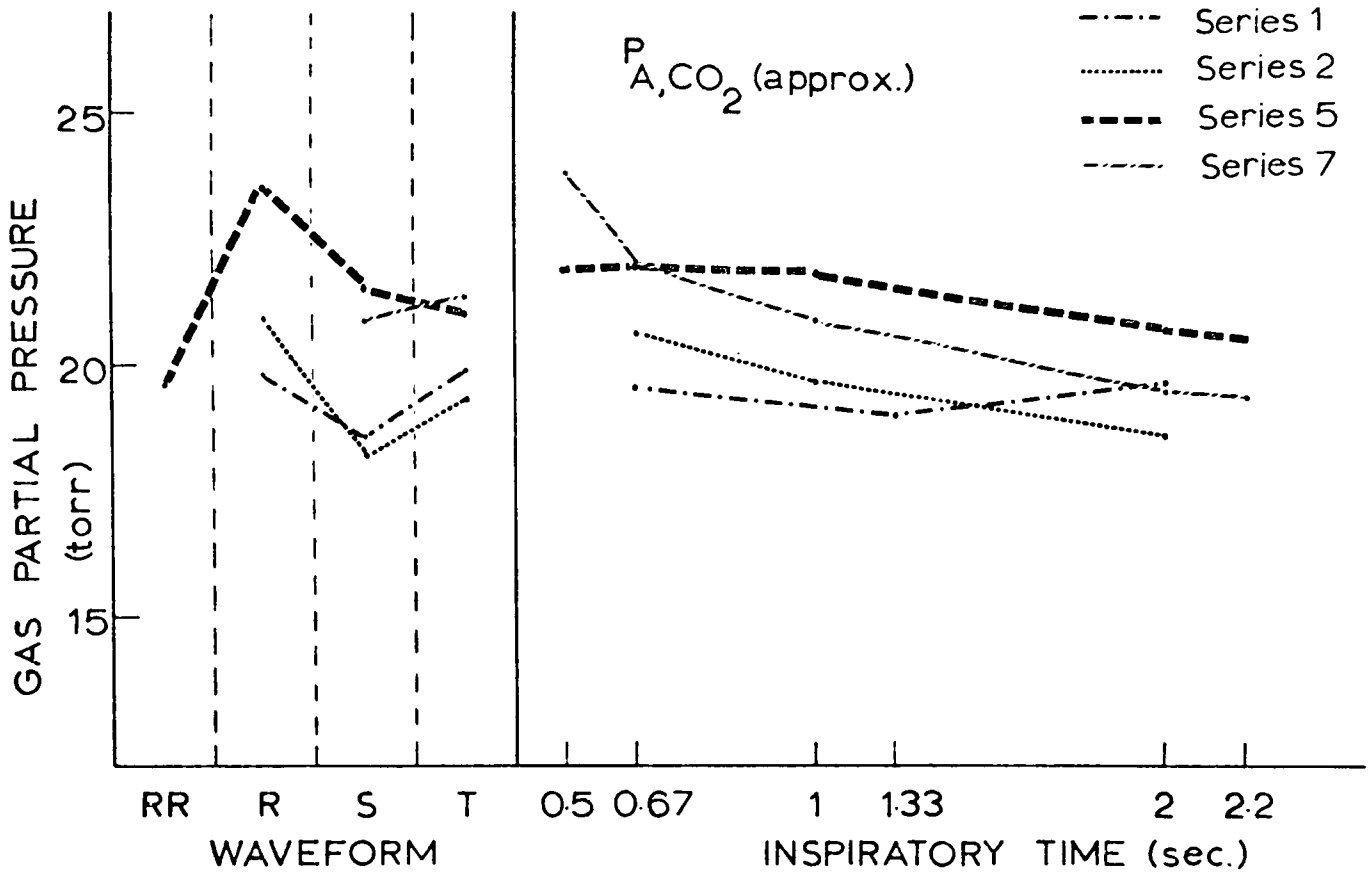

Fig. 6:13 Changes in mean P_{A,CO_2} with different inspiratory waveforms and times. Waveform symbols as for Fig. 6:6.

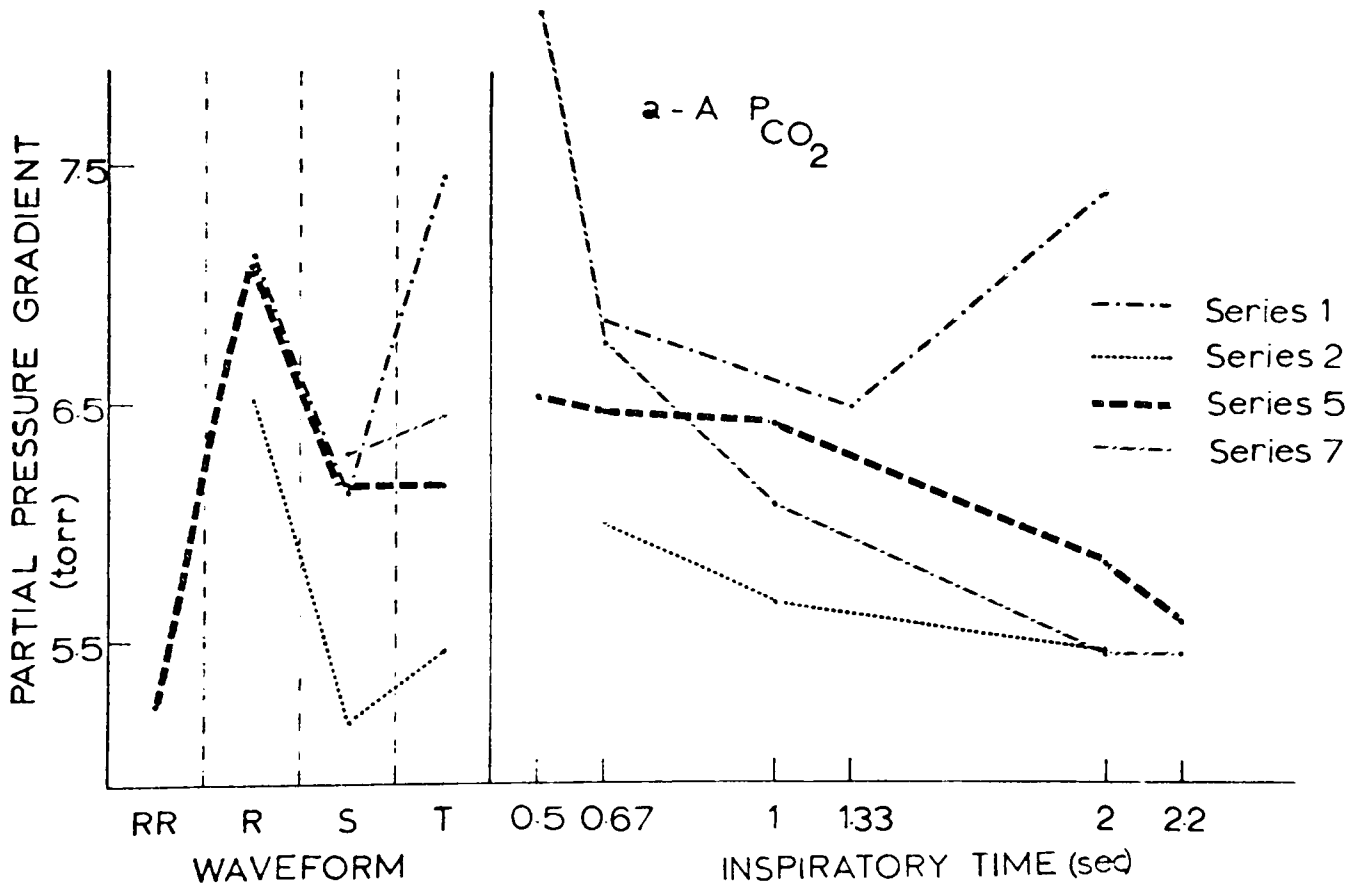

Fig. 6:14 Changes in mean a - A P_{CO_2} gradient with different inspiratory waveforms and times. Waveform symbols as for Fig. 6:6.

TABLE 6:9

Inspiratory variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
			Means (torr)				
2.2			15.8±2.7	20.6±6.5	20.6±6.5	22.5±6.5	19.4±3.8
2.0	19.7±3.5	18.6±1.4	16.5±2.5	20.7±6.2	20.7±6.2	22.5±6.2	19.5±3.9
1.33	19.1±3.3						
1.0		19.7±2.0	16.6±2.4	21.9±6.5	21.9±6.5	23.7±6.6	20.9±3.8
0.67	19.6±3.8	20.1±2.7	17.3±2.4	22.0±5.5	22.0±5.5	23.6±5.8	22.1±4.3
0.5					21.9±6.6	23.6±6.7	23.8±5.3
S.E.D.	0.27	0.76	0.67	0.54	0.54	0.68	0.57
R.R.				19.5±4.8	19.6±4.8	21.3±4.8	
R.	19.8±3.5	20.9±2.6	19.2±1.1	23.7±7.2	23.5±7.2	25.0±8.1	
S.	18.6±3.4	18.2±1.4	15.3±1.7	21.1±6.8	21.5±6.8	23.4±6.6	20.9±5.0
T.	19.9±3.6	19.3±1.4	15.1±1.4	20.9±5.4	21.0±5.4	22.9±5.0	21.4±3.9
S.E.D.	0.27	0.76	0.58	0.54	0.48	0.60	0.36

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Inspiratory variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
				Statistical Probability			
2.2/2.0							
2.0/1.33	.025						
1.33/0.67	.05						
2.2/1.0				.02	.02		.01
2.0/1.0				.05	.05		.02
2.0/0.67				.02	.025		.001
1.0/0.67							
0.67/0.5							.005
1.0/0.5							.001
2.2/0.67				.01	.01		.001
2.2/0.5					.02		.001
2.0/0.5					.05		.001
R.R/R				.001	.001	.001	
R./S.	.001	.005	.001	.001	.001	.02	
R.R./S.				.005	.001	.001	
S./T.	.001						
R.R./T.				.02	.005	.02	
R./T.		.05	.001	.001	.001	.001	
Synergism	+						

Table: Statistical results and significance for $P_{A,CO_2}(approx)$.
Abbreviations are as shown in Table 6: 2

TABLE 6: 10

Inspiratory variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
			Means (torr)				
2.2			4.2±1.2	5.6±1.9	5.6±1.9	6.2±1.8	5.5±1.7
2.0	7.4±2.0	5.5±0.5	4.9±1.3	5.8±1.9	5.8±1.9	6.3±1.9	5.4±1.7
1.33	6.5±1.1						
1.0		5.7±0.8	4.6±0.6	6.4±2.1	6.4±2.1	7.0±2.1	6.1±1.6
0.67	6.9±2.0	6.0±1.5	4.8±0.8	6.5±2.0	6.5±2.0	7.0±2.1	6.8±2.0
0.5					6.5±2.5	7.1±2.5	8.2±3.2
S.E.D.	0.27	0.33	0.33	0.21	0.21	0.26	0.31
R.R.				5.2±1.6	5.2±1.6	5.8±1.6	
R.	7.1±1.8	6.5±0.9	5.7±0.6	7.1±2.2	7.1±2.2	7.6±2.4	
S.	6.1±1.2	5.2±0.5	4.1±0.7	5.9±2.1	6.1±2.1	6.7±2.0	6.3±2.7
T.	7.5±2.0	5.5±1.0	4.1±0.4	6.1±1.9	6.2±1.9	6.8±1.8	6.5±1.9
S.E.D.	0.27	0.33	0.29	0.21	0.19	0.23	0.20

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Inspiratory variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
				Statistical Probability			
2.2/2.0							
2.0/1.33	.025						
1.33/0.67	.05						
2.2/1.0				.001	.001	.005	.05
2.0/1.0				.01	.01	.01	.05
2.0/0.67				.001	.001	.01	.001
1.0/0.67							.05
0.67/0.5							.001
1.0/0.5							.001
2.2/0.67				.001	.001	.005	.001
2.2/0.5					.001	.001	.001
2.0/0.5					.001	.01	.001
R.R/R				.001	.001	.001	
R./S.	.001	.001	.001	.001	.001	.001	.001
R.R./S.				.001	.001	.001	
S./T.	.001						
R.R./T.				.001	.001	.001	
R./T.		.005	.001	.001	.001	.005	
Synergism	+			+	+		

Table: Statistical results and significance for a - A P_{CO_2}.

Abbreviations are as shown in Table 6:2

gradient are shown in Figs. 6:13 and 14 and Tables 6:9 and 10. The P_{A,CO_2} increased marginally with shortening of inspiration in most experiments except in Series 7 where the increase was much greater. The a - A P_{CO_2} gradient responded in a similar manner. Changes in inspiratory flow waveform change the P_{A,CO_2} and a - A P_{O_2} gradient. In both cases the reversed ramp flow produces the lowest values and ramp flow the highest, with sine and tophat flow waveforms intermediate and not statistically different from one another. Synergism between waveform and inspiratory time was found for a - A P_{CO_2} gradient with one Series exhibiting synergism for P_{A,CO_2}.

Discussion

As explained in Chapter 3 (c) these results are an approximation and must be regarded with reserve. Studies by Bergman (1963) and Finlay et al. (1970) confirm these findings with measured end-tidal CO_2 readings. No other studies of the variation of gas flow pattern upon P_{A,CO_2} or a - A P_{CO_2} gradient have been reported.

Cardiac Output and Mean Airway and Intrathoracic Pressures.

Results

Figs. 6:15 and 16 show the relationship obtained between the cardiac output measured by dye dilution and direct Fick methods and the inspiratory time and waveform. Tables 6: 11 and 12 illustrate the means and S.D. of the results together with their statistical significance. Figs. 6:17 and 18 and Tables 6:13 and 14 illustrate similar relationships for mean airway and intrathoracic pressures.

Variations in the I:E ratio did not affect the

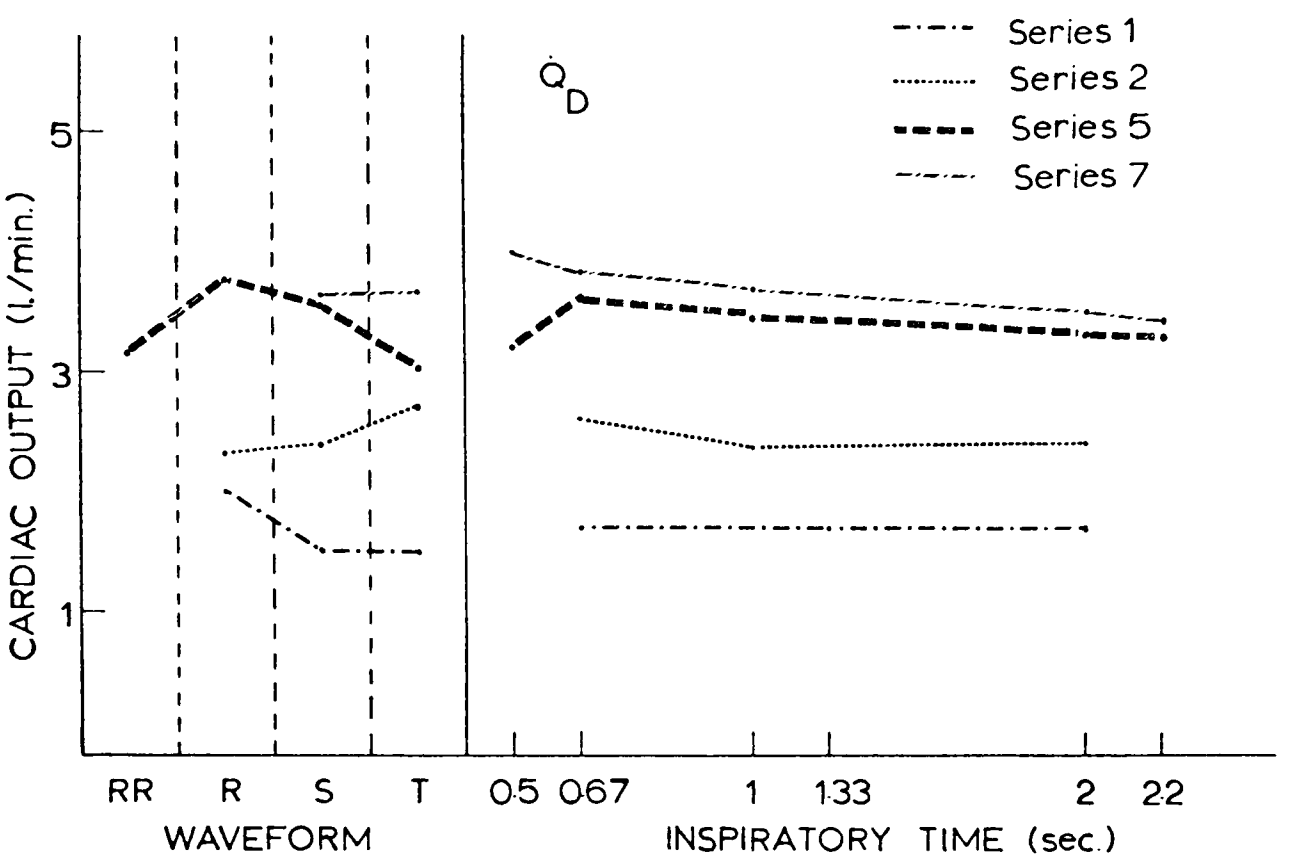

Fig. 6:15 Changes in mean cardiac output (measured by the dye dilution technique) with different inspiratory waveforms and times. Waveform symbols as for Fig. 6:6.

Fig. 6:16 Changes in mean cardiac output (measured by the direct Fick method) with different inspiratory waveforms and times. Waveform symbols as for Fig. 6:6.

TABLE 6: 11

Inspiratory variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
			Means (l./min.)				
2.2			1.72±0.24	3.32±2.66	3.32±2.66	3.90±2.82	3.45±0.97
2.0	1.67±0.35	2.42±1.14	1.88±0.33	3.31±2.48	3.31±2.48	3.83±2.63	3.53±1.03
1.33	1.70±0.36						
1.0		2.40±0.95	2.09±0.45	3.46±2.42	3.47±2.42	3.97±2.55	3.70±0.84
0.67	1.71±0.38	2.62±1.05	2.21±0.65	3.63±1.95	3.62±1.95	4.06±2.20	3.84±0.93
0.5					3.22±2.44	3.73±2.52	3.99±1.27
S.E.D.	0.08	0.17	0.14	0.23	0.23	0.29	0.15
R.R.				3.20±1.58	3.16±1.58	3.67±1.58	
R.	2.01±0.41	2.32±0.63	2.39±0.49	3.89±2.67	3.78±2.67	4.26±3.05	
S.	1.53±0.17	2.41±1.04	1.76±0.34	3.55±2.83	3.56±2.83	4.14±3.03	3.66±1.15
T.	1.53±0.16	2.71±1.38	1.77±0.08	3.08±2.04	3.05±2.04	3.51±2.16	3.75±0.88
S.E.D.	0.08	0.17	0.12	0.23	0.20	0.26	0.10

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Inspiratory variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
			Statistical Probability				
2.2/2.0							
2.0/1.33							
1.33/0.67							
2.2/1.0							
2.0/1.0							
2.0/0.67							.05
1.0/0.67							
0.67/0.5							
1.0/0.5							
2.2/0.67							.02
2.2/0.5							.001
2.0/0.5							.005
R.R/R				.005	.005	.05	
R./S.	.001		.001				
R.R./S.					.05		
S./T.				.05	.02	.02	.001
R.R./T.							
R./T.	.001		.001	.001	.001	.01	
Synergism							

Table: Statistical results and significance for cardiac output (dye dilution method). Abbreviations as shown in Table 6: 2

TABLE 6: 12

Inspiratory Variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
			Means (1/min.)				
2.2			1.99±0.60	3.35±2.43	3.35±2.43	3.87±2.58	3.52±0.96
2.0	1.42±0.77	2.70±0.43	1.67±0.71	3.44±2.90	3.44±2.90	4.04±3.05	3.74±0.93
1.33	1.64±0.59						
1.0		3.10±0.28	2.06±0.49	3.65±2.75	3.66±2.75	4.22±2.91	4.05±0.80
0.67	1.61±0.59	2.83±0.43	2.42±0.96	3.86±2.32	3.84±2.32	4.29±2.61	4.31±1.17
0.5					3.38±2.53	3.88±2.59	4.13±1.24
S.E.D.	0.098	0.17	0.25	0.33	0.32	0.41	0.23
R.R.				3.35±1.70	3.39±1.70	3.92±1.70	
R.	1.75±0.59	2.83±0.39	2.72±0.78	3.44±3.31	4.08±3.31	4.57±3.81	
S.	1.57±0.52	2.87±0.50	1.73±0.44	3.65±2.92	3.71±2.92	4.33±3.10	3.83±1.03
T.	1.36±0.79	2.93±0.37	1.66±0.33	3.86±1.74	2.95±3.03	3.41±1.79	4.07±1.08
S.E.D.	0.098	0.17	0.22	0.33	0.29	0.37	0.14

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Inspiratory Variable	Series 1	Series 2	Series 3	Series4	Series 5	Series 6	Series 7
			Statistical Probability				
2.2/2.0							
2.0/1.33							
1.33/0.67							
2.2/1.0							.025
2.0/1.0							
2.0/0.67							.02
1.0/0.67							
0.67/0.5							
1.0/0.5							
2.2/0.67							.001
2.2/0.5							.01
2.0/0.5							
R.R./R.				.02	.02		
R./S.			.005				
R.R./S.							
S./T.		.05		.05	.02	.02	
R.R./T.							
R./T.		.001	.001	.001	.001	.005	
Synergism							

Table: Statistical results and significance for cardiac output (direct Fick method). Abbreviations are as shown in Table 6:2

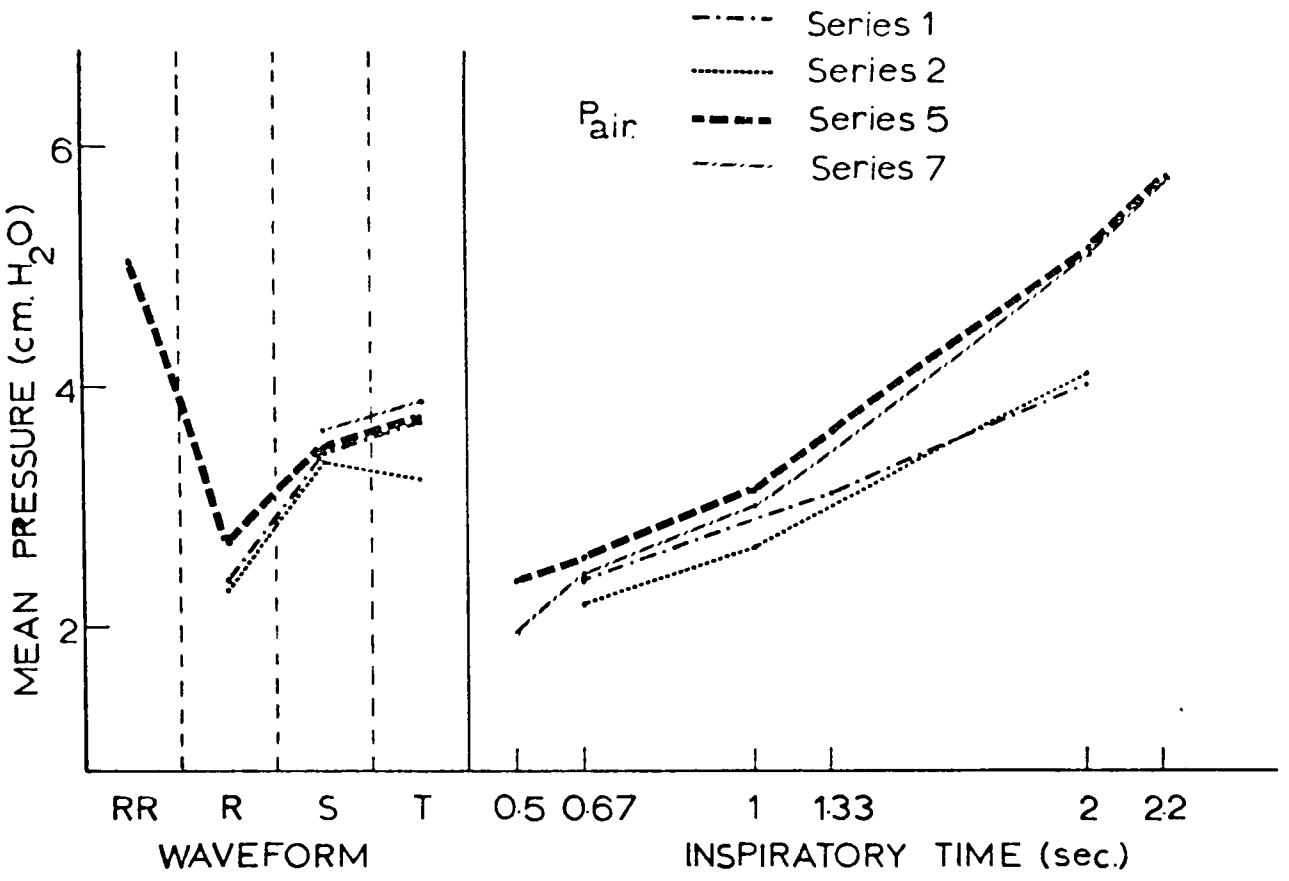

Fig. 6:17 Changes in means of the mean airway pressure with different inspiratory waveforms and times. Waveform symbols as for Fig. 6:6.

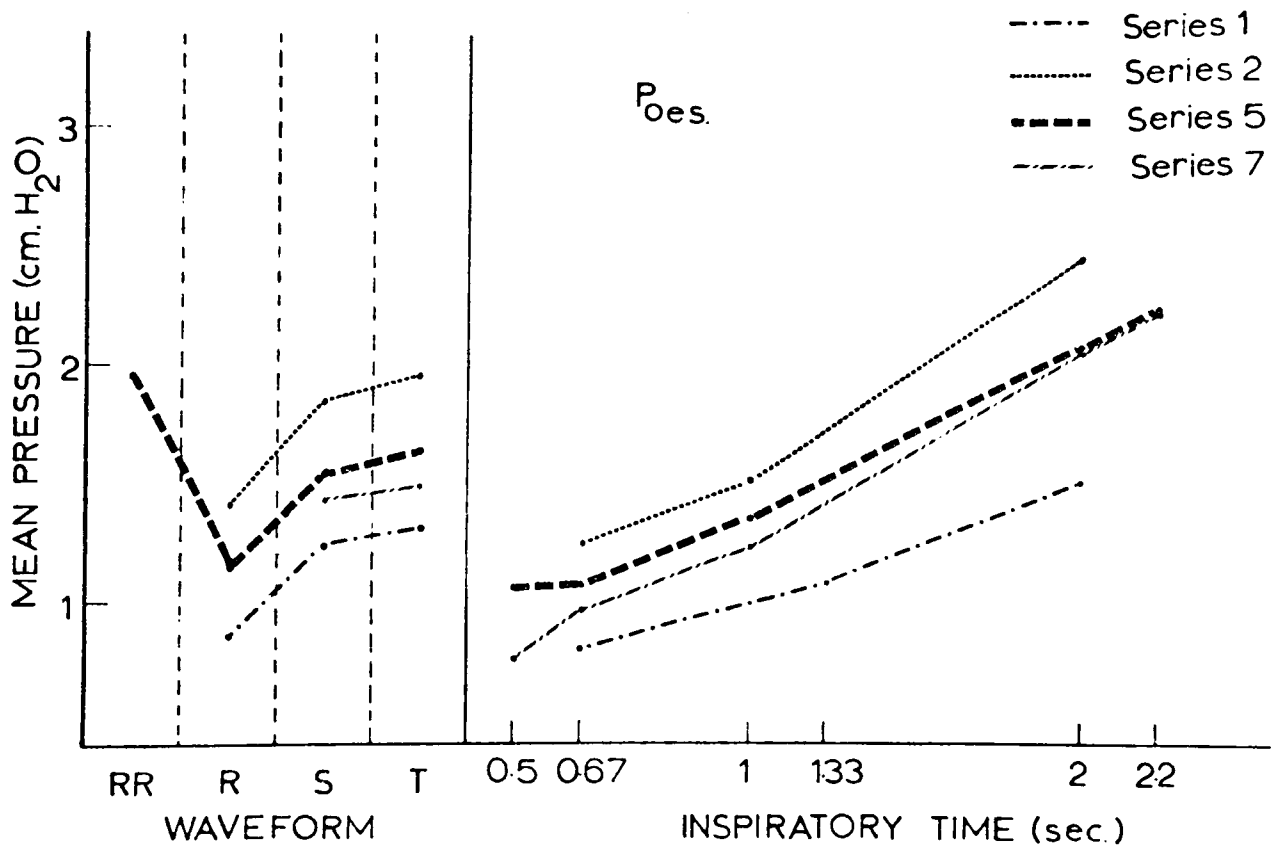

Fig. 6:18 Changes in means of the mean oesophageal pressure with different inspiratory waveforms and times. Waveform symbols as for Fig. 6:6.

TABLE 6: 13

Inspiratory variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
			Means (cm. H_2O)				
2.2			4.81±0.99	5.77±1.94	5.77±1.94	5.86±2.08	5.72±0.98
2.0	4.03±1.04	4.15±0.97	4.08±0.79	5.18±1.61	5.18±1.61	5.31±1.68	5.13±0.90
1.33	3.14±0.76						
1.0		2.69±0.47	2.91±0.47	3.16±0.63	3.16±0.63	3.20±0.65	3.03±0.40
0.67	2.40±0.56	2.10±0.32	2.45±0.31	2.61±0.54	2.61±0.54	2.61±0.59	2.45±0.35
0.5					2.41±0.35	2.43±0.36	1.96±0.36
S.E.D.	0.16	0.10	0.18	0.16	0.16	0.20	0.106
R.R.				5.38±2.27	5.03±2.27	5.08±2.27	
R.	2.40±0.49	2.31±0.55	2.90±0.62	3.00±0.76	2.72±0.76	2.74±0.82	
S.	3.44±1.13	3.38±1.22	3.74±1.13	4.08±1.47	3.68±1.47	3.78±1.57	3.65±1.65
T.	3.72±0.93	3.24±1.12	4.05±1.48	4.25±1.86	3.87±1.86	3.93±1.97	3.66±1.64
S.E.D.	0.16	0.10	0.15	0.16	0.14	0.18	0.067

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Inspiratory variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
			Statistical Probability				
2.2/2.0			.005	.001	.001	.01	.001
2.0/1.33	.001						
1.33/0.67	.001						
2.2/1.0			.001	.001	.001	.001	.001
2.0/1.0		.001	.001	.001	.001	.001	.001
2.0/0.67	.001	.001	.001	.001	.001	.001	.001
1.0/0.67		.001	.05	.001	.001	.005	.001
0.67/0.5							.001
1.0/0.5					.001	.001	.001
2.2/0.67			.001	.001	.001	.001	.001
2.2/0.5					.001	.001	.001
2.0/0.5					.001	.001	.001
R.R/R				.001	.001	.001	.001
R./S.	.001	.001	.001	.001	.001	.001	.001
R.R./S.				.001	.001	.001	.001
S./T.							
R.R./T.				.001	.001	.001	.001
R./T.	.001	.001	.001	.001	.001	.001	.001
Synergism	+	+	+	+	+	+	+

Table: Statistical results and significance for mean airway pressure. Abbreviations are as shown in Table 6: 2

TABLE 6: 14

Inspiratory variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
			Means (cm. H_2O)				
2.2			2.58±0.93	2.26±0.71	2.26±0.71	2.10±0.63	2.25±0.66
2.0	1.52±0.51	2.46±0.86	2.26±0.72	2.10±0.69	2.10±0.69	2.00±0.69	2.07±0.61
1.33	1.08±0.36						
1.0		1.53±0.49	1.59±0.62	1.36±0.46	1.36±0.46	1.25±0.41	1.25±0.44
0.67	0.80±0.27	1.24±0.31	1.34±0.42	1.08±0.36	1.08±0.36	0.97±0.30	0.97±0.33
0.5					1.06±0.23	0.92±0.24	0.78±0.27
S.E.D.	0.061	0.104	0.15	0.052	0.052	0.058	0.072
R.R.				2.08±0.80	1.96±0.80	1.83±0.80	
R.	0.86±0.29	1.41±0.50	1.54±0.53	1.25±0.50	1.15±0.50	1.05±0.46	
S.	1.23±0.52	1.85±0.87	2.06±0.90	1.68±0.72	1.54±0.72	1.42±0.61	1.44±0.73
T.	1.31±0.52	1.96±0.89	2.23±0.96	1.79±0.80	1.64±0.80	1.49±0.69	1.49±0.79
S.E.D.	0.061	0.104	0.131	0.052	0.046	0.052	0.045

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Inspiratory variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
				Statistical Probability			
2.2/2.0				.001	.005		.01
2.0/1.33	.001						
1.33/0.67	.001						
2.2/1.0			.001	.001	.001	.001	.001
2.0/1.0		.001	.005	.001	.001	.001	.001
2.0/0.67	.001	.001	.001	.001	.001	.001	.001
1.0/0.67		.02		.001	.001	.001	.001
0.67/0.5						.001	.01
1.0/0.5					.001		.001
2.2/0.67			.001	.001	.001	.001	.001
2.2/0.5					.001	.001	.001
2.0/0.5					.001	.001	.001
R.R/R				.001	.001	.001	
R./S.	.001	.001	.005	.001	.001	.001	.001
R.R./S.				.001	.001	.001	
S./T.	.001			.05			
R.R./T.				.001	.001	.001	.001
R./T.		.001	.001	.001	.001	.001	.001
Synergism		+		+	+	+	

Table: Statistical results and significance for mean oesophageal pressure. Abbreviations are as shown in Table 6: 2

cardiac output, but variations in the flow waveform did affect cardiac output in some Series. Ramp flow allows the greatest cardiac output whilst reversed ramp and tophat flow usually produced the lowest level of cardiac output. No synergism was found.

The results for airway and intrathoracic pressures demonstrate that the longer the period of inspiration the higher the mean pressures. The inspiratory waveform affects the mean pressures of both airway and oesophagus in the same way. Ramp flow in inspiration produces the lowest mean pressure rise and this is followed by sine, tophat and finally reversed ramp flow which produces the highest mean pressure rise. Both mean pressure observations exhibited synergism for flow waveform and inspiratory time.

Discussion

The absence of significant changes of cardiac output with I:E ratio agrees with previous studies by Finlay et al. (1970) and Lyager (1970). In the only other study of cardiac output with changes in the inspiratory flow waveform, Adams et al. (1970) did not find any effect on cardiac output. They did, however, suggest that different flow waveforms would change mean airway pressure and hence could be expected to affect cardiac output, P_{a,O_2} and P_{a,CO_2}. Their predictions have been borne out experimentally in this study.

The results of this study for mean airway pressure confirms the studies of Bergman (1963 and 1967), Fairley and Blenkarn (1966) and Finlay et al. (1970). In the study by Adams et al. (1970) no significant alteration in mean airway pressure occurred with alteration in the inspiratory flow waveform. This fact might be taken as confirmatory evidence to the suggestion made earlier that Adams et al. (1970) did not use sufficiently different inspiratory flow waveforms. No studies on mean oesophageal

pressure changes have been reported.

Cournand et al. (1948) found that the cardiac output was influenced by mean airway pressure. These authors found that the cardiac output decreased when the mean airway pressure was raised by an increase in the I:E ratio of inspiration during intermittent positive pressure breathing through a mask. This finding was later confirmed by Morgan et al. (1966) during I.P.P.V. in tracheotomised dogs. Morgan et al. (1969) however, found that the interaction between cardiac output and mean airway pressure was modified by hypervolaemia. In hypervolaemia alteration in mean airway pressure did not significantly alter the cardiac output, and Sykes et al. (1970b) confirmed this finding. In the present study an increase in mean airway pressure due to change in the inspiratory waveform depressed cardiac output whereas an increase in mean airway pressure due to change in the I:E ratio did not. There was a statistically significant fall in cardiac output in Series 7 after dogs in the control state were subjected to pharmacological block of the autonomic nervous system. The fall was not, however, of any considerable physiological significance and this finding emphasises the difficulties of interpreting studies of cardiac output in the healthy or hypervolaemic animal. Reserves and compensatory mechanisms are so effective that only very gross changes in mean airway pressure can be expected to have a consistent physiologically significant effect (Watson et al. 1962b). It is surprising, however, that there was not a greater fall in cardiac output when mean airway pressure was raised in the animals with blocked autonomic nervous systems.*

Pulmonary Venous Admixture.

Results

Fig. 6:19 and Table 6:15 show the results for $\dot{Q}_s/\dot{Q}$ with inspiratory time and waveform. These results

* See further discussion on page 249 concerning the cardiovascular effects of pharmacological blockade of the autonomic nervous system.

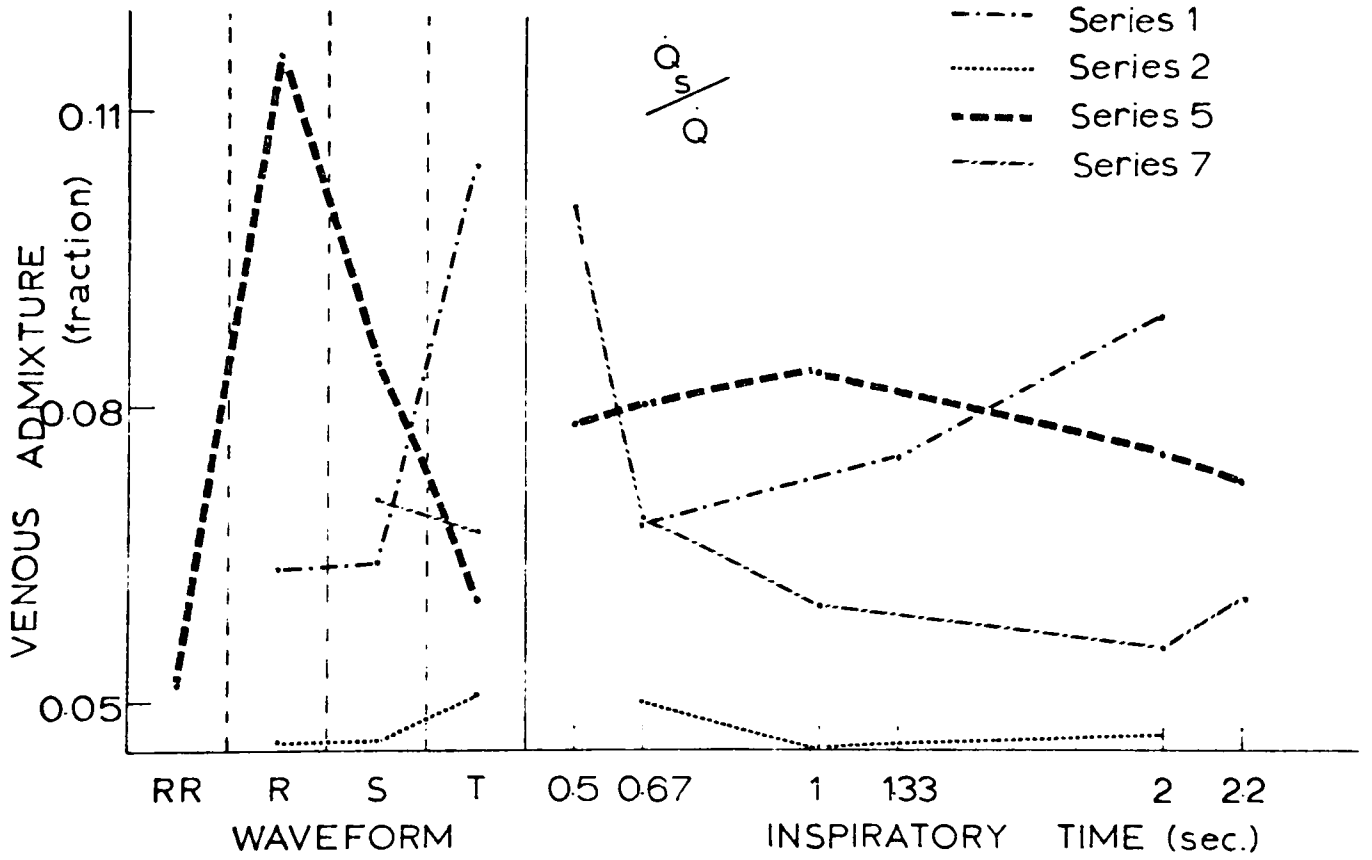

Fig. 6:19 Changes in mean pulmonary venous admixture with different inspiratory waveforms and times. Waveform symbols as for Fig. 6:6.

TABLE 6: 15

Inspiratory Variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
				Means			
2.2			0.034±0.023	0.073±0.071	0.073±0.071	0.183±0.075	0.061±0.049
2.0	0.090±0.049	0.047±0.0170	0.037±0.034	0.075±0.094	0.076±0.094	0.189±0.101	0.055±0.035
1.33	0.075±0.041						
1.0		0.045±0.012	0.030±0.018	0.084±0.067	0.084±0.067	0.199±0.068	0.060±0.030
0.67	0.068±0.036	0.050±0.014	0.036±0.015	0.081±0.051	0.081± 0.051	0.206±0.053	0.069±0.040
0.5					0.079±0.058	0.187±0.056	0.100±0.082
S.E.D.	0.013	0.005	0.013	0.012	0.012	0.018	0.012
R.R.				0.052±0.040	0.052±0.040	0.197±0.040	
R.	0.064±0.047	0.046±0.015	0.052±0.029	0.121±0.102	0.116±0.102	0.206±0.109	
S.	0.064±0.026	0.046±0.015	0.027±0.010	0.080±0.066	0.085±0.066	0.203±0.066	0.071±0.060
T.	0.105±0.043	0.051±0.015	0.024±0.008	0.060±0.033	0.060±0.033	0.166±0.031	0.067±0.044
S.E.D.	0.013	0.005	0.011	0.012	0.011	0.016	0.007

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Inspiratory variable	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7
			Statistical Probability				
2.2/2.0							
2.0/1.33							
1.33/0.67							
2.2/1.0							
2.0/1.0							
2.0/0.67							
1.0/0.67							
0.67/0.5							.01
1.0/0.5							.001
2.2/0.67							
2.2/0.5							.001
2.0/0.5							.001
R.R/R				.001	.001	.001	
R./S.			.05	.005	.01	.025	
R.R/S.				.05	.005	.02	
S./T.	.005				.05	.05	
R.R./T.							
R./T.	.005		.05	.001	.001	.001	
Synergism							+

Table: Statistical results and significance for pulmonary venous admixture. Abbreviations are as shown in Table 6: [2]

suggest that variation of the I:E ratio does not affect the $\dot{Q}_s/\dot{Q}$, but Series 7 is again an exception demonstrating a statistically significant rise with shortening of inspiration. There was also no significant difference between control and blocked animals in this series. The results with variation in inspiratory flow waveform would suggest that the highest $\dot{Q}_s/\dot{Q}$ is obtained with a ramp flow and the lowest by reversed ramp or tophat flow waveforms. Synergism for waveform and inspiratory time was found only in Series 7.

Discussion

The results for inspiratory time are in general agreement with Finlay et al. (1970) whose results suggested that such an increase in $\dot{Q}_s/\dot{Q}$ occurred. Their finding was only statistically significant in dogs with a hypervolaemic circulation, but was also present as a trend, as in the present series. Fairley and Blenkarn (1966) and Sykes and Lumley (1969) found no alteration in $\dot{Q}_s/\dot{Q}$ with variation in I:E ratio. The study by Adams et al. (1970), which is the only reported study for $\dot{Q}_s/\dot{Q}$ with variation in flow waveform, did not find any alteration. The present study is contradictory, but the strongly significant difference in $\dot{Q}_s/\dot{Q}$ with waveform in the series with the largest number of experiments might suggest that the differences were real.

Miscellaneous Physiological Variables.

Certain other measured variables which did not alter significantly throughout any of the manipulations of I:E ratio or inspiratory waveform are listed with their mean values in Table 6:16.

The combined results of all experiments are shown as means and standard deviations (S.D.) in Figs. 6:20-27

TABLE 6:16

Inspiratory variable	$\dot{V}_{O_2}$ (ml/min)	$\dot{V}_{CO_2}$ (ml/min)	R	"Filley Factor"	Time (hours)	Temperature (°C)	V_T (ml)	Mean Pulmonary Artery Blood Pressure (torr)	Arterial Blood Pressure (torr) Systolic	Diastolic
2.2	133.1±50.5	108.7±35.1	0.85±0.16	1.17±0.17	5.21±1.92	37.5±1.1	510±85	21±2	125±9	92±7
2.0	116.4±51.7	99.6±33.6	0.93±0.23	1.11±0.18	5.00±1.82	37.3±1.1	495±86	21±2	126±8	95±9
1.33	75.7±29.2	79.1±18.1	1.13±0.29	0.95±0.15	4.24±1.58	36.3±0.6	462±56	22±2	129±5	101±8
1.0	126.6±45.7	105.1±31.3	0.86±0.13	1.15±0.14	4.73±1.95	37.6±1.1	513±82	21±2	125±9	93±9
0.67	110.6±45.9	97.7±29.9	0.96±0.29	1.09±0.25	4.11±1.95	37.3±1.0	505±82	21±2	126±8	95±9
0.5	121.1±38.2	97.3±27.0	0.82±0.14	1.20±0.15	4.36±2.04	37.5±1.0	476±83	21±2	123±9	91±8
R.R.	122.0±50.6	106.2±37.8	0.90±0.15	1.11±0.13	3.23±1.53	37.4±1.1	476±97	21±2	125±8	90±7
R.	104.7±49.1	94.3±34.9	0.95±0.19	1.07±0.15	3.99±2.08	37.5±1.3	490±92	22±2	128±7	94±10
S.	123.1±48.6	102.6±29.9	0.88±0.18	1.14±0.19	4.99±1.93	37.4±1.1	498±76	21±2	125±9	95±9
T.	120.5±45.0	100.5±26.8	0.91±0.29	1.14±0.22	5.06±1.69	37.3±0.9	512±80	21±2	125±9	94±8

Table: Means ± S.D. for those physiological variables which did not alter with changes in the inspiratory waveform. Abbreviations are as shown in Table 6: 2.

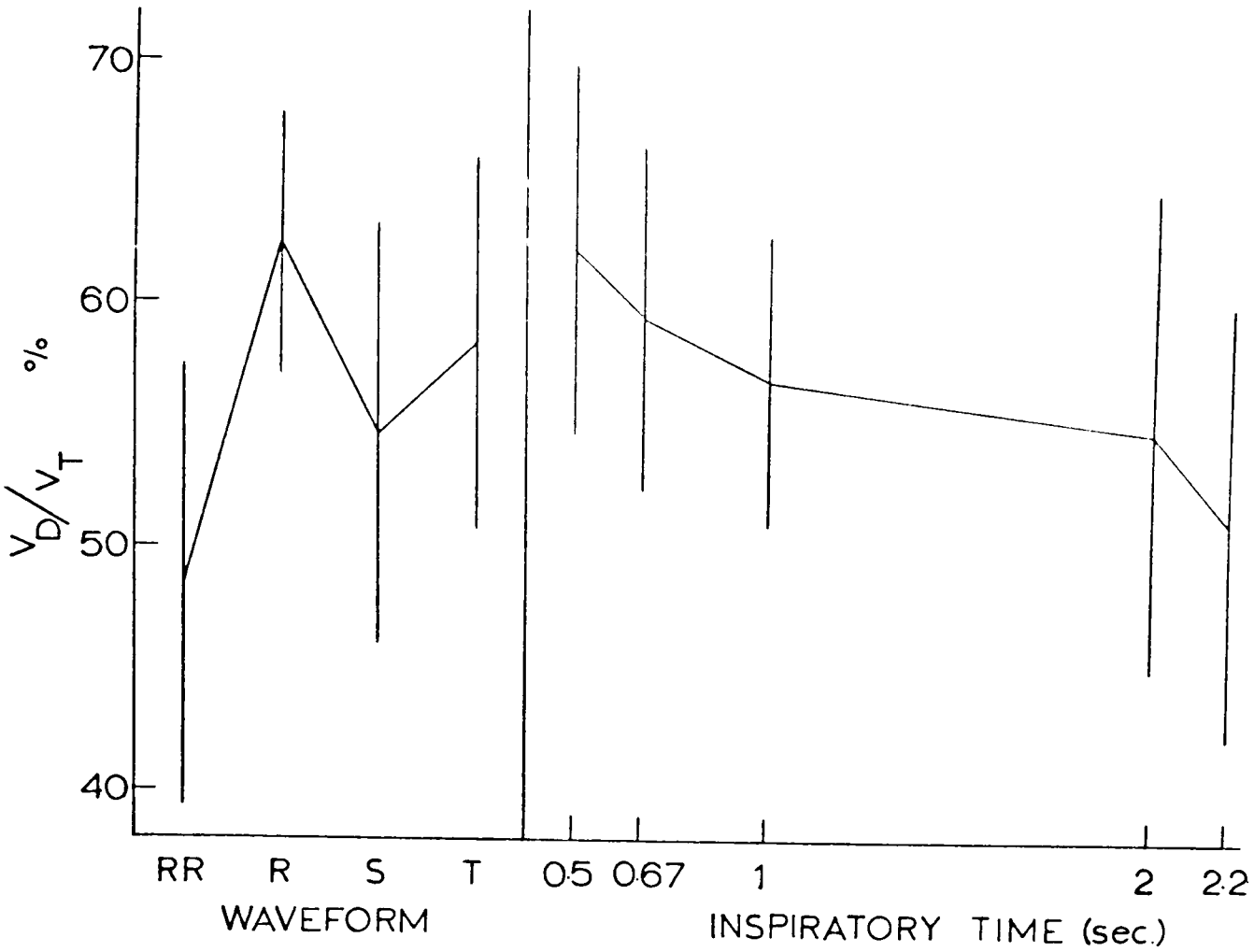

Fig. 6:20 Means ± S.D. for V_D/V_T with changes in inspiratory waveform and time for all the dog experiments combined. Waveform symbols as for Fig. 6:6.

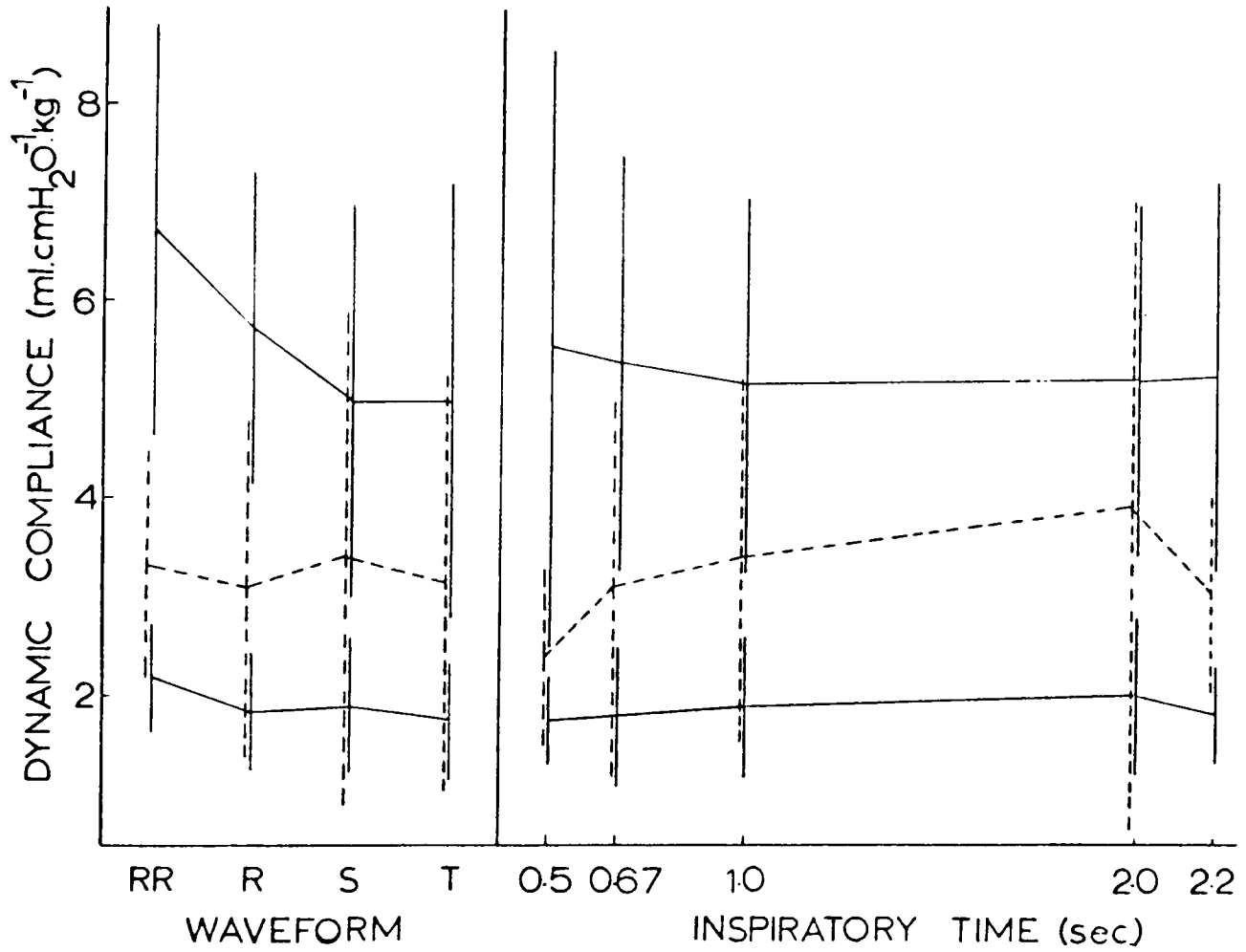

Fig. 6:21 Means ± S.D. for dynamic compliances with changes in inspiratory waveform and time for all the dog experiments combined. Upper trace represents chest wall compliance, middle trace represents lung compliance and lower trace represents total compliance. Waveform symbols as for Fig. 6:6.

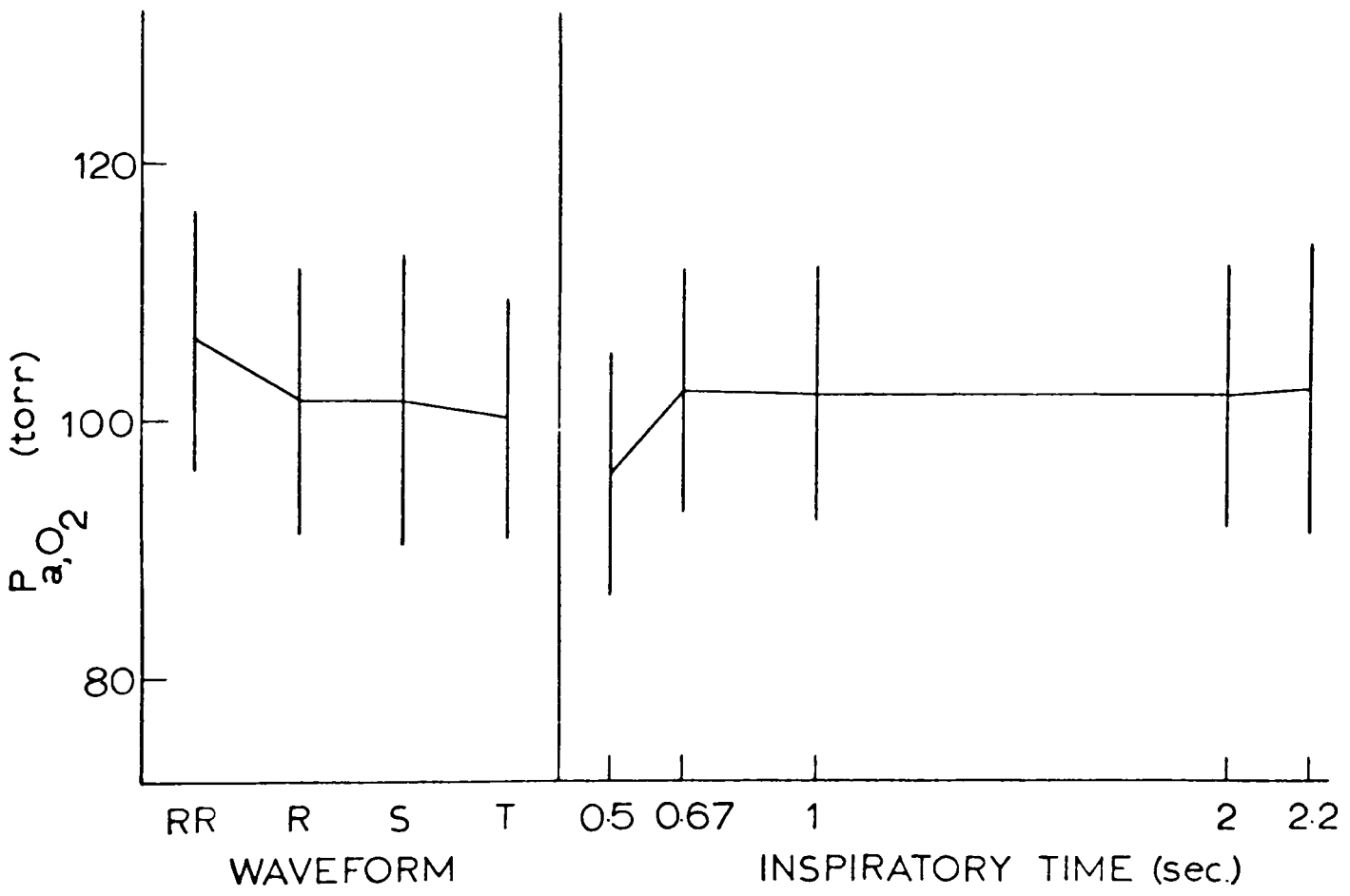

Fig. 6:22 Means ± S.D. for P_{a,O_2} with changes in inspiratory waveform and time for all the dog experiments combined. Waveform symbols as for Fig. 6:6.

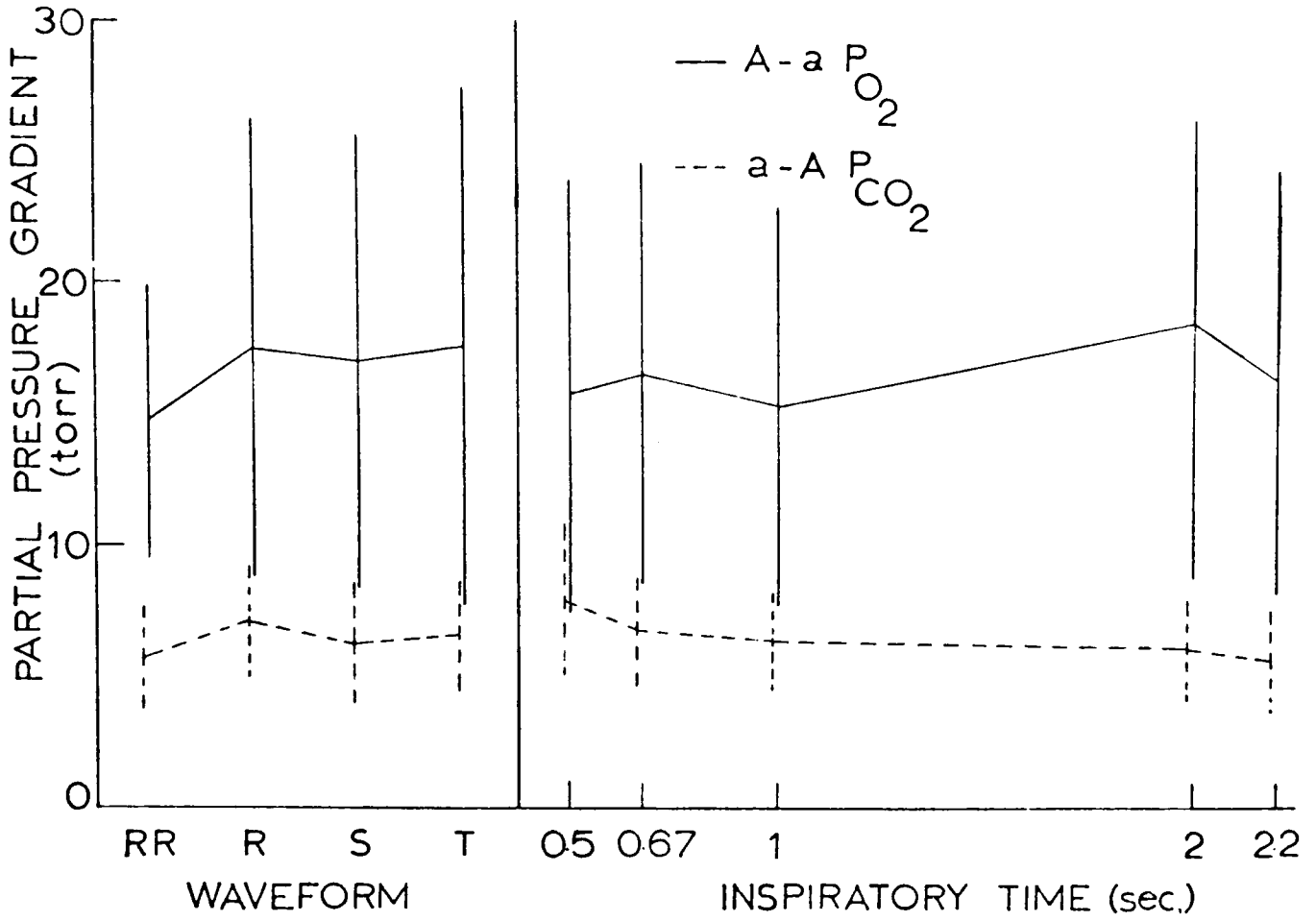

Fig. 6:23 Means ± S.D. for A - a P_{O_2} gradient and a - A P_{CO_2} gradient with changes in inspiratory waveform and time for all the dog experiments combined. Upper trace represents P_{O_2} gradient and lower trace P_{CO_2} gradient. Waveform symbols as for Fig. 6:6.

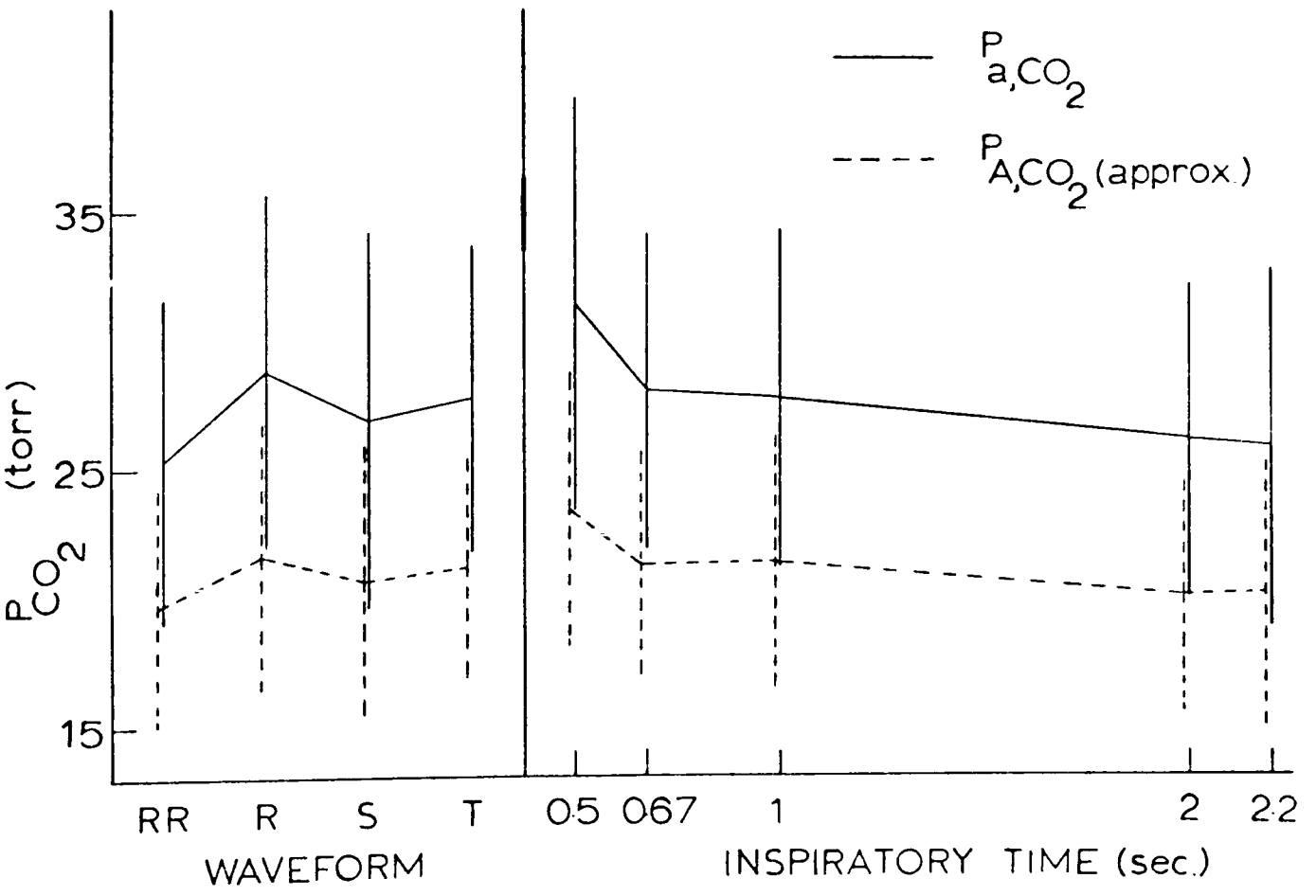

Fig. 6:24 Means ± S.D. for P_{a,CO_2} and P_{A,CO_2} with changes in inspiratory waveform and time for all the dog experiments combined. Waveform symbols as for Fig. 6:6.

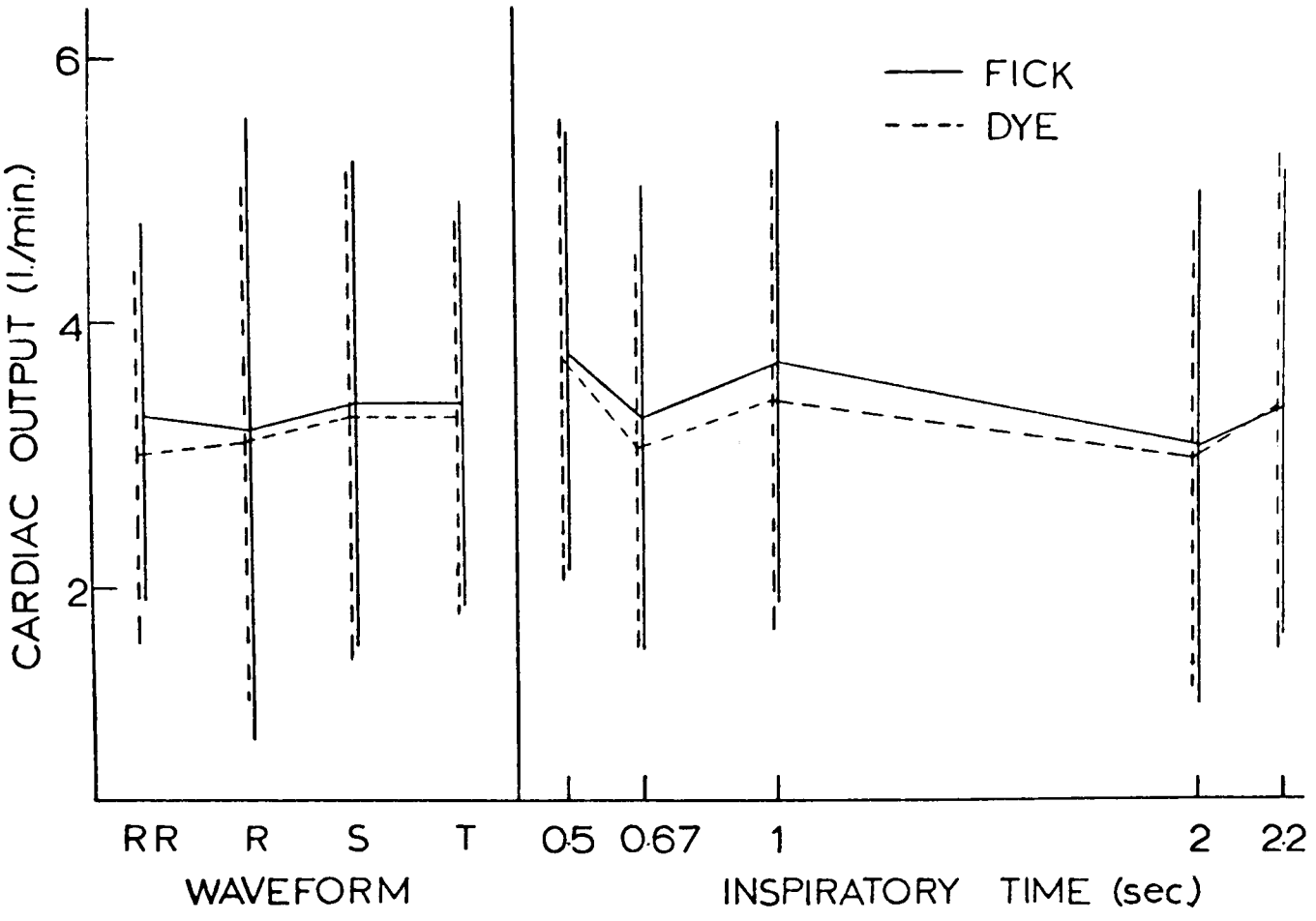

Fig. 6:25 Means + S.D. for cardiac output with changes in inspiratory waveform and time for all the dog experiments combined. Waveform symbols as for Fig. 6:6.

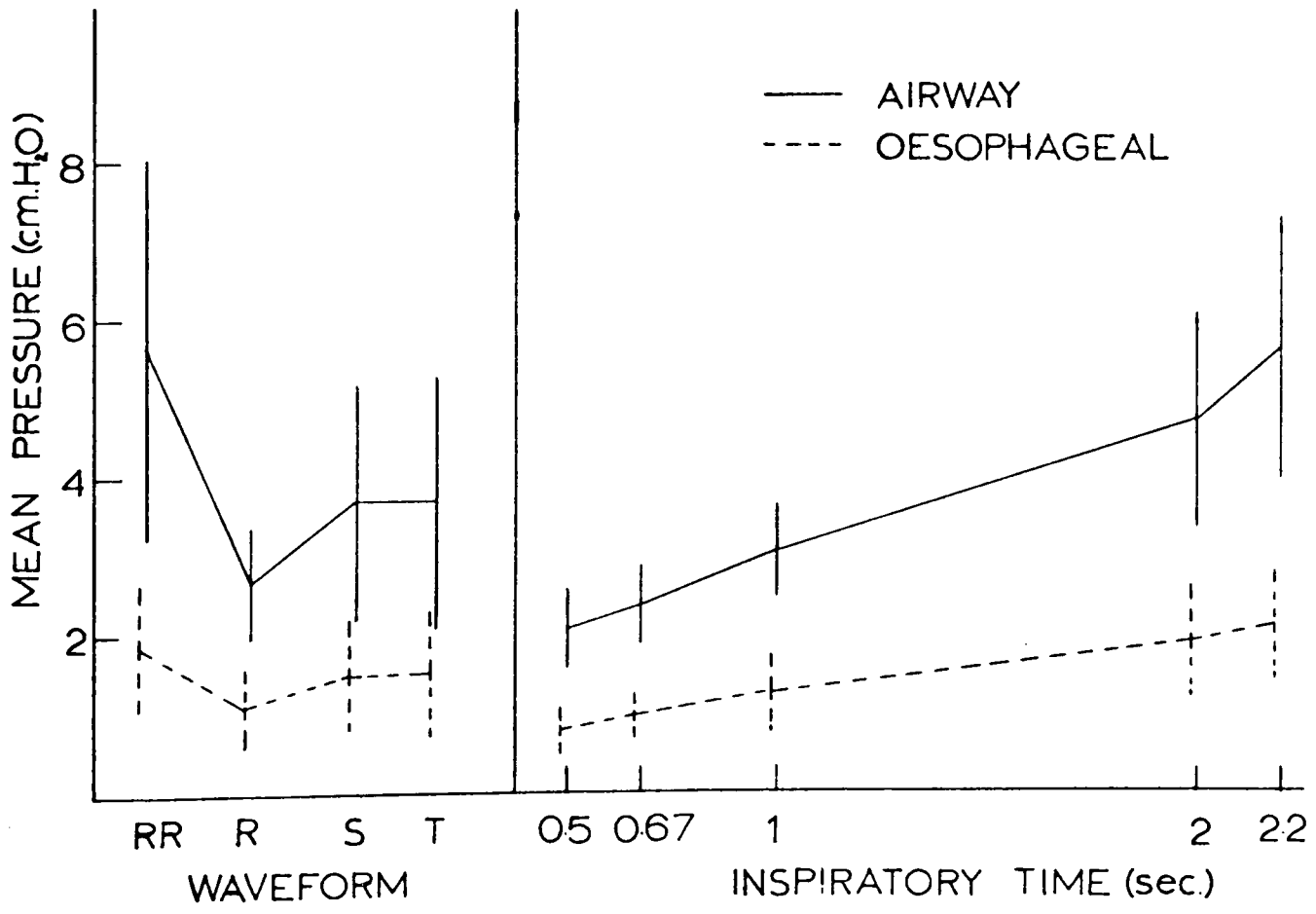

Fig. 6:26 Means + S.D. for mean airway pressure and mean oesophageal pressure with changes in inspiratory waveform and time for all the dog experiments combined. Upper trace represents mean airway pressure and lower trace mean oesophageal pressure. Waveform symbols as for Fig. 6:6.

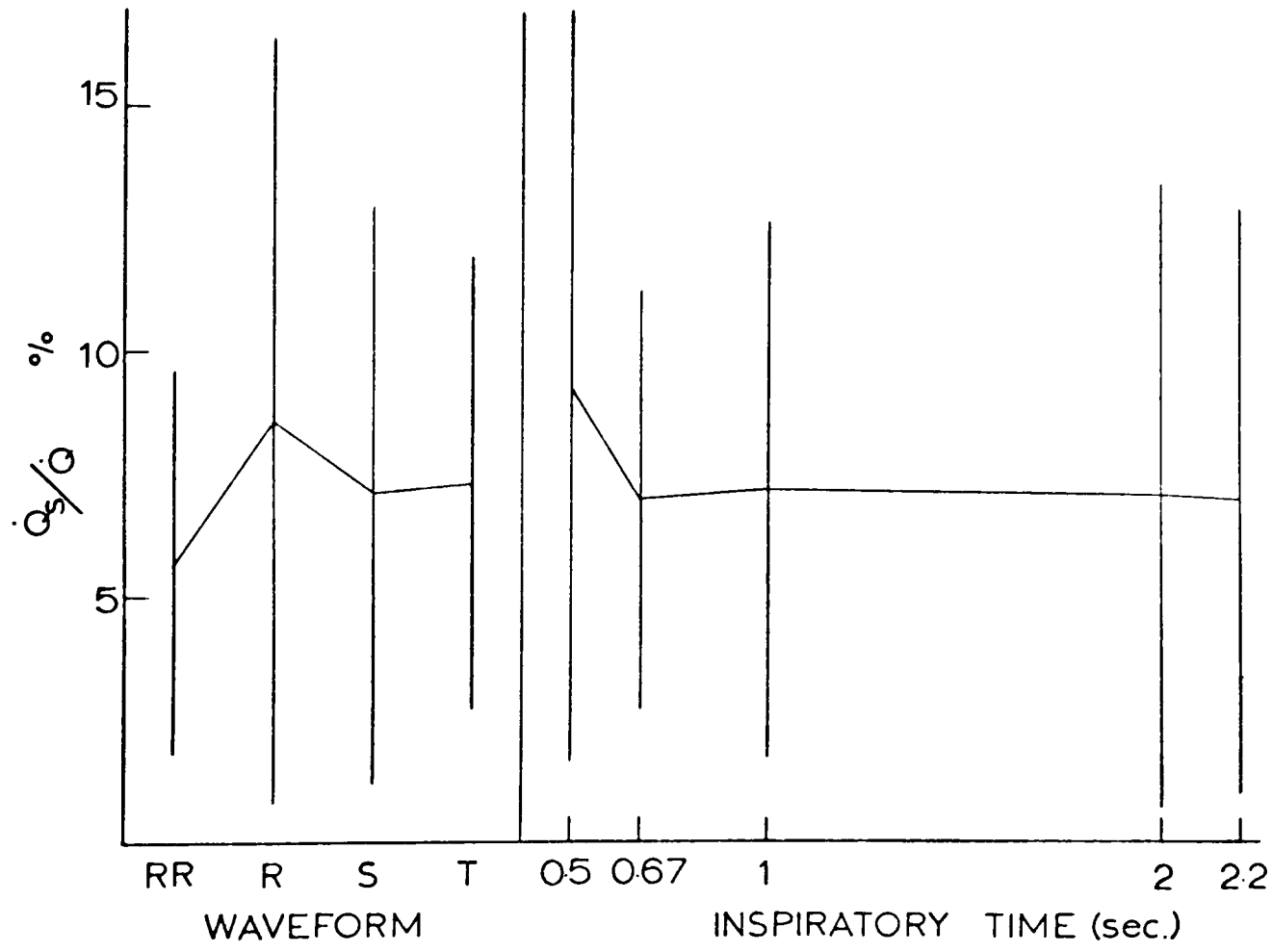

Fig. 6:27 Means ± S.D. for pulmonary venous admixture with changes in inspiratory waveform and time for all dog experiments combined.

and Table 6:17 together with their statistical significance.

ADDITIONAL RESULTS AND DISCUSSION

Physiological Significance.

In the discussion of the results of the cardiac output studies, the difficulty of inducing consistent changes in the healthy animal without creating an experimental situation very unlikely to have a parallel in the human situation was mentioned. In order to depress the filling pressure of the right heart Watson et al. (1962b) used mean intrathoracic pressures which would not normally be encountered in clinical I.P.P.V. In many cases in the results presented above, where statistically significant effects were induced by changing I:E ratios or waveforms, these effects were still within the physiological range. These statistically significant effects may well be of clinical importance when the same changes are applied to patients with disorders of cardio-vascular and respiratory systems.

Comparison with Predictions made from the Electrical Analogue.

Chapter 4 includes predictions made from observations on an electrical analoge of the lung and thorax with respect to inspiratory waveform and I:E ratio, and these predictions were made before any physiological data were available. These observations suggested that the least disruptive waveforms would be sine, triangle and reversed ramp. The 'best' inspiratory time in a 4 second cycle was predicted to be 1 - 1.5 sec. The physiological studies on the other hand suggest that in dogs with normal chests the reversed ramp inspiratory flow has the least disruptive effect on general cardio-respiratory physiology. When the effect on cardiac output is considered specifically this waveform is not the best available. Ramp flow which allows the greatest cardiac output also

TABLE 6: 17

Means

Inspiratory variable	V_D/V_T	Dynamic Compliance Total	Chest Wall	Lung	P_{a,O_2}	A - a P_{O_2} gradient	P_{a,CO_2}
2.2	0.513±0.089	1.85±0.52	5.30±1.98	3.07±1.09	102.9±11.2	16.4±8.2	25.9±7.0
2.0	0.549±0.098	2.04±0.80	5.26±1.81	3.96±3.20	102.3±10.4	18.6±9.8	26.1±6.1
1.33	0.612±0.064	1.78±0.45	5.48±0.84	2.82±1.11	100.0±11.9	24.8±11.6	25.4±4.3
1.0	0.568±0.059	1.91±0.70	5.17±1.90	3.38±1.85	102.3±10.0	15.4±7.6	27.7±6.6
0.67	0.593±0.070	1.81±0.68	5.41±2.09	3.08±1.93	102.4±9.6	16.6±8.0	28.0±6.2
0.5	0.611±0.075	1.56±0.43	5.57±3.06	2.39±0.89	95.9±9.6	15.8±8.2	31.4±8.1
R.R.	0.484±0.090	2.17±0.55	6.77±2.08	3.34±1.16	106.4±10.0	14.7±5.2	25.3±6.3
R.	0.614±0.054	1.87±0.63	5.77±1.59	3.09±1.68	101.6±10.4	17.5±8.7	28.8±6.9
S.	0.546±0.086	1.88±0.74	5.04±1.97	3.44±2.53	101.6±11.2	17.0±8.6	26.9±7.3
T.	0.583±0.076	1.76±0.63	5.01±2.21	3.14±2.12	100.3±9.4	17.6±9.8	27.7±6.0

Table continued on following page

TABLE 6: 17 (continued from previous page)

Inspiratory variable	a - A P_{CO_2} gradient	$P_{A,\ CO_2}$	$\dot{Q}_D$	$\dot{Q}_F$	Mean airway pressure	Mean oesophageal pressure	$\dot{Q}_s/\dot{Q}$
2.2	5.75±2.03	20.1±5.3	3.46±1.92	3.46±1.75	5.75±1.70	2.18±0.68	0.070±0.060
2.0	6.10±1.96	20.0±4.5	2.98±1.72	3.09±1.94	4.81±1.40	1.98±0.70	0.071±0.064
1.33	6.39±1.19	19.0±3.3	1.78±0.51	1.71±0.64	3.27±0.95	1.14±0.46	0.076±0.041
1.0	6.44±1.93	21.3±4.9	3.45±1.74	3.73±1.82	3.07±0.60	1.30±0.45	0.072±0.055
0.67	6.78±2.10	21.2±4.4	3.05±1.49	3.29±1.75	2.44±0.50	0.99±0.34	0.070±0.043
0.5	8.04±2.95	23.4±5.4	3.80±1.74	3.85±1.64	2.13±0.47	0.81±0.26	0.093±0.077
R.R.	5.69±2.05	19.6±4.6	3.00±1.39	3.27±1.45	5.65±2.43	1.86±0.77	0.057±0.039
R.	7.14±2.07	21.6±5.2	3.07±1.98	3.22±2.35	2.66±0.68	1.10±0.47	0.086±0.078
S.	6.27±2.35	20.6±5.2	3.28±1.85	3.43±1.83	3.68±1.50	1.49±0.72	0.071±0.059
T.	6.59±2.06	21.1±4.3	3.26±1.48	3.36±1.51	3.74±1.59	1.56±0.77	0.073±0.046

Table continued on following page

Continuation of TABLE 6: 17 from previous page

Statistical Probability

Inspiratory variable	V_D/V_T	Dynamic Compliance: Total	Dynamic Compliance: Chest Wall	Dynamic Compliance: Lung	P_{a,O_2}	A - a P_{O_2} gradient	P_{a,CO_2}	a - A P_{CO_2} gradient	$P_{A,\ CO_2}$	$\dot{Q}_D$	$\dot{Q}_F$	Mean airway pressure	Mean oesphageal pressure	$\dot{Q}_s/\dot{Q}$
2.2/2.0	.02											.001		
2.0/1.33						.02						.001	.001	
1.33/0.67						.001			.05					
2.2/1.0								.05						
2.0/1.0											.025			.05
2.0/0.67		.05				.05	.05	.025						
1.0/0.67	.02											.001		
0.67/0.5					.001		.01	.005	.02	.01		.001	.005	
1.0/0.5	.001				.001		.01	.001	.05			.001		
2.2/0.67							.05	.005						
2.2/0.5		.005		.001	.001		.001	.001	.001					
2.0/0.5		.001			.001				.001	.01	.025			
R.R/R			.01		.025		.02	.001	.05					
R./S.			.005					.01						
R.R./S.	.001	.05	.001		.02									.01
S./T.	.001													
R.R./T.	.001	.001	.001		.001		.05	.02						.05
R./T.		.025												

Table: Means ± S.D. of the combined data from all the dog experiments, with statistical significance by means of unpaired t-tests using both an equal variances test and an unequal variances test. Abbreviations are as shown in Table 6:2.

produces the least mean airway and oesophageal pressure, and may affect cardiac output through this mechanism. Figs. 6:28-31, however, do not suggest close correlation between thoracic pressures and cardiac output. The inspiratory time of 1 - 1.5 sec. would again seem to be the best time.

Autonomic Nervous System Blockade.

It has been suggested that deleterious effects on the cardiovascular system resulting from the application of I. P. P. V. are, in dogs and humans, enhanced by the absence of circulatory reflexes (Maloney et al. 1953; Watson et al. 1962b). Doubt has recently been cast on this assertion by other authors (Auchincloss and Gilbert 1967; Morgan et al. 1969; Prys-Roberts 1968; Sykes et al. 1970) all of whom have stated that, in the presence of normo- or hypervolaemia, the effects of I. P. P. V. on the circulation are negligible.

Series 7 included experiments on 7 dogs, all of which were subjected to pharmacological blockade of the autonomic nervous system. Atropine, propranolol and phenoxybenzamine were used as detailed on page 111, and the doses used were in excess of those recommended for this purpose (Goodman and Gilman 1970). The effectiveness of the pharmacological blockade was tested in 2 animals not included in Series 7 by injecting adrenaline (1 mg diluted in 20 ml of saline) slowly over two minutes. There was no change in pulse rate or blood pressure in either dog and this was interpreted as meaning that the sympathetic nervous system was effectively blocked. This test could not be undertaken prior to the experiments in Series 7 because the injection of adrenaline might have compromised the experimental situation. Additional evidence that the autonomic nervous system in the animals in Series 7 was blocked is that there was a fall of cardiac output and heart rate and a decrease in diastolic arterial blood pressure (Tables 6: 18 and 19).

The present study showed that there was a statistically significant depression of the mean cardiac output, heart rate and total dynamic

compliance between the control and the blocked states (Tables 6: 18). None of these effects could, however, be considered to be of pathological importance. Within the framework of this general depression, changes of I: E ratio or waveform in control or blocked animals did not have a statistically significant effect (Tables 6: 19).

The results of this study suggest that a combination of I. P. P. V. and autonomic blockade results in fall in cardiac output (which is not, however, of pathological importance) when compared with I. P. P. V. in the control animals. It is interesting to speculate what the effect of this combination might be in the presence of additional stress to the cardiovascular system either from increases in mean intrathoracic pressure larger than those used in this study, or from minor degrees of hypovolaemia. In the dogs studied there was no difference, even in the blocked state, between the effect of changing either the I: E ratio or waveform. With hindsight, however, it is unfortunate that the waveforms chosen had similar effects on all the variables studied and in repeating this work the author would choose a different combination of waveforms.

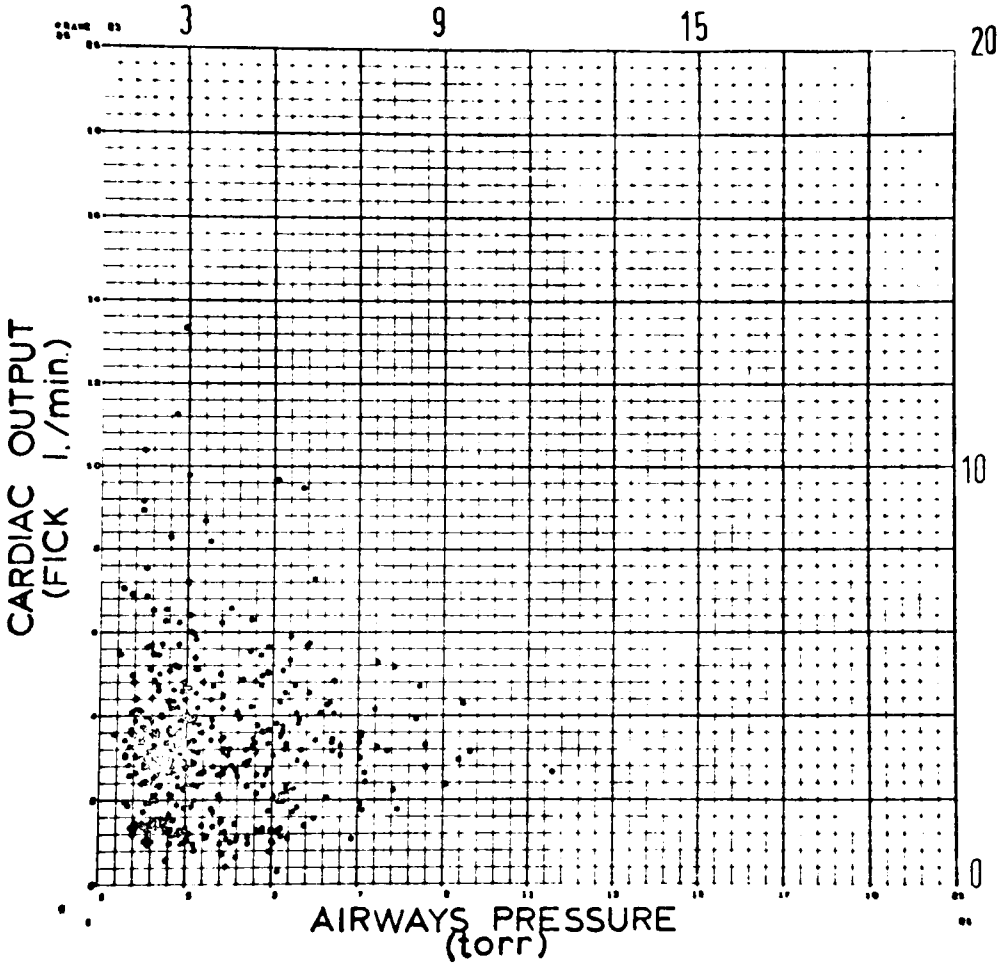

Fig. 6:28 Cardiac output response, measured by the direct Fick method, to mean airway pressure.

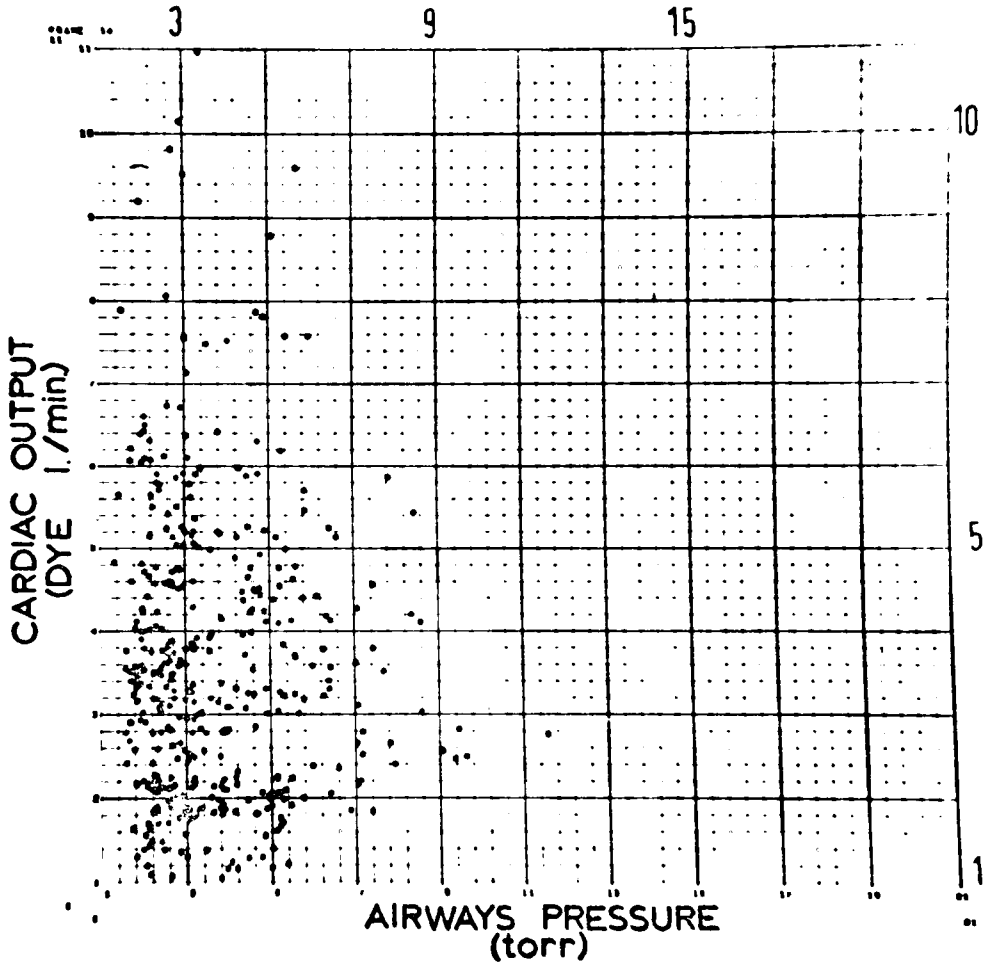

Fig. 6:29 Cardiac output response, measured by the dye dilution technique, to mean airway pressure.

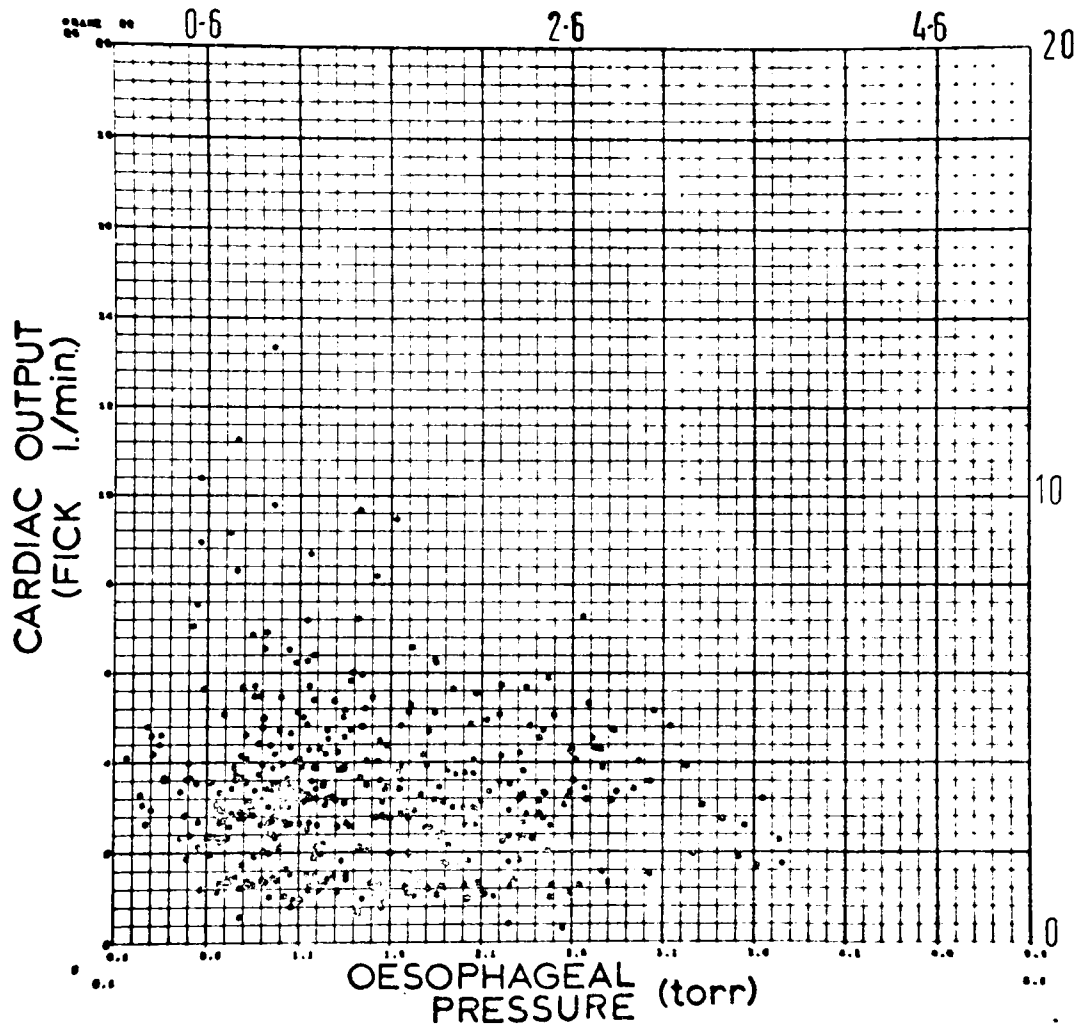

Fig. 6:30 Cardiac output response, measured by the direct Fick method, to mean oesophageal pressure.

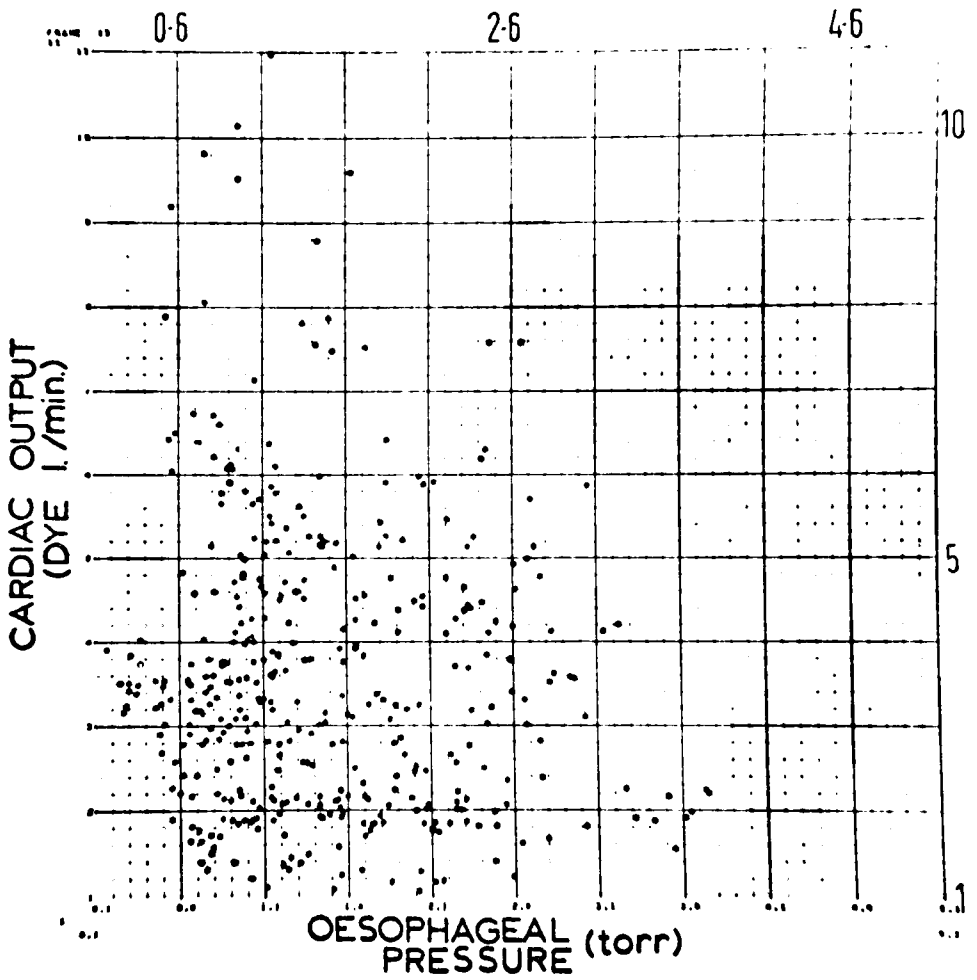

Fig. 6:31 Cardiac output response, measured by the dye dilution technique, to mean oesophageal pressure.

TABLE 6:18

	Control	Blocked	Probability
V_D/V_T	0.549±0.105	0.548±0.95	
Total dynamic compliance	1.48±0.22	1.44±0.22	.005
Chest wall compliance	4.44±2.31	4.67±2.73	
Lung compliance	2.41±0.57	2.30±0.44	
P_{a,O_2}	101.9±11.2	100.6±9.2	
A - a P_{O_2}	13.7±8.7	15.7±7.8	.05
P_{a,CO_2}	28.1±7.2	27.0±6.4	.05
P_{A,CO_2}	21.6±4.8	20.7±4.1	.02
a - A P_{CO_2}	6.5±2.4	6.3±2.3	
$\dot{Q}_D$	3.98±1.12	3.43±0.85	.001
$\dot{Q}_F$	4.20±1.12	3.71±0.94	.001
Mean airway pressure	3.63±1.64	3.68±1.65	
Mean oesophageal pressure	1.45±0.72	1.48±0.80	
$\dot{Q}_s/\dot{Q}$	0.071±0.064	0.067±0.038	

Table: Means ± .SD. with statistical probability for Series 7 experiments.

Table 6:19

Inspiratory Variable	$\dot{Q}_D$ (l./min.)		$\dot{Q}_F$ (l./min.)		Heart Rate (l./min.)		Arterial Blood Pressure systolic (torr)		Arterial Blood Pressure diastolic (torr)		Mean Pulmonary Artery Blood Pressure (torr)		Vascular Tone	
	C	B	C	B	C	B	C	B	C	B	C	B	C	B
2.2	3.75 ±0.99	3.16 ±0.93	3.66 ±0.81	3.38 ±1.11	193.6 ±15.1	182.5 ±9.6	123.9 ±9.2	120.7 ±10.4	95.4 ±6.6	93.7 ±6.3	22 ±2	21 ±2	+	-
2.0	3.70 ±0.97	3.37 ±1.09	3.99 ±1.04	3.50 ±0.77	196.8 ±10.1	180.7 ±7.5	123.2 ±9.1	120.4 ±10.5	95.0 ±6.2	93.9 ±6.3	22 ±2	21 ±2	+	±
1.0	3.87 ±0.89	3.52 ±0.78	4.20 ±0.83	3.91 ±0.78	195.7 ±14.3	174.3 ±7.2	123.2 ±8.2	120.7 ±11.1	96.1 ±5.9	94.6 ±6.3	22 ±2	22 ±2	±	-
0.67	4.13 ±1.05	3.55 ±0.72	4.62 ±1.16	4.01 ±1.14	192.1 ±12.5	172.9 ±8.1	123.6 ±10.6	121.1 ±11.0	97.1 ±7.3	94.6 ±6.3	21 ±2	22 ±2	+	±
0.5	4.43 ±1.55	3.56 ±0.73	4.52 ±1.49	3.74 ±0.82	197.9 ±13.9	174.3 ±6.9	125.4 ±9.7	122.7 ±9.3	95.4 ±7.2	94.2 ±6.7	21 ±2	21 ±2	+	-
S	3.95 ±1.15	3.36 ±0.85	4.04 ±1.03	3.63 ±0.94	182.6 ±12.9	176.3 ±8.0	123.0 ±10.0	121.0 ±10.5	96.0 ±6.6	94.0 ±6.4	22 ±2	22 ±2	+	-
T	4.01 ±1.12	3.50 ±0.88	4.35 ±1.12	3.79 ±1.08	207.9 ±13.6	177.6 ±7.8	124.0 ±9.1	120.7 ±10.7	95.6 ±6.5	94.4 ±6.2	22 ±2	22 ±2	+	-

Table: Means ± S.D. for cardiovascular measurements in Series 7 experiments with the animals in the control state (C) or pharmacologically blocked state (B). Abbreviations are as shown in Table 6:2 with the addition of + (for present) and - (for absent) signs for vascular tone, indicating the response of the vascular system at the end of the "Valsalva manoeuvre" demonstrated in Fig. 6:1. This manoeuvre as performed in these experiments is not a good stimulus so that this test is not particularly useful for eliciting the responsiveness of vascular tone.

EPILOGUE

EPILOGUE

The studies in this thesis indicate that the inspiratory flow waveform has a statistically significant effect on general cardiorespiratory physiology in the normal dog. These studies have always been regarded as preliminary to the study of the human patient with pulmonary and cardiovascular disease to whom the inspiratory flow waveform may well be of considerable clinical importance.

The usefulness of the simple theoretical approach used in this thesis prior to the biological studies encourages the author to believe that this approach may be applied to further investigation. The step function rise in alveolar pressure had not previously been described, was predicted by the electrical analogue and confirmed by observation. Another interesting analogue prediction was that, with constant tidal volume, peak alveolar pressure does not vary with inspiratory time or with flow rate if sine, triangular or reversed ramp flow waveforms are used. As a preliminary to further studies of the application of I.P.P.V. to ill patients, the author has also used a simple mathematical representation of expiration which may be applied to patients with chronic obstructive lung disease.

If expiration in I.P.P.V. is passive to atmospheric pressure the duration depends upon the airways resistance and compliance. The expired gas volume increases exponentially and may be calculated from the equation

$$V_E = V_I\left(1 - e^{-\frac{t}{\tau}}\right) \text{ ml} \qquad \text{(Wald et al. 1968)}$$

where τ = time constant of the system and is equal to airways resistance x compliance, V_I = inspired volume, V_E = expired volume and t = time of expiration. If the

expired volume is assumed to be v ml less than the inspired volume

$$V_E = V_I - v \text{ ml}$$

By combining these two equations the expiratory time at $(V_I - v)$ ml may be calculated from the equation

$$t^* = \tau \log_e (V_I/v) \text{ sec}$$

and if v ml is taken to equal 1 ml then

$$t^* = \tau \log_e (V_I/1) \text{ sec}$$

This relationship is represented by the family of curves in Fig. E:1. Each curve represents the behaviour of lungs with different expiratory time constants. Superimposed on these curves is a family of straight lines derived from the standard equations

$$f = \frac{60}{T_I + T_E} = \frac{\dot{V}_A}{V_T - (V_D/V_T)V_T}$$

where $\dot{V}_A$ = alveolar ventilation, V_T = tidal volume, T_I = inspiratory time, T_E = expiratory time, f = respiratory frequency. The particular straight lines appearing in Fig. E:1 were calculated assuming that $\dot{V}_A$ was constant at 5 1/min. Different lines could be calculated for a different alveolar ventilation. Considering a V_T of 500 ml, the point at which the ordinate at 500 ml cuts the curve representing normal lung indicates that approximately 1.7 sec is required for complete expiration. The point at which the ordinate at 500 ml cuts the straight line representing an I:E ratio of 1:2 and a V_D/V_T ratio of 0.3 indicates that 2.8 sec will be available for expiration. If the curve representing a lung with high airways resistance is substituted, for the curve representing normal lung, approximately 3.4 sec will be required for expiration so that the abnormal lung cannot completely

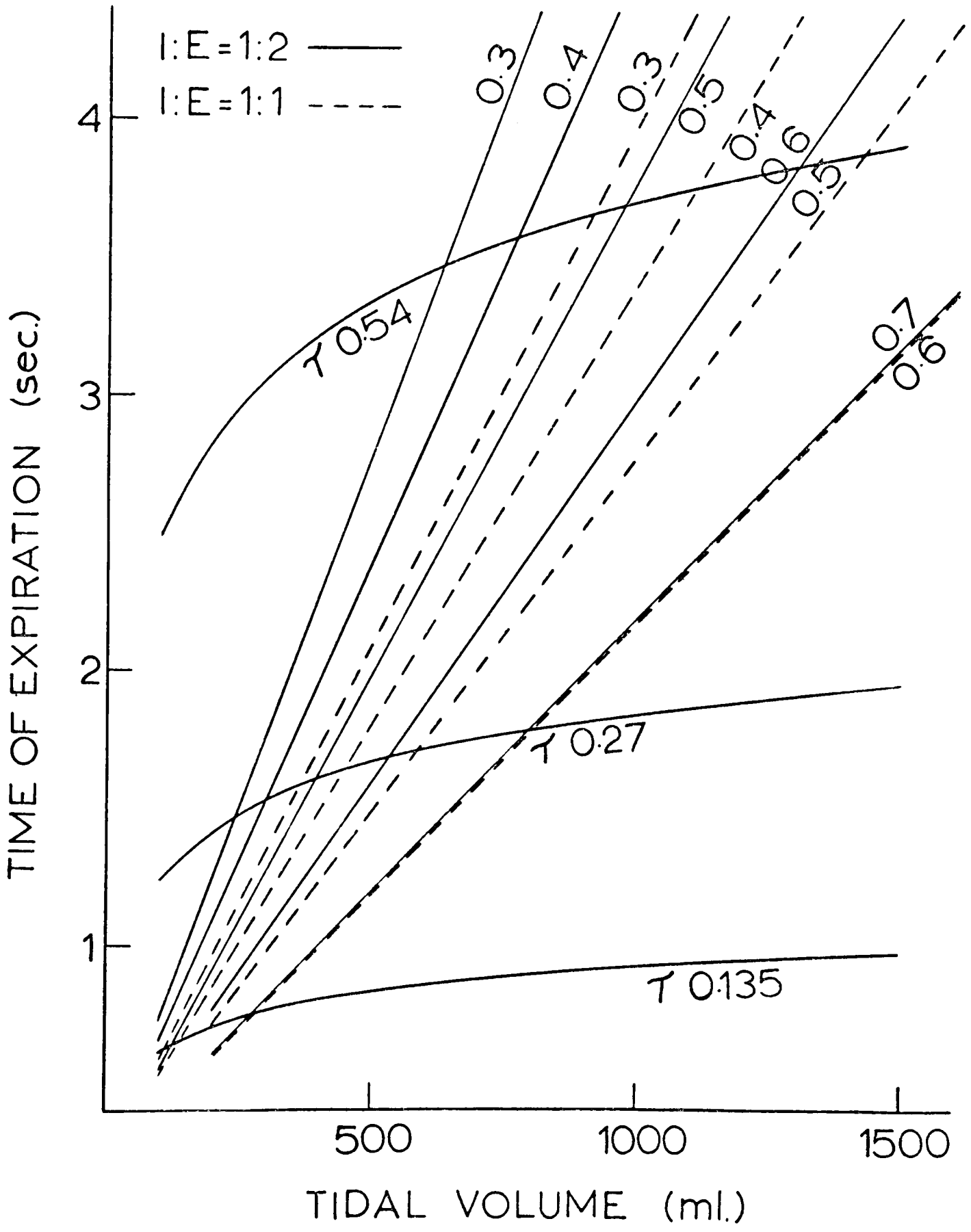

Fig. E:1 Nomogram to obtain expired time for a given tidal volume when alveolar ventilation is constant at 5 1/min, and when I:E ratio and V_D/V_T, or the inspiratory time constant. are known.

expire in the 2.8 sec available. If the V_D/V_T ratio is more than 0.3 expiration will be even less complete.

It may well be that the representation could be improved by assuming less complete expiration. In any event no originality is claimed for this prediction which can readily be observed when patients with obstructive lung disease are being artificially ventilated. The graph is included to emphasise the value of a simple theoretical approach in clarifying problems and suggesting areas for further biological investigation. There is no doubt in the author's mind that the effects of different inspiratory flow waveforms on patients with respiratory and cardiovascular disease should be investigated. It is likely to be valuable to approach the patients' problems through simple electrical or mathematical analogues before proceeding to definitive studies.

APPENDICES

APPENDIX A

Dog	Weight (kg.)	Hb (g/100 ml)	Haematocrit(%)
5	15.3	14.9	44
6	13.0	11.5	41
8	24.0	14.4	42
9	15.7	11.1	40.5
10	15.5	10.6	31
11	16.2	18.5	54
12	21.5	17.8	49
13	27.3	17.3	44
14	15.2	11.5	33
15	10.7	16.5	46
18	13.3	15.0	42.5
19	24.3	15.0	39
20	21.3	18.6	49
22	8.1	10.3	30
24	18.0	14.4	41
25	16.0	14.2	38
27	22.8	13.5	36
28	22.5	12.1	32
29	28.0	14.2	38
30	23.8	12.5	39
31	24.1	15.1	45
32	21.6	15.8	45

APPENDIX B

Symbols and Abbreviations

O_2	oxygen
P_{O_2}	partial pressure of oxygen
P_{a,O_2}	partial pressure of oxygen in arterial blood
P_{A,O_2}	partial pressure of oxygen in alveolar gas
$P_{\bar{v},O_2}$	partial pressure of oxygen in mixed venous blood
P_{I,O_2}	partial pressure of oxygen in inspired gas
$P_{\bar{E},O_2}$	partial pressure of oxygen in mixed expired gas
A - a P_{O_2} gradient	difference between alveolar and arterial partial pressure of oxygen
S_{O_2}	saturation of oxygen
S_{a,O_2}	saturation of oxygen in arterial blood
S_{A,O_2}	theoretical "saturation" of oxygen in alveolar gas
$S_{\bar{v},O_2}$	saturation of oxygen in mixed venous blood
C_{O_2}	content of oxygen
C_{a,O_2}	content of oxygen in arterial blood
C_{c',O_2}	theoretical "content" of oxygen in end capillary blood of lungs
$C_{\bar{v},O_2}$	content of oxygen in mixed venous blood
$\dot{V}_{O_2}$	minute volume ventilation for oxygen
F_{I,O_2}	fractional oxygen concentration in inspired gas
$F_{\bar{E},O_2}$	fractional oxygen concentration in mixed expired gas
CO_2	carbon dioxide
P_{CO_2}	partial pressure of carbon dioxide
P_{a,CO_2}	partial pressure of carbon dioxide in arterial blood

P_{A,CO_2}	partial pressure of carbon dioxide in alveolar gas
$P_{\bar{v},CO_2}$	partial pressure of carbon dioxide in mixed venous blood
$P_{\bar{E},CO_2}$	partial pressure of carbon dioxide in mixed expired gas
a - A P_{CO_2} gradient	difference between arterial and alveolar partial pressure of carbon dioxide
$\dot{V}_{CO_2}$	minute volume ventilation for carbon dioxide
$F_{\bar{E},CO_2}$	fractional carbon dioxide concentration in mixed expired gas
pH_a	pH of arterial blood
$pH_{\bar{v}}$	pH of mixed venous blood
Capac.	oxygen combining capacity of haemoglobin
Filley	"Filley factor"
T	patient temperature
P_b	barometric pressure
$V_{D(app.)}$	apparatus dead space
$V_{D(anat.)}$	anatomical dead space
S.T.P.D.	standard temperature and pressure dry
B.T.P.S.	body temperature and pressure saturated
I.P.P.V.	intermittent positive pressure ventilation
I:E ratio	inspiratory to expiratory time ratio
T_I	inspiratory time
T_E	expiratory time
V_T	tidal volume
V_E	expiratory volume
V_I	inspiratory volume
$\dot{V}_A$	alveolar minute ventilation

C_T	total dynamic compliance
C_L	dynamic lung compliance
C_{C-W}	dynamic chest wall compliance
R_T	total airways resistance
R_L	bronchial and lung airways resistance
R_{C-W}	chest wall resistance
V_D/V_T ratio	physiological dead space to tidal volume ratio
$\dot{Q}$	cardiac output
$\dot{Q}_D$	cardiac output measured by the dye dilution technique
$\dot{Q}_F$	cardiac output measured by the direct Fick method
$\dot{Q}_s/\dot{Q}$	pulmonary venous admixture
E.C.G.	electrocardiogram
Hb	haemoglobin
RR	reversed ramp flow waveform
R	ramp flow waveform
S	sine flow waveform
T	tophat flow waveform
I.D.	inner diameter
O.D.	outer diameter
S.D.	standard deviations
f.	frequency of respiration per minute

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p 266/267. Reference 44. should occur after Reference 46.

p 274. References 118. and 119. should be reversed in order.

p 275/277. Reference 151. should occur after Reference 139.

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ABSTRACT

ABSTRACT

A review of the literature revealed that there was no comprehensive history of artificial ventilation and the historical section of the thesis has been expanded to fill this gap. The history of artificial ventilation has been traced from myth to reality and from hesitant attempts to confident application.

In the last two decades intermittent positive pressure ventilation has become increasingly commonly used in the management of patients with respiratory failure. There is a large number of mechanical ventilators available for this purpose and in many instances the manufacturers claim superiority for their machines because of the inspiratory flow waveform and inspiratory-expiratory time ratio (I:E ratio). There is, however, very little scientific evidence available on which to base such assertions and the present study is an attempt to assess the physiological implications of changing only the inspiratory flow waveform or I:E ratio in artificial ventilation.

A variable waveform ventilator was built so that selected flow waveforms could be administered with independent control of the duration of inspiration and expiration. The ventilator consists of a variable electronic signal generator which acts through an attenuator upon an electropneumatic converter which linearly converts the electrical signal to a pressure signal of up to 150 p.s.i. This pressure is then transformed to a flow by passing the gas through a choke, and the size of the choke may be changed by substitution. The resulting flow is linearly related

to the original electrical signal so that faithful reproduction of the signal is achieved. The patchboard of the signal generator allows a large number of waveforms to be studied but in this study only sine, tophat, ramp and reversed ramp waveforms were used. This ventilator includes a new mechanical approach to the production of variable flow waveforms and allows greater flexibility than any previously designed.

Before embarking on the physiological study, an analogue study of the lung/thorax system was performed using electrical, mathematical and computer models. The analogue study predicted some interesting phenomena. One of these predictions was that the chest wall resistance was of importance in the response of the alveolar pressure. This resistance causes an instantaneous pressure step to occur in alveolar pressure, and also in oesophageal pressure, when an instantaneous step change is made in either the pressure or flow being applied to the patient in artificial ventilation. This observation was confirmed experimentally in humans and dogs. The analogue study also predicted that sine, triangular or reversed ramp waveforms with an inspiratory time of 1 to 1.5 seconds in a 4 second cycle would be the least harmful in the general application of artificial ventilation. This conclusion was, however, based on compromise and may be in error when any particular physiological variable is being considered. The analogue study also showed that some previous studies of lung analoges in artificial ventilation were in error.

Physiological studies were performed on mongrel dogs and measurements were made of cardiac output by two methods, blood pressures, airway and oesophageal pressures, blood gas partial pressures, gas flow and

tidal volume, end-tidal carbon dioxide concentration, electrocardiograph, haemoglobin, barometric pressure and temperatures. Certain physiological indices of cardio-respiratory efficiency were then computed and analysed. The experimental procedure was arranged in such a manner that factorial design statistical analysis could be applied to the data, and this analysis tested for synergism between flow waveform and duration of inspiration.

The results of investigations of the physiological effects of changing the I:E ratio, within a four second respiratory cycle, were largely in agreement with previous studies. Inspiratory times of 2.2 to 0.5 seconds were investigated and the physiological dead space to tidal volume ratio (V_D/V_T ratio) increased, total dynamic compliance decreased, and mean airway and oesophageal pressure fell with reduction of the duration of inspiration. No change was found in cardiac output, pulmonary venous admixture, dynamic chest wall compliance, or alveolar to arterial oxygen partial pressure gradient (A - a P_{O_2} gradient). There were suggestions that arterial partial pressure of oxygen (P_{a,O_2}) fell, arterial partial pressure of carbon dioxide (P_{a,CO_2}) rose, and the arterial to alveolar carbon dioxide partial pressure gradient (a - A P_{CO_2}) rose with reduction of the duration of inspiration. It might be expected that an increase in inspiratory time with increased mean airway and oesophageal pressures would reduce cardiac output. In the event, no doubt due to compensatory mechanisms in the healthy dog, this did not occur, but might be expected to occur in patients with cardiovascular disorders. For this reason the shortest inspiratory

time which did not seriously affect other variables, 1 to 1.5 seconds in a 4 second cycle, was considered to be the "best".

Studies on flow waveforms indicated that for most of the physiological variables investigated (V_D/V_T ratio, total dynamic compliance, P_{a,CO_2}, alveolar partial pressure of carbon dioxide (P_{A,CO_2}), a - A P_{CO_2}, P_{a,O_2}, A - a P_{O_2} gradient and $\dot{Q}_s/\dot{Q}$) the reversed ramp flow waveform was the least disruptive and ramp flow the most disruptive of the four waveforms examined. This did not apply, however, to studies on cardiac output or mean airway and oesophageal pressures where the effects were reversed, ramp flow being the least harmful. The results of the studies of the effects of flow waveforms are in disagreement with previously reported investigations.

Synergism between the effects of flow waveform and I:E ratio was found when V_D/V_T ratio, P_{a,CO_2}, P_{A,CO_2}, a - A P_{CO_2} gradient, mean airway pressure and mean oesophageal pressure were studied. Previous reports have not considered this possibility.

The controversy concerning the characteristics of the ideal ventilator is thus only partially resolved. Analogue studies suggested that sine, triangular or reversed ramp flow waveforms, at an inspiratory time of 1 to 1.5 seconds in a 4 second cycle, would be satisfactory if the effects of all factors were considered. In the physiological studies, the reversed ramp flow waveform proved least disruptive in most circumstances, but this flow waveform had the most disruptive effects on mean airway and oesophageal pressures and cardiac output. It may therefore be necessary to employ different waveforms in different cardiopulmonary disorders, and observations in such disorders should be made.