# HAEMODYNAMIC AND METABOLIC STUDIES IN MAN WITH SPECIAL REFERENCE TO THE EFFECTS OF OXYGEN

Thesis presented to the University of Glasgow for the degree of Doctor of Medicine

Volume I

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# Preface

Studies in the field of hyperbaric medicine have been in progress at the Western Infirmary in Glasgow since 1956. The first clinical trial of the effects of hyperbaric oxygen in the treatment of patients with myocardial infarction was carried out by Dr. A.J.V. Cameron and colleagues in 1963 - 64. I obtained the post of registrar in cardiology in 1965 and since then, under Dr. Cameron's continued guidance and interest, I have taken part in further research on the effects of oxygen in healthy subjects and in patients. In 1967 I gained the post of Senior Registrar in Medicine at the Western Infirmary and this has allowed me to continue studies in this field and to develop new techniques such as methods of estimation of myocardial blood flow. This thesis is the result of these investigations.

The plan of the thesis is as follows. In the first chapter a short history of the use of oxygen in medicine is followed by a discussion of the physiological aspects of oxygen therapy and the methods of administration. The results of the present investigations are given in Chapters II - V. After each experimental section the results of that section are summarised and conclusions drawn. This is followed in each chapter by a general discussion

of the results obtained in the present work in relation to previous studies. The hazards of oxygen therapy are discussed in Chapter Vl and the general conclusions resulting from this work are given in Chapter Vll.

The detailed findings of the investigations are given in the tables in Volume II and only the mean results are shown graphically in the main body of the thesis (Volume I). This arrangement was followed in order to allow the tables to be consulted conveniently while reading the text.

Finally, a critique of the methods used in this in vestigation is given in Volume II and some examples of the original recordings are shown.

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# Chapter I.

## Introduction.

Section A: A short historical review of the use of oxygen in medicine.

Section B: Physiological aspects of oxygen inhalation.

Section C: Methods of administration of oxygen.

Section A.

A Short Historical Review of the Use of Oxygen in Medicine.

*"From the greater strength and vivacity of the flame of a candle, in this pure air, it may be conjectured that it might be peculiarly salutary to the lungs in certain morbid cases ..... But, perhaps, we may also infer from these experiments that though pure dephlogisticated air might be very useful as a medicine, it might not be so proper for us in the usual healthy state of the body: for, as a candle burns out much faster in dephlogisticated than in common air, so we might, as may be said, live out too fast, and the animal powers be too soon exhausted in this pure kind of air. A moralist, at least, may say, that the air which nature has provided for us is as good as we deserve .... The feeling of it to my lungs was not sensibly different from that of common air; but I fancied that my breast felt peculiarly light and easy for some time afterwards. Who can tell but that, in time, this pure air may become a fashionable article in luxury. Hitherto, only two mice and myself have had the privilege of breathing it."*

Thus wrote Joseph Priestley (1733 - 1804)

shortly after his discovery of oxygen in 1774. Although Priestley was the first to isolate oxygen, it had been shown by John Mayow (1645 - 79) more than a hundred years before that there was a substance present in air which is concerned both with combustion and respiration and which causes venous blood to change colour when aerated. Mayow's work appears to have been ignored or forgotten at the time and it was Priestley who demonstrated that oxygen was necessary for repiration and combustion and was given off by growing plants. Priestley, however, adhered to the phlogiston theory and failed to recognise fully the nature of his discovery. In 1777, the French chemist, Antoine Laurent Lavoisier (1743 - 94) made a quantitative investigation of the changes occurring during respiration and this demonstrated the physiological properties of oxygen. For this reason he is credited by many as the true discoverer of oxygen, but it can be seen from the above quotation that the therapeutic possibilities of oxygen and also the potential dangers of treatment had been tentatively considered by Priestley.

Although oxygen was first used as a form of treatment by Beddoes in Bristol in 1795 it was not until the end of the nineteenth century that it was introduced to any great extent. It was the French

physiologist Paul Bert (1833 - 86) (fig. 1) who laid the foundations for all subsequent studies of the effects of oxygen in his book "La Pression Barometrique" (1878) (fig. 2). Bert proved that it was the partial pressure of oxygen in the inspired air which was important to life and not the total atmospheric pressure. He performed experiments in animals and man with both high and low atmospheric pressures using a pressure chamber for the purpose. He showed that lowering of the atmospheric pressure was no longer lethal as long as the oxygen concentration was increased. As a result of his experiments he was the first to administer oxygen in balloon ascents. He was also the first to show that pure oxygen at high pressure can be toxic.

Following his meticulous and classic work there was still a delay in the introduction of oxygen to medical treatment. While this delay may partly have been due to the difficulty and expense of obtaining supplies of oxygen until it could be easily obtained commercially by the liquefaction of air in 1890, it was mainly as a result of the current view of physiologists. They stated that increasing the oxygen in the inspired air could have no physiological effects as the circulatory haemoglobin was already fully saturated and the amount of oxygen carried in

PAUL BERT
Born October 17, 1833. Died November 11, 1886.

Fig. 1. Photograph of Paul Bert (1833 - 86), French physiologist and author of the book "La Pression Barometrique" which described his numerous experiments concerning the effects of oxygen at various atmospheric pressures. (See Fig. 2).

# PRESSION BAROMÉTRIQUE

RECHERCHES

DE PHYSIOLOGIE EXPÉRIMENTALE

PAR

PAUL BERT

PROFESSEUR A LA FACULTÉ DES SCIENCES DE PARIS

LAURÉAT DE L'ACADÉMIE DES SCIENCES
(Prix de physiologie expérimentale, 1865)
LAURÉAT DE L'INSTITUT (Grand Prix biennal, 1875)

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AVEC 89 FIGURES DANS LE TEXTE

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PARIS

G. MASSON, ÉDITEUR

LIBRAIRE DE L'ACADÉMIE DE MÉDECINE

BOULEVARD SAINT-GERMAIN, EN FACE DE L'ÉCOLE DE MÉDECINE

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Fig. 2. Title-page of "La Pression Barometrique" published 1878.

solution in the blood was negligible. However, by the early 1900's oxygen was beginning to be used clinically, although the methods of administration were largely unsatisfactory and must have resulted in a very small increase in oxygen concentration in the inspired air. In a letter to the "British Medical Journal" the use of oxygen inhalation in the treatment of "severe angina pectoris" is described (Steele, 1900). The author stated that "the severe cyanosis, dyspnoea, gasping and horror and also the chest pains have been promptly arrested" by this treatment. A considerable amount of work on the physiological effects of oxygen was carried out by L. Hill and colleagues. They claimed that the performance of athletes could be improved by prior administration of oxygen (Hill, Flack and Just, 1908), and described how an ageing carthorse could climb better after oxygen, whereas race-horses in peak condition were unaffected (Hill, 1908). In 1909 Hill described an apparatus for the generation and administration of oxygen to patients, and claimed that by this means the period of cardiac "irregularity" which occurred after exercise in a subject with mitral stenosis could be shortened. Oxygen mixed with alcohol vapour was recommended in cardiac patients by Willcox and Collingwood (1910) who passed the gas through absolute alcohol before

administration claiming an improved result by this means. Brunton (1912) described the use of oxygen as a cardiac stimulant and noted that in a patient with "cardiac asthma" the radial arterial pressure increased with oxygen.

Apart from the scientific studies of Paul Bert, the first modern approach to the use of oxygen as a therapeutic agent appears to have been its assessment by Haldane (1917) although its physiological effects had been previously studied (Benedict and Higgins, 1911, Parkinson, 1912). He recommended that oxygen should be used in the treatment of carbon monoxide poisoning, pneumonia and circulatory failure. The toxic effects of oxygen noted by Bert (1878) and Lorrain Smith (1899) were recalled, and Haldane stated that the concentration of oxygen should therefore be kept as low as possible, care being taken to determine accurately the level at which it is given. He described a facemask for oxygen administration with expiratory and inspiratory valves. At about the same time Melzer (1917) strongly advocated the therapeutic use of oxygen, pointing out that blood is normally not quite fully saturated and moreover that the amount of oxygen in simple solution in the plasma is not negligible if the tension in the inspired air is increased.

He commented that one of the reasons for the lack of enthusiasm for oxygen therapy was because the prevailing systems of administration gave such a low percentage of oxygen that its beneficial effects were not properly seen. He therefore recommended the rhythmic oral insufflation of oxygen, describing a simple apparatus for this purpose, and considered that this method actually produced a degree of assisted respiration. While his paper largely refers to the use of this regime in patients with respiratory disease he also found oxygen to be "of great benefit" in a patient with pulmonary oedema and hypertension.

Since then, oxygen has gradually been accepted as a standard form of treatment in patients with cardiac disease. A reduction in oxygen content of both arterial and venous blood was shown to be frequently present in patients with congestive cardiac failure (Harrop, 1919) and it was later demonstrated that inhalation of 40 to 50 per cent oxygen could increase both arterial and venous oxygen saturation in these patients (Barach and Woodwell, 1921). Prevention or alleviation of cardiac pain by the use of oxygen was also recommended (Rizer, 1929) and the results of inhalation of oxygen by patients with myocardial infarction were reported (Levy and Barach, 1930). These workers administered 45 per cent oxygen by means

of a tent to four patients with acute myocardial infarction. This resulted in subjective improvement, reduction of cyanosis, slowing of the respiratory and heart rates and increase of blood pressure. From about this time oxygen therapy in heart disease has gained a place in most standard textbooks. In Conybeare's "Text-Book of Medicine" (1932) it was stated that oxygen is undoubtedly of value in the treatment of cardiac failure if the patient is cyanosed. In the 1948 edition of "Recent Advances in Cardiology" oxygen is advised in the treatment of myocardial infarction: "Oxygen is valuable if cyanosis develops at any stage and also if pain persists, or recurs, in spite of adequate doses of morphine at the onset." (East and Bain, 1948). Most standard textbooks currently recommend the use of oxygen in the treatment of circulatory failure and also myocardial infarction (Dunlop and Alstead, 1966, Friedberg, 1966).

The striking feature when reviewing the literature relating to oxygen therapy is the almost complete absence of any objective attempts to assess its efficiency. Thus all the early reports of its use refer to small numbers of patients, while improvement with oxygen has been judged mainly by the change in colour of the patient and the relief of

dyspnoea or other symptoms. The effect of oxygen therapy on mortality is largely unknown and there is, as far as can be ascertained, only one controlled trial available (Cameron et al., 1965). Until recently it was difficult to measure accurately the oxygen tension in the blood of severely ill patients and this may partly account for the lack of objective evidence regarding the effects of oxygen administration. Advance in technology has made the measurement of arterial oxygen tension relatively easy. Interest in the use of oxygen has been stimulated thereby, especially as it has now been shown that the arterial oxygen tension is frequently reduced in patients with myocardial infarction even when there is no clinical evidence of cardiac failure (MacKenzie et al., 1964). Nevertheless, at the present time the benefits of oxygen therapy are largely conjectural and for this reason it was decided to investigate the effects of oxygen in health and disease in an attempt to obtain a better understanding of its place in the treatment of cardiac patients.

Section B.

Physiological Aspects of Oxygen Therapy.

In man, oxygen is essential in order to allow the oxidative metabolic processes to take place in the cells of the body. These processes are essential if life is to be maintained and without oxygen the cells cannot function and death follows rapidly. Oxygen is transported to the cells by means of the blood and circulatory systems. In the presence of a normal haemoglobin level, the arterial blood contains approximately 19 volumes per cent of oxygen. While most of the oxygen is carried in chemical combination with the haemoglobin, which is normally 95 per cent saturated in arterial blood, there is also a small amount in simple solution in the plasma. The quantity in solution follows Henry's Law and is directly proportional to the oxygen tension: at an arterial oxygen tension of 100 mm.Hg. the amount in solution is 0.31 vols. per cent.

In the lungs, oxygen is taken up by the blood and carbon dioxide is removed. The oxygen is normally supplied from the atmospheric air which contains 20.94 per cent oxygen and varies only within narrow limits. At a barometric pressure of

760 mm.Hg. in moist conditions the partial pressure of oxygen in inspired air is therefore about 150 mm.Hg. This pressure is further reduced in the alveoli where the oxygen in diluted by carbon dioxide given off from the venous blood and where the gases are fully saturated with water vapour. As a result the alveolar oxygen tension is commonly only 100 - 110 mm.Hg. The alveolar walls in health present little barrier to the diffusion of oxygen, and blood leaving the lungs is almost fully equilibrated, the arterial oxygen tension lying between 80 and 95 mm.Hg. The oxygen tension in the tissues will, of course, vary with the rate of metabolism but it is thought that it usually lies between 30 - 0 mm.Hg. There exists, therefore, a difference of oxygen tension of about 65 mm.Hg. between arterial blood and the tissue cells. It is known that the rate of passage of oxygen from the capillaries to the tissues is proportional to the size of this difference (Evans, 1952). If 100 per cent oxygen is inhaled alveolar oxygen tension will rise as nitrogen is displaced and will eventually be equal to the barometric pressure less the alveolar carbon dioxide tension and the pressure of water vapour. By inhalation of oxygen at atmospheric pressure an alveolar oxygen tension of about 667 mm.Hg.

can be attained. It has been shown that the diffusion continues normally as the alveolar oxygen tension is increased and therefore an arterial oxygen tension of about 650 mm.Hg. can be expected (McDowall et al., 1965). It is therefore obvious that by this means the difference in oxygen tension between arterial blood and tissues can be greatly increased and this should enhance the rate of uptake of oxygen by the tissues. Further increase in the ambient pressure above atmospheric should likewise further increase the blood-tissue gradient and theoretically should increase the oxygen supply to the tissues.

The amount of oxygen carried by the blood depends on the amount of haemoglobin available as well as the partial pressure of oxygen. The haemoglobin in the blood reaches full saturation at an oxygen tension of 100 mm.Hg. and further increase in oxygen tension will not increase the amount of oxygen carried in chemical combination. Conversely, if the haemoglobin is reduced, the blood oxygen content will be less than normal, even although the arterial tension is 100 mm.Hg. and the haemoglobin is fully saturated. However, the quantity of oxygen carried in physical solution will increase proportionately with the partial pressure of oxygen. Thus if the arterial oxygen tension is raised from 100 mm.Hg. to 2,000 mm.Hg. the amount of oxygen

in solution in the plasma will rise from 0.31 ml. to 6.2 ml. per 100 ml. blood. It has been shown in pigs that they can be kept alive temporarily without apparent ill-effect following total replacement of their haemoglobin by saline solution while inhaling oxygen at a pressure of three atmospheres absolute (Boerema et al., 1960). In this situation it is therefore demonstrated that sufficient oxygen is carried in simple solution to maintain life.

The term anoxia is used to describe oxygen lack of the body from any cause. While there are many pathological processes which produce this condition as a secondary effect, there are only four basic types of anoxia.

(1) Anoxic anoxia. In this type the arterial blood is insufficiently oxygenated and has a low oxygen tension, due to a defect in the lungs or to a deficiency of oxygen in the air breathed.

(2) Anaemic anoxia. In this form the arterial oxygen tension is normal but there is insufficient haemoglobin to carry the oxygen required to the tissues.

(3) Stagnant anoxia. The arterial blood in this type of anoxia has a normal oxygen content at a normal tension, but failure of the circulation with slowing

of the blood results in a deficient tissue oxygen supply.

(4) Histotoxic anoxia. In this category, the oxygen tension of the blood is normal and the circulation is satisfactory but the tissues are unable to take up oxygen due to poisoning of their oxidative mechanism.

It is only the first three types of anoxia which are commonly found in the clinical situation. Anoxic anoxia should be largely relieved by the administration of oxygen even at atmospheric pressure. Anaemic and stagnant anoxic states cannot be greatly improved by inhalation of oxygen at normal pressure but should benefit from oxygen at increased ambient pressure.

There remains, of course, the problem of local anoxia, where due to a deficiency of blood supply a localised area of tissue is deprived of oxygen. It is hoped that here, too, an increase of arterial oxygen tension may be of benefit by increasing the gradient of oxygen between the surrounding areas and the ischaemic zone, thus allowing diffusion of oxygen to take place by physical means into the area which is lacking in blood supply. This has been shown to occur in experimental animals (Sayen et al., 1951) and it is by such a mechanism

that it is anticipated that hyperbaric oxygen might be of greatest assistance.

Section C.

Methods of Oxygen Administration.

There are two basic methods by which oxygen can be administered. In the first, the patient is nursed in a normal atmosphere and is supplied with oxygen by means of a facemask or nasal tubes. In the second method the patient is placed in an environment enriched with oxygen, such as an oxygen tent or room and breathes normally without the use of a special mask. Several factors must be taken into account when assessing the efficiency of any system for oxygen delivery. These include the level of oxygen which is obtained in the alveoli, the safety of the method including any tendency to cause carbon dioxide retention and perhaps the most important feature, the degree of comfort or discomfort experienced by the patient when he receives this treatment. It must be remembered that there are different aims of oxygen therapy in different conditions. In cardiac patients as a general rule, the object is to administer oxygen in the highest possible concentration. On the other hand, with patients in respiratory failure, it is essential that only a small increase in the level of inspired oxygen is achieved in order to

prevent further respiratory depression and subsequent carbon dioxide retention. This investigation is not, however, concerned with the latter problem and it is only devices which supply a high concentration of oxygen which will be discussed.

Early methods of oxygen administration consisted of a simple paper funnel which was held above the patient's nose and mouth. By this means the inspired oxygen concentration must have been increased by only a very small percentage. Haldane (1917) described a close-fitting facemask with an inspiratory and expiratory valve and stressed the importance of measuring the concentration of oxygen delivered. Since then there have been detailed improvements in mask design but the general principles of administration remain remarkably unchanged and there still does not exist a totally satisfactory method of giving oxygen in high concentration. Apparatus which is most efficient in terms of the level of oxygen inspired is often very uncomfortable and therefore unsuitable for prolonged use in severely ill patients, whereas apparatus which is well tolerated often provides only low inspiratory values for oxygen.

Perhaps the most effective method is to supply oxygen through a scuba-type mouthpiece which fits between the patient's gums and lips and is used together with a nose-clip. If correctly applied this mouthpiece attached to an oxygen supply gives almost 100 per cent oxygen as there can be little or no dilution by air and leakage at the face is minimal. It is, however, fairly uncomfortable and while it can be used for short periods during investigative procedures, it is quite unsuitable for routine therapy. At the other extreme lie intra-nasal catheters of the type described by Tudor Edwards (1938) or Addis (1963). While these devices are reasonably comfortable, they give only a very low concentration of inspired oxygen (Catterall, Kazantzis and Hodges, 1967). The common types of mask in use in hospital wards currently are the "Polymask" (Burns and Hall, 1953) and the MC mask. (fig. 3). Both these masks are moderately efficient and provide an inspiratory oxygen content of 40 to 60 per cent when oxygen is given at a flow rate of 6 - 8 litres per min. (Flenley, Hutchison and Donald, 1963, Catterall et al., 1967). With the use of close-fitting oro-nasal masks it is possible to give a higher inspiratory oxygen concentration. A modification of the "B.L.B." mask (Boothby, Lovelace

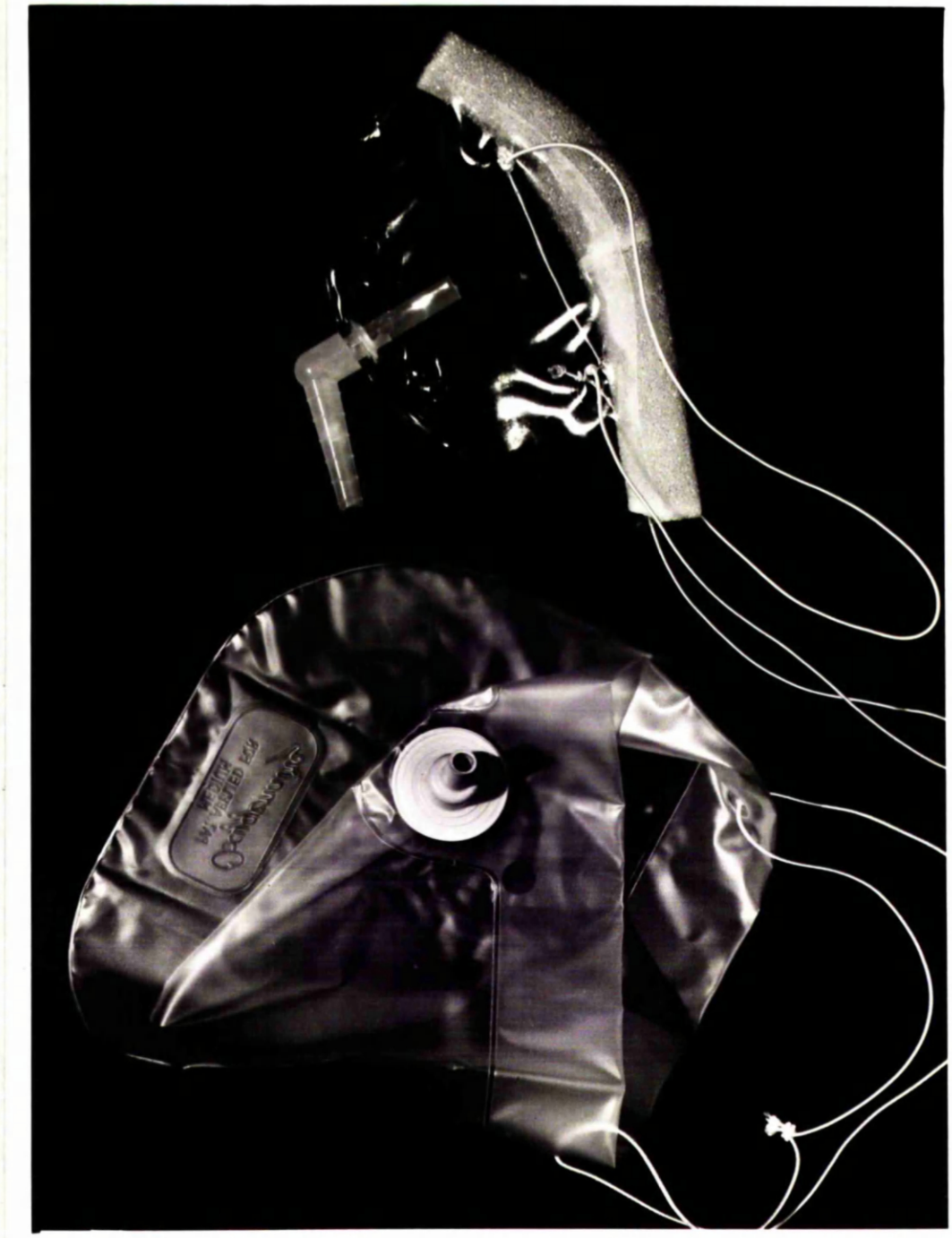

Fig. 3. Photograph of masks in common use for the administration of oxygen. The upper mask is an "M.C." mask (B.X.L. Ltd.) and the lower mask is a "Pneumask" (Oxygenaired Ltd.) which is very similar to the "Polymask" (British Oxygen Company Ltd.)

and Bulbulian, 1938), is now commercially available and consists of a plastic nose and facepiece with a rebreathing bag of 500 ml. capacity. This sytem yields high concentrations of oxygen with a flow rate of 6 - 8 litres per min. (Ball, 1963). Another type of oro-nasal mask, which was originally designed for aircrew, has also been shown to be highly efficient (McDowall et al., 1965) and was used on most occasions in this study. This mask allows a very high inspiratory oxygen concentration to be inhaled, although it does have the disadvantage of causing a degree of discomfort to the patient and moreover has to be frequently adjusted if it is to remain efficient. A demand valve is incorporated in the system between the oxygen supply and the patient so that oxygen flows only when the patient inhales. In any system where high concentrations of oxygen are inhaled from a piped oxygen supply it is important that the dry gas should be moistened prior to reaching the patient and a humidifier is used with this apparatus.

The alternative approach to the use of a mask is to place the patient in an environment enriched with oxygen. Hill (1912), experimented with an "oxygen bed" which consisted of an air-tight chamber for this purpose, and later an oxygen chamber was

constructed by Stadie (1922) for the treatment of patients with pneumonia. At the present time there are many different designs of oxygen tent available, which fit over the patient and enclose him in an oxygen-rich environment. While these methods are useful, and may indeed be essential in paediatric practice, their place in adult medicine is limited. They require elaborate equipment for maintaining the correct temperature and a means for the removal of carbon dioxide must be provided. Moreover, they are prone to much leakage of oxygen and the final inspiratory concentration is often little greater than that achieved by the "polymask" or "MC" facemasks (Simpson and Russell, 1967).

The use of oxygen at increased atmospheric pressures requires even more elaborate apparatus. One of the first hyperbaric chambers was that used by Bert (1878) although it was used for experimentation rather than treatment. (fig. 4.) In Glasgow, work in the field of hyperbaric medicine began in 1956 (Illingworth et al., 1961) and subsequently several pressure chambers have been installed in the Western Infirmary for the treatment of patients and experimental studies.

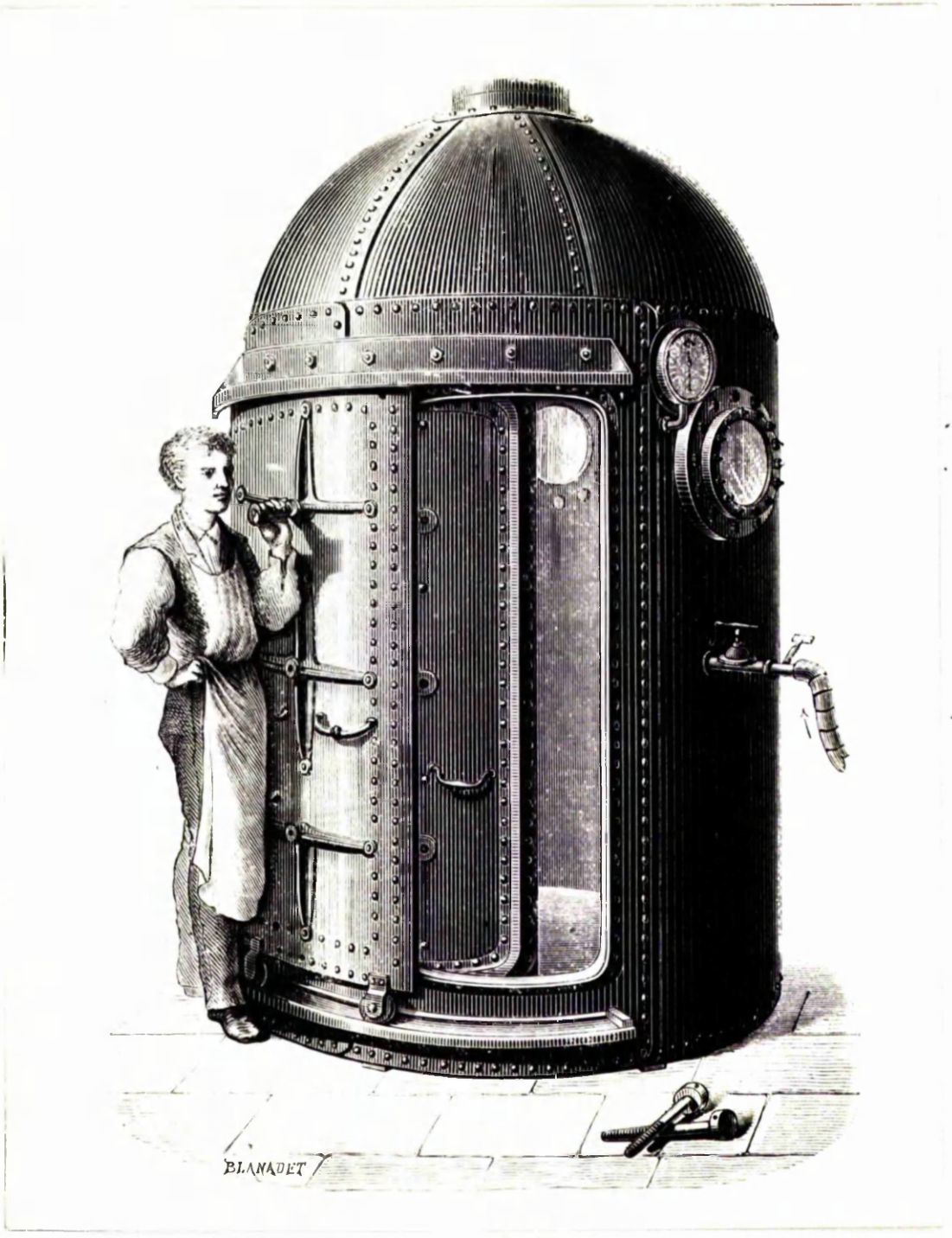


Fig. 4. Early pressure chamber used by Paul Bert in his experiments.

There are two methods by which oxygen can be administered at increased ambient pressures. The method employed in this investigation was to increase the pressure within the hyperbaric chamber by compressed air and then administer oxygen to the patient by means of a facemask in a similar fashion to that used at atmospheric pressure. The other method, which is frequently used in single-patient pressure chambers, is to compress the chamber with pure oxygen which the patient breathes without a mask (Ashfield and Gavey, 1969). In the latter method the fire risk is very greatly increased and for this reason is not applicable to large pressure chambers containing apparatus for measurement and patient monitoring which would increase the hazard. The use of oxygen at increased pressures by either method requires the availability of skilled personnel and expensive apparatus and in order to be therapeutically and economically justifiable must be shown to produce results which cannot be achieved at atmospheric pressure. The following chapters will describe investigations aimed at assessing the relative values of oxygen administration at one and two atmospheres pressure in cardiac patients.

# CHAPTER II

Chapter II — Effects of the inhalation of oxygen in healthy subjects

Section A: Haemodynamic effects of inhalation of oxygen at pressures of one and two atmospheres absolute in healthy subjects at rest

Section B: Haemodynamic effects of the inhalation of oxygen at pressures of one and two atmospheres absolute in healthy subjects during exercise

For the proper evaluation of the use of oxygen as a form of treatment in patients with heart disease an understanding of the physiological circulatory responses to oxygen at normal and increased ambient pressures is obviously of great importance. Although the changes which occur in healthy subjects breathing oxygen in high concentrations at ordinary atmospheric pressure have been widely studied, there is little information available concerning the effects of oxygen in man at increased atmospheric pressures. Indeed, the only investigation in recent years of the physiological effects of oxygen at high pressure on the circulatory system was carried out by Whalen et al., (1965), in which haemodynamic and blood gas measurements were made in ten healthy young men during the inhalation of oxygen at a pressure of 3.04 atmospheres absolute. This environment, however, is not greatly different from the level of 3.7 atmospheres absolute which has long been known to be liable to cause oxygen poisoning even after relatively brief exposures (Donald, 1947) and two of their subjects experienced manifestations of oxygen toxicity. One had a major epileptiform seizure after 24 minutes of

oxygen breathing, and the other developed early signs of toxicity after only 14 minutes exposure to oxygen. The development of oxygen toxicity appears to be quite unpredictable and the susceptibility is variable both between individuals and in the same subject at different times. For this reason it seems desirable that the clinical use of hyperbaric oxygen should be limited to pressures not exceeding two atmospheres absolute except perhaps for very short periods of treatment.

The present investigation was therefore undertaken in order to determine the haemodynamic effects of the inhalation of oxygen at pressures of one and two atmospheres absolute in healthy men at rest and after exercise. These levels of oxygen pressure were considered to be those most likely to be of therapeutic benefit and it was hoped that a comparative basis would be obtained for the further assessment of the value of oxygen in clinical practice especially in the treatment of myocardial infarction.

Section A. Haemodynamic effects of inhalation of oxygen in healthy subjects at rest.

In this investigation the haemodynamic effects of inhalation of oxygen was studied in healthy subjects at rest. Measurement of heart rate, cardiac output and blood pressure was performed while breathing air at one atmosphere and oxygen at one and two atmospheres absolute pressure.

Subjects and Methods

Twenty male subjects were investigated. Fifteen were medical students and five were members of the medical staff. All were in good health at the time of the study and the results of clinical examination, X-ray of chest and electrocardiogram were normal. The age, height, weight and body surface area of the twenty subjects are shown in Table 1. The surface area was calculated from the height and weight using a nomogram constructed from the formula of Du Bois and Du Bois (1916).

All observations were made in the pressure chamber in the Department of Surgery at the Western Infirmary, Glasgow. This chamber was constructed as an operating theatre and is large enough to accommodate a bed for the subject along with medical and technical staff (fig. 1). All the apparatus for making haemodynamic and blood gas measurements

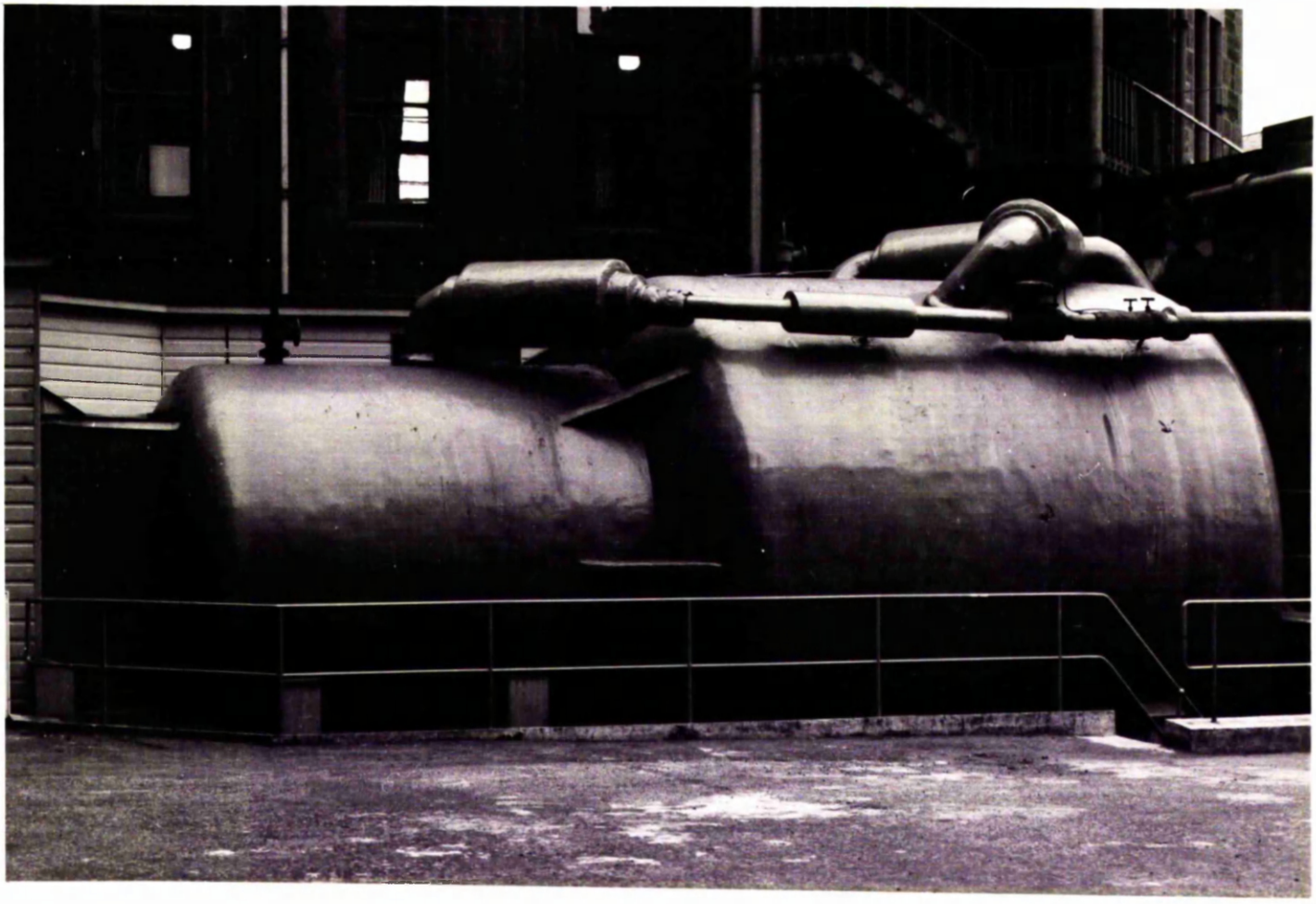

Fig. 1. External view of pressure chamber at the Western Infirmary, Glasgow. The smaller cylinder on the left is the air lock and the large cylinder on the right is the main chamber.

was also located within the chamber. The chamber is equipped with a large air lock to enable the entrance of medical and nursing personnel without decompression of the main chamber and also a small air lock for the passage of biochemical and other samples to and from the main chamber as required. Compression of the chamber is performed using air in order to reduce the fire hazard and to eliminate the possibility of oxygen toxicity in attendant personnel. Compression to two atmospheres absolute is carried out gradually over a period of approximately 15 minutes, but the rate of compression can be varied as required. Decompression takes place slowly in order to avoid decompression illness. The temperature of the chamber can be held constant by means of air conditioning and in this investigation a level of 20°C was maintained throughout. Communication is maintained between the chamber and the attendants outside by means of a two-way microphone.

The subjects were studied while breathing air at one atmosphere absolute pressure, 100 per cent oxygen at one atmosphere absolute pressure and 100 per cent oxygen at two atmospheres absolute pressure. Air or oxygen was administered by means of a close-fitting oro-nasal mask connected to a

humidifier and a demand valve. The mask is fitted with an expiratory valve to prevent accumulation of carbon dioxide. This system when connected to the oxygen supply has been shown to give an alveolar oxygen concentration in excess of 80 per cent in healthy young men (McDowall et al., 1965).

After a light lunch the subject rested in the supine position on a couch in the hyperbaric chamber for one hour before observations were commenced (fig. 2). Air or oxygen was then breathed for successive periods of 45 minutes and measurements were taken at the end of each period. There was random allocation of the sequence of gas administration. In ten subjects it was (1) air at one atmosphere, (2) oxygen at one atmosphere and (3) oxygen at two atmospheres, while in the other ten the order was reversed. When the study commenced at one atmosphere inhalation of oxygen was continued during compression and conversely when it commenced at two atmospheres inhalation of oxygen was continued during decompression but these times were not included in the 45 minute periods of oxygen breathing air at one and two atmospheres before measurements were made.

The heart rate was monitored continuously and the rates used in the final analysis were derived

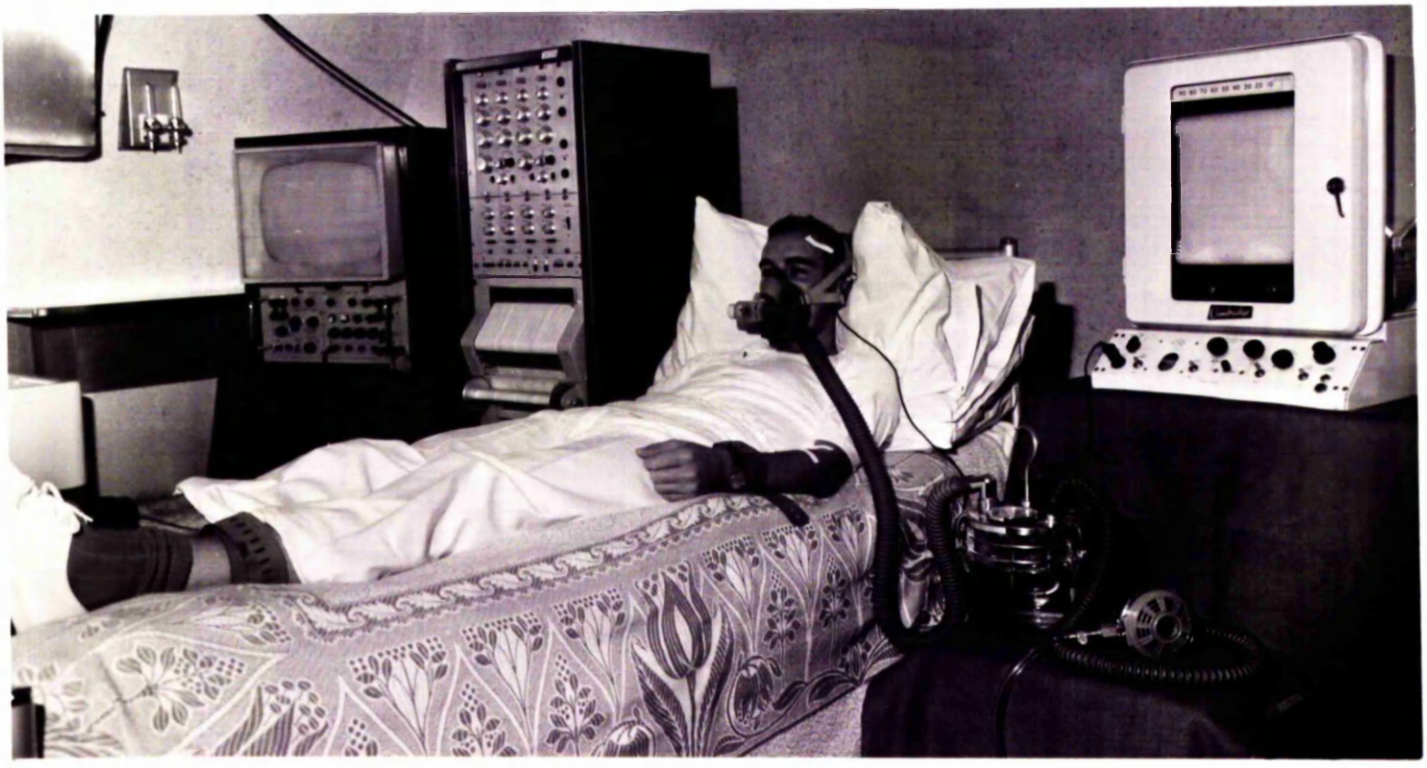

Fig. 2. Healthy subject at rest within hyperbaric chamber. Apparatus for monitoring and recording the electrocardiogram and the cardiac output is seen on either side of the bed.

from electrocardiographic recordings made immediately before, during and after the inscription of each dye dilution curve. Cardiac output was measured by a dye dilution method as described by Gabe and Shillingford (1961), using a Cambridge Mk II dye dilution recorder (fig. 3). In this method the passage of dye is recorded through the pinna of the ear which acts as an arterial cuvette. A bright light source is positioned on one side of the ear and a photo-electric cell placed on the other side records the change in translucency as the dye reaches the ear (fig. 4). The method has the advantage of simplicity and eliminates the necessity for arterial sampling and the placement of an intra-arterial catheter. Coomassie blue dye was injected rapidly from a calibrated syringe, the usual dose being 40 mg. and this was followed at once by an injection of normal saline from another syringe, both being attached to the same three-way stop-cock. This in turn was connected to a polythene catheter inserted percutaneously under sterile conditions into an antecubital vein and advanced until the tip lay near the superior vena cava. A sample of venous blood for estimation of dye concentration was obtained from the opposite

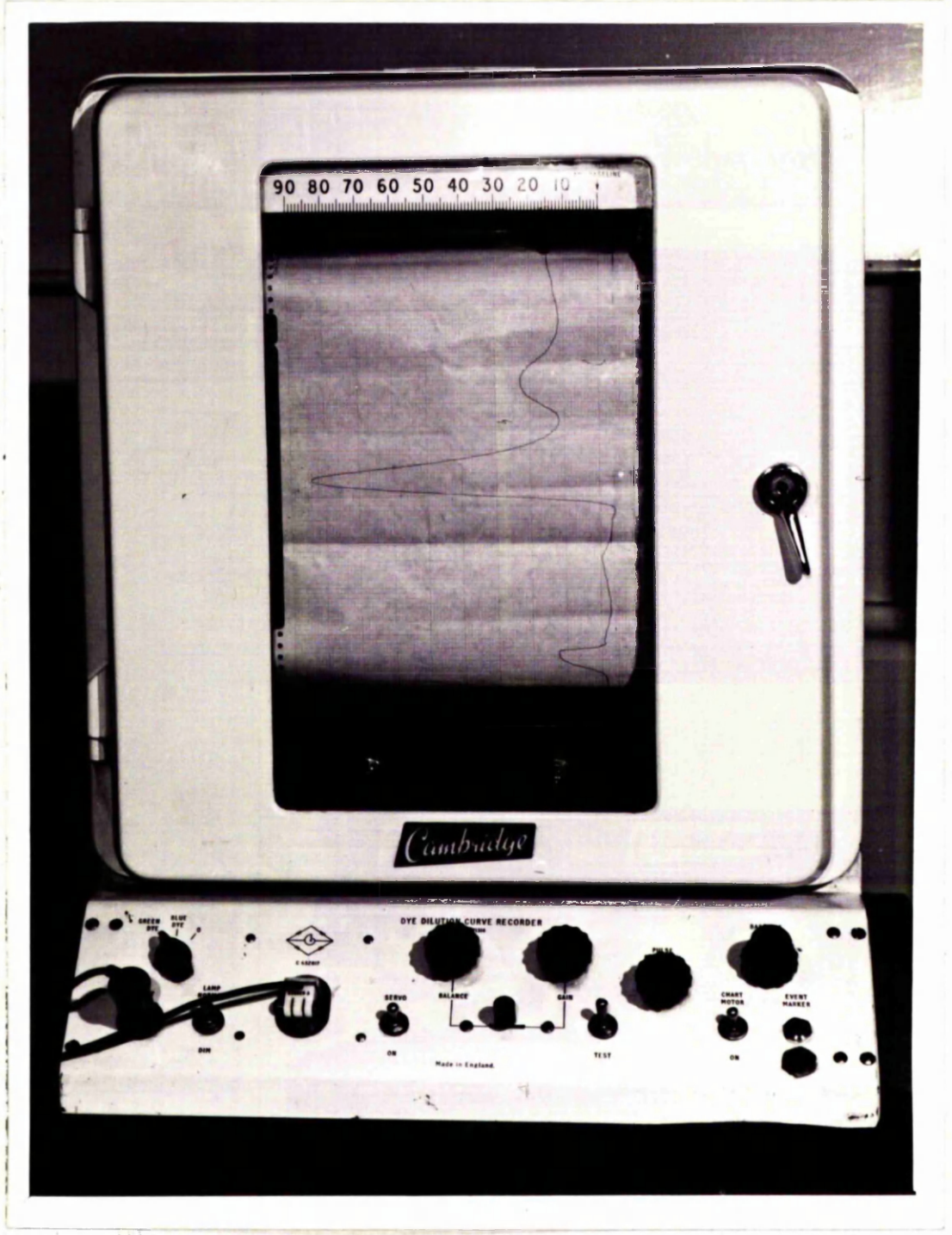


Fig. 3. Cambridge Mark II Dye dilution curve recorder.

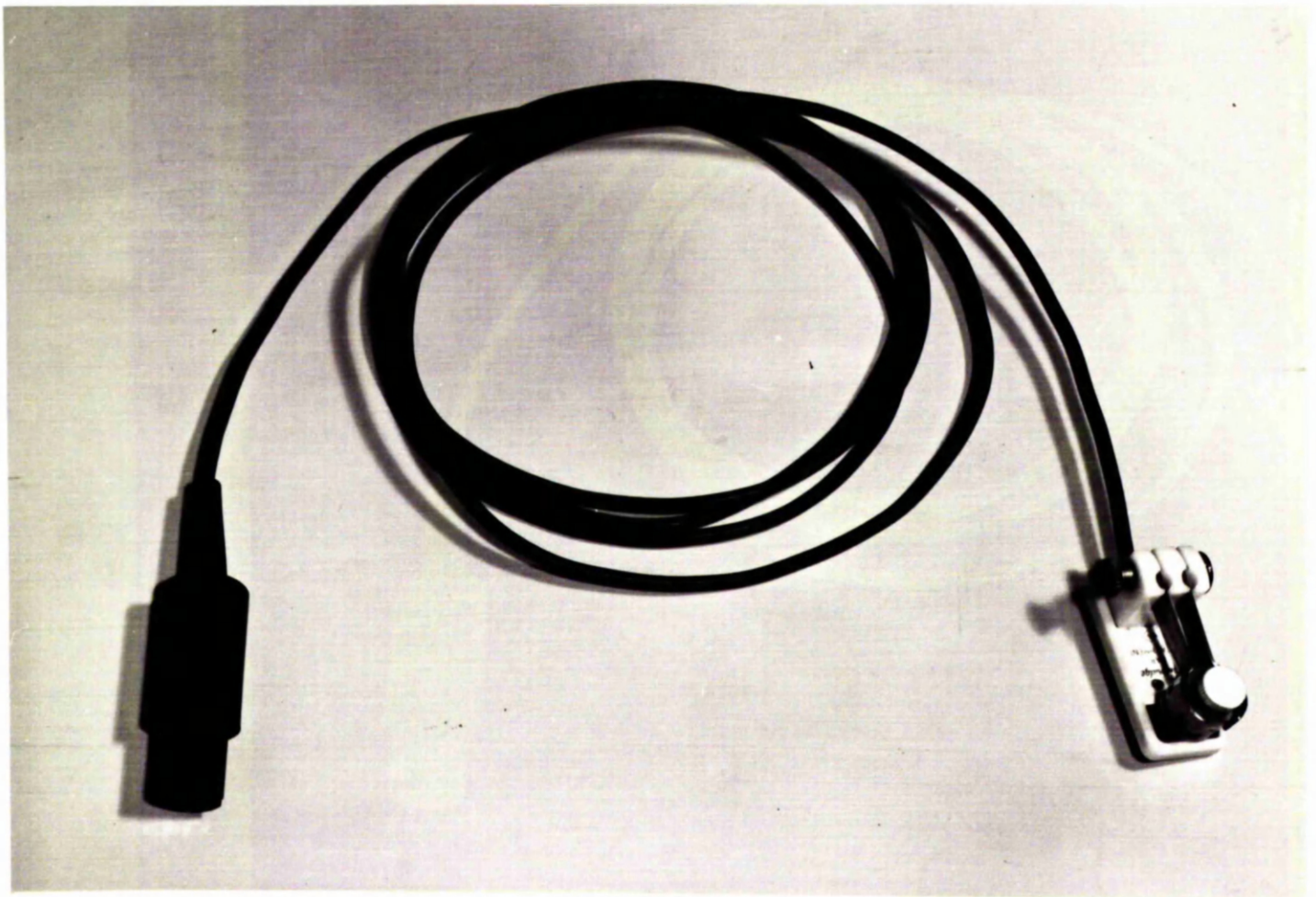

Fig. 4. Ear cuvette for use with Cambridge dye dilution recorder. The cuvette lies on the right and consists of a bright light source and a photo-sensitive cell.

arm by venepuncture at three minutes after inscription of the first dilution curve, when a steady tail-height was obtained. The concentration of dye in the plasma was estimated by extraction (Taylor and Shillingford, 1959) or by a modification of the method of Deane, Phinney and McLean (1966). The curves obtained were replotted on semilogarithmic graph paper and extrapolated to a value approaching zero. The area of the first curve was measured by numerical summation at one-second intervals. The area of subsequent curves was measured by planimetry and compared with the first curve. Calibration of the curves to obtain absolute values for the cardiac output was obtained from the dye concentration in the sample of venous blood and the tail-height of the curve at that time. Duplicate measurements of cardiac output were made at each stage of the investigation and the average value was converted to cardiac index. The arterial blood pressure was measured by a single observer using a sphygmomanometer and standard arm cuff (12 x 24 cm.). The mean arterial blood pressure was calculated from these readings by adding one third of the pulse pressure to the diastolic pressure in mm.Hg. This figure had previously been found to correlate well with the mean intra-arterial

blood pressure obtained by electronic integration. The stroke index was calculated from the cardiac index divided by the heart rate. The systemic vascular resistance was derived from the formula:-

$$\text{Systemic vascular resistance (dyne. sec. cm.}^{-5}\text{ per m}^2\text{)} = \frac{\text{Mean arterial blood pressure (mm.Hg.) x 80}}{\text{Cardiac Index (litres per min. per m}^2\text{)}}$$

Left ventricular work was calculated from the formula:-

$$\text{Left ventricular work (kg. m. per min. per m}^2\text{)} = \frac{\text{Mean arterial blood pressure (mm.Hg.) x 13.6 x cardiac index (litres per min. per m}^2\text{)}}{1{,}000}$$

In ten subjects serial samples of arterial blood were withdrawn from the brachial artery under local anaesthesia using a fine needle and a heparinised syringe. The arterial blood oxygen tension was measured with a portable oxygen analyser (Instrumentation Laboratories Inc.) (fig. 5). The system was calibrated with known gas samples and carefully tonometered blood.

The results were treated statistically by an analysis of variance. The values for inhalation of oxygen at one and two atmospheres were compared with those obtained for inhalation of air and the values for oxygen at two atmospheres were also compared with those for oxygen at one atmosphere.

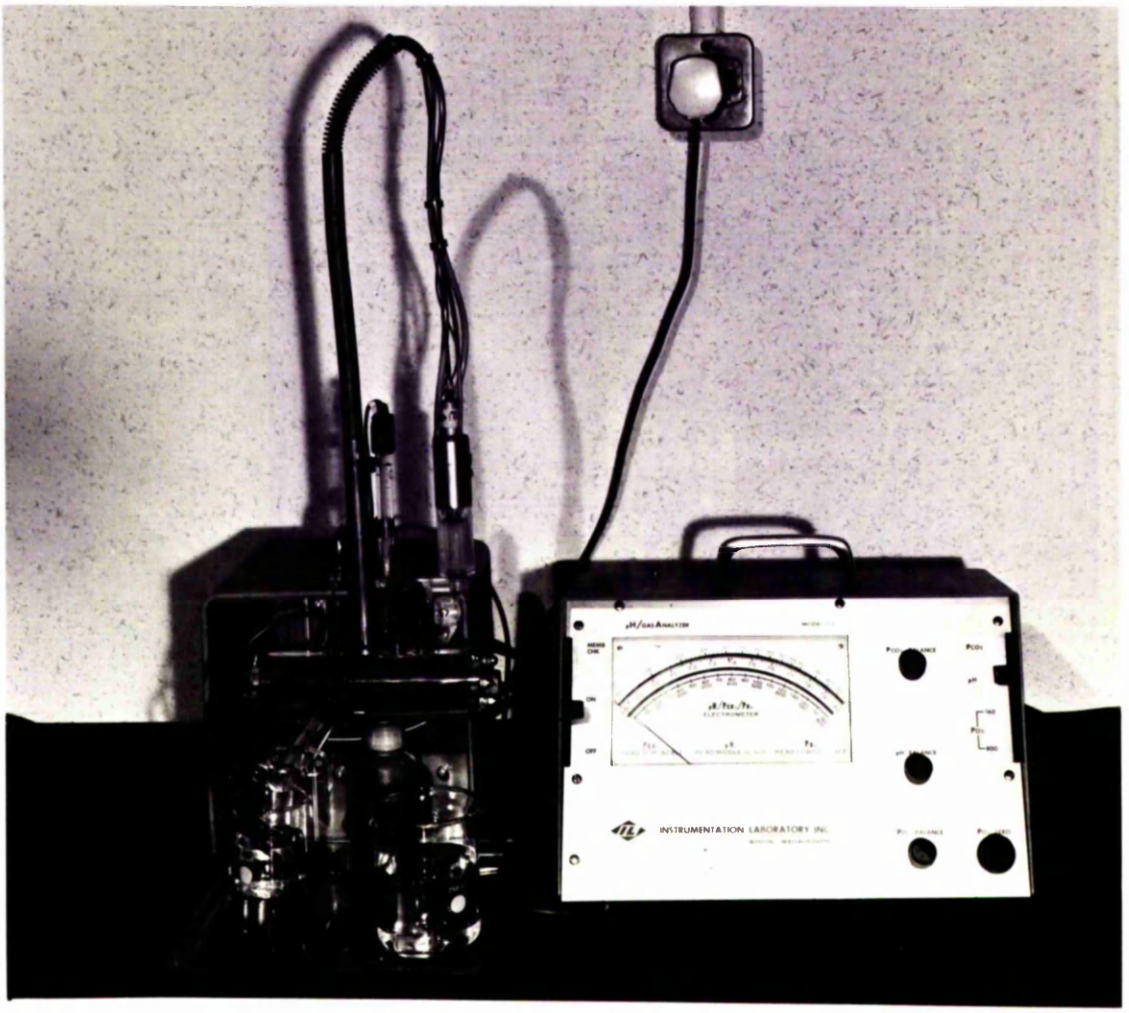


Fig. 5. Apparatus for measurement of blood oxygen and carbon dioxide tensions and pH values. (Instrumentation Laboratories Inc., Model 1L 113).

Results

The detailed haemodynamic findings in the twenty subjects for inhalation of air at one atmosphere absolute pressure, oxygen at one atmosphere absolute pressure and oxygen at two atmospheres absolute pressure are shown in Tables 2 and 3. Mean values for heart rate, arterial blood pressure, cardiac index and systemic vascular resistance are illustrated in figure 6.

A progressive fall in heart rate occurred as the pressure of inspired oxygen was increased. The decrease was significant at both one and two atmospheres pressure when compared with air ($P < 0.01$), but the decrease in rate between oxygen at one and two atmospheres was not significant. Similarly the cardiac index fell significantly with oxygen at one and two atmospheres compared with air at one atmosphere ($P < 0.001$), and although the fall in the mean value was progressive, there was again no significant difference between the values obtained for oxygen at one and two atmospheres pressure. No significant change occurred in the stroke index with oxygen at either one or two atmospheres pressure when compared with air.

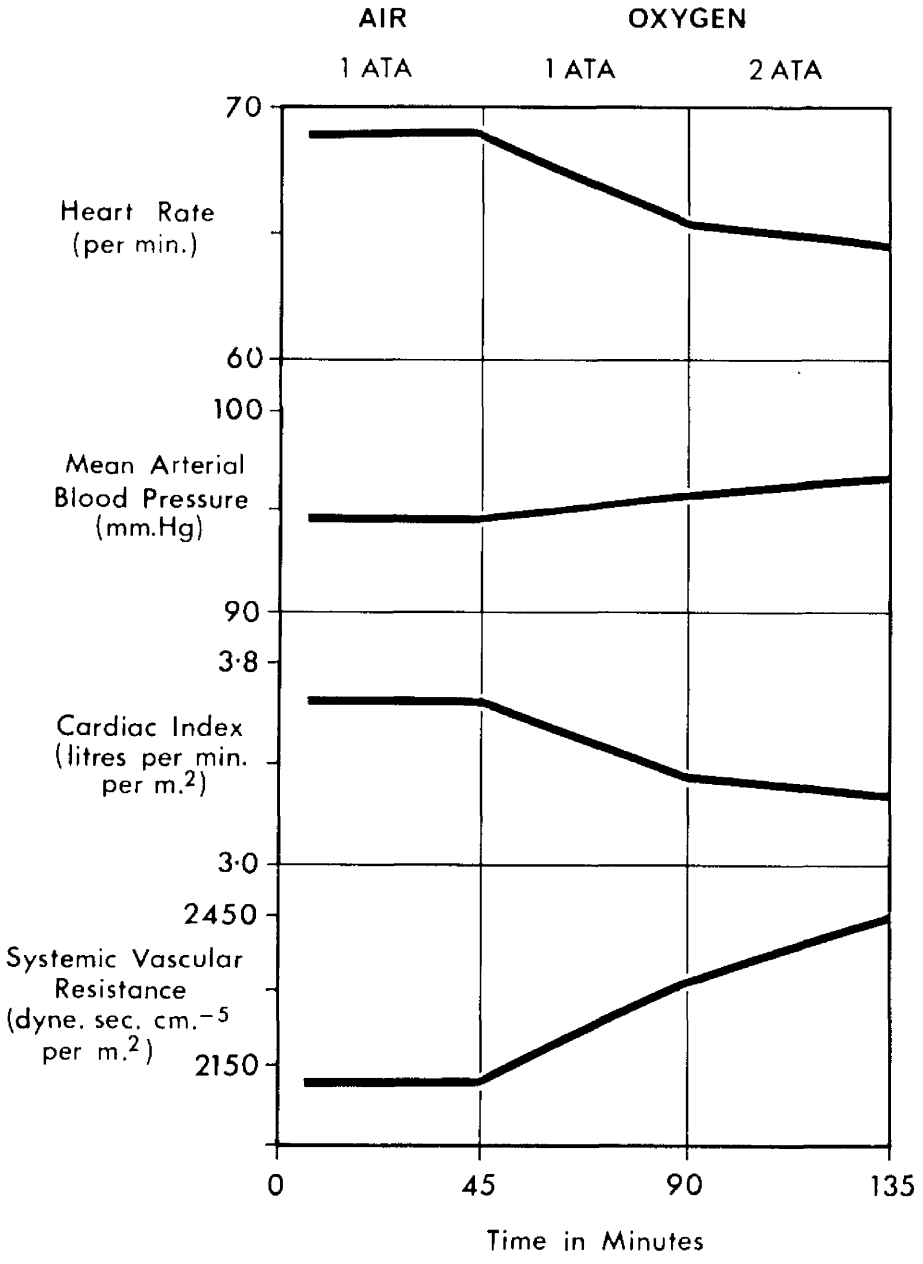


Fig. 6. Mean values for heart rate, arterial blood pressure, cardiac index and systemic vascular resistance in 20 healthy men at rest breathing air at one atmosphere and 100 per cent oxygen at one and two atmospheres absolute pressure.

ATA = atmospheres absolute pressure.

Although the mean values for systolic, diastolic and mean arterial blood pressure all showed a small progressive rise with oxygen at one and two atmospheres, there was no significant difference in the overall results. The systemic vascular resistance also rose with oxygen at both one and two atmospheres and in this case the rise at each stage was highly significant when compared with air ($P < 0.001$). Again, however, the increase which occurred between oxygen at one and two atmospheres did not reach significance.

As a result of these haemodynamic changes, the calculated left ventricular work fell with oxygen at one atmosphere ($P < 0.05$) and a more significant reduction occurred with oxygen at two atmospheres ($P < 0.01$), but again the difference of the values obtained with oxygen at one and two atmospheres was not significant.

The levels of arterial blood oxygen tension found in ten of the subjects are given in Table 4. The mean value for arterial blood oxygen tension while breathing air was 91 mm.Hg. which is within normal limits for healthy young subjects. On inhalation of oxygen the mean value rose to 537 mm.Hg. at one atmosphere pressure and

1204 mm.Hg. at two atmospheres pressure. These values represent a rise by a factor of 5.9 and 13.2 respectively.

During this investigation no signs of oxygen toxicity, either neurological or respiratory, developed in any of the subjects. Some minor difficulties were experienced with pain in the ears or nasal sinuses during compression, but this was easily overcome by temporarily stopping compression and then recommencing at a slower rate once the pain had disappeared. Decompression produced no untoward symptoms and no evidence of decompression sickness appeared in subjects or attendant personnel.

Conclusions

The results of this investigation indicate that inhalation of oxygen at one and two atmospheres pressure in healthy subjects at rest produces a significant reduction in heart rate and cardiac index without any significant change in stroke index. A slight but insignificant rise in arterial blood pressure was found. The systemic vascular resistance is, however, increased by inhalation of oxygen, and despite this, due to the fall in cardiac index, left ventricular work is significantly reduced.

Although progressive changes occurred when the pressure of inhaled oxygen was increased from one to two atmospheres, the difference was not significant and thus the effects of inhalation of oxygen at two atmospheres absolute pressure are very similar to those produced by breathing 100 per cent oxygen at one atmosphere absolute pressure.

Section B Haemodynamic effects of the inhalation of oxygen at pressures of one and two atmospheres absolute in healthy subjects during exercise.

This study was undertaken in order to discover if similar haemodynamic effects are produced by inhalation of oxygen during exercise compared with those obtained in the resting subject. It seemed possible that, as oxygen consumption is increased by exercise, inhalation of oxygen might produce more marked changes. The effect of oxygen at atmospheric pressure on exercise has been previously investigated (Asmussen and Nielsen, 1955), but so far there have been few reports on the effects of oxygen at increased atmospheric pressures during muscular work (Telfer and Jennett, 1965).

Subjects and Methods.

The subjects were healthy students and members of the medical staff. Two groups were studied while performing light and heavy exercise.

Group 1 consisted of 18 healthy men who had also taken part in the project concerning the effects of inhalation of oxygen at rest (Section A). Their ages, height, weight and body surface area have already been given. (The first eighteen

subjects in Table 1). Group 2 consisted of a further 17 healthy male students. In these subjects also, clinical examination, chest X-ray and electrocardiogram had revealed no abnormality. The data with respect to their ages, height, weight and body surface area are given in Table 5.

The experimental methods were similar to those described in section A, and oxygen or air was administered by means of a close-fitting facemask as before.

Following a light lunch the subject rested in the supine position on a couch in the hyperbaric chamber for one hour before observations were commenced. Random allocation of the sequence of gas administration was carried out as previously described. When the subject had been breathing the appropriate gas for a period of 45 minutes at rest, exercise was then commenced. Exercise was performed by pedalling a bicycle ergometer which was attached to the end of the couch on which the subject lay, at a predetermined resistance for a specific period of time (fig. 7). Group 1 performed exercise at the rate of 600 Kilopond-metres per minute (K.p.m.) for a period of 10 minutes (light exercise) while Group 2

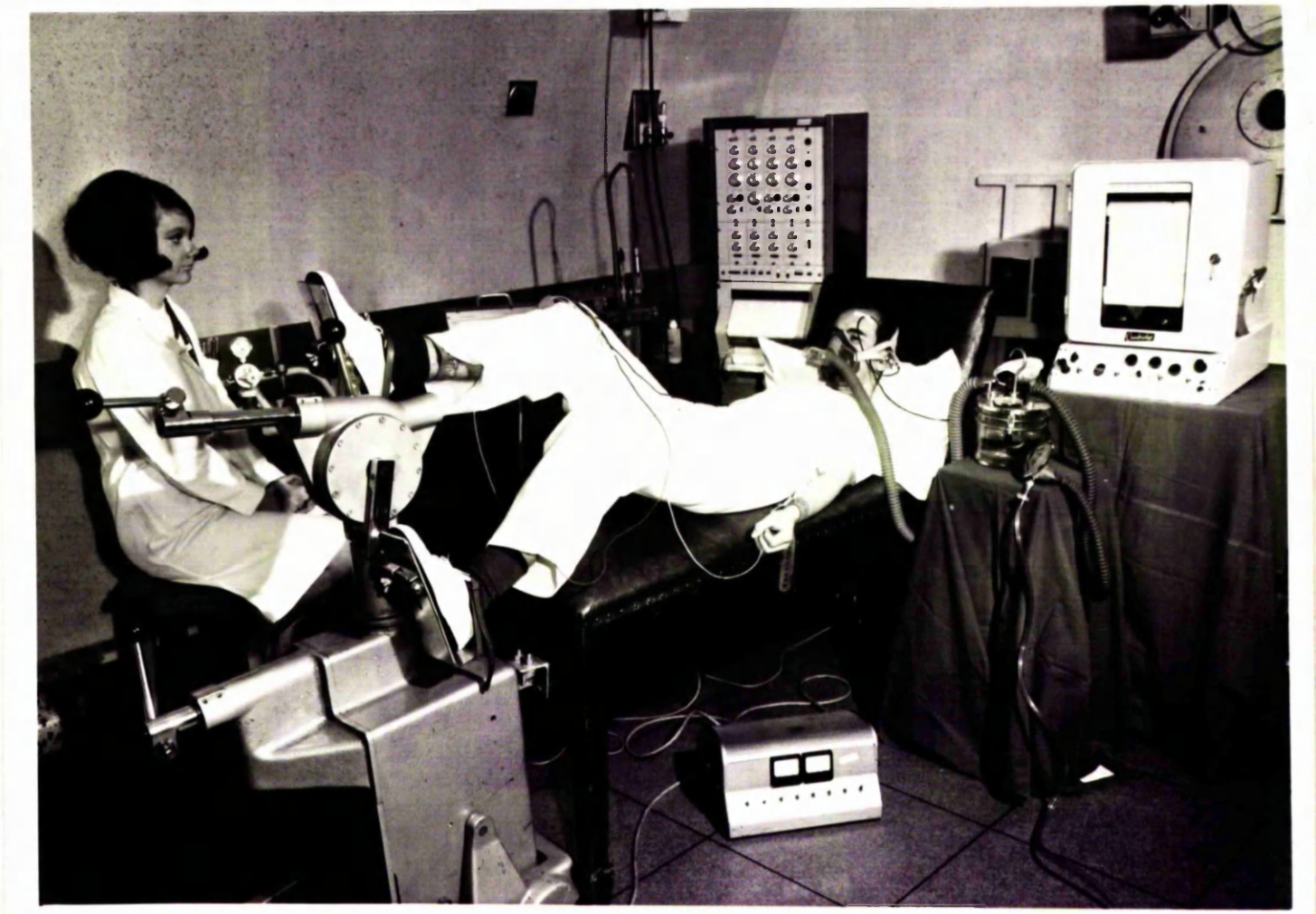

Fig. 7. Healthy subject performing exercise on bicycle ergometer within the pressure chamber.

performed exercise at the rate of 1,500 K.p.m. for a period of six minutes (heavy exercise). Measurements of heart rate and arterial blood pressure were carried out during the last minute of exercise. It was found impractical to measure the cardiac output while exercise was in progress due to the slight movement of the couch, and thus the subject's head, which was produced. Cardiac output was, therefore, measured immediately following cessation of exercise. For this reason only single dye dilution curves could be performed at each stage of the procedure, since the haemodynamic state of the patient would obviously have altered before preparations could have been completed for a repeat estimation.

From these findings, stroke index, mean arterial blood pressure, systemic vascular resistance and left ventricular work were calculated as in Section A.

Samples of venous blood were obtained through the indwelling cannula used for injection of the indicator dye immediately before and during the last minute of exercise in Group 2. 15 ml. of blood were rapidly mixed with ice-cold 10% perchloric acid and analysed for lactate and pyruvate levels using

Boehringer enzymatic techniques (Varley, 1962).

The results were analysed statistically using students paired t test (Fisher 1954).

Results

Group 1

The detailed haemodynamic findings in the eighteen subjects for inhalation of air at one atmosphere absolute pressure, oxygen at one atmosphere absolute pressure and oxygen at two atmospheres absolute pressure, while performing exercise at a rate of 600 K.p.m. are shown in Tables 6 and 7. Mean values for heart rate, arterial blood pressure, cardiac index, systemic vascular resistance and stroke index are shown in fig. 8.

There was a progressive fall in heart rate which was significant between air and oxygen at both one and two atmospheres pressure ($P < 0.005$). The difference between the value obtained with oxygen at one and two atmospheres pressure, was not however significant. The cardiac index also fell significantly when oxygen was inhaled ($P < 0.001$), but again the difference between oxygen at one and two atmospheres was not significant. Nevertheless a progressive fall in the mean value did occur as the pressure of oxygen

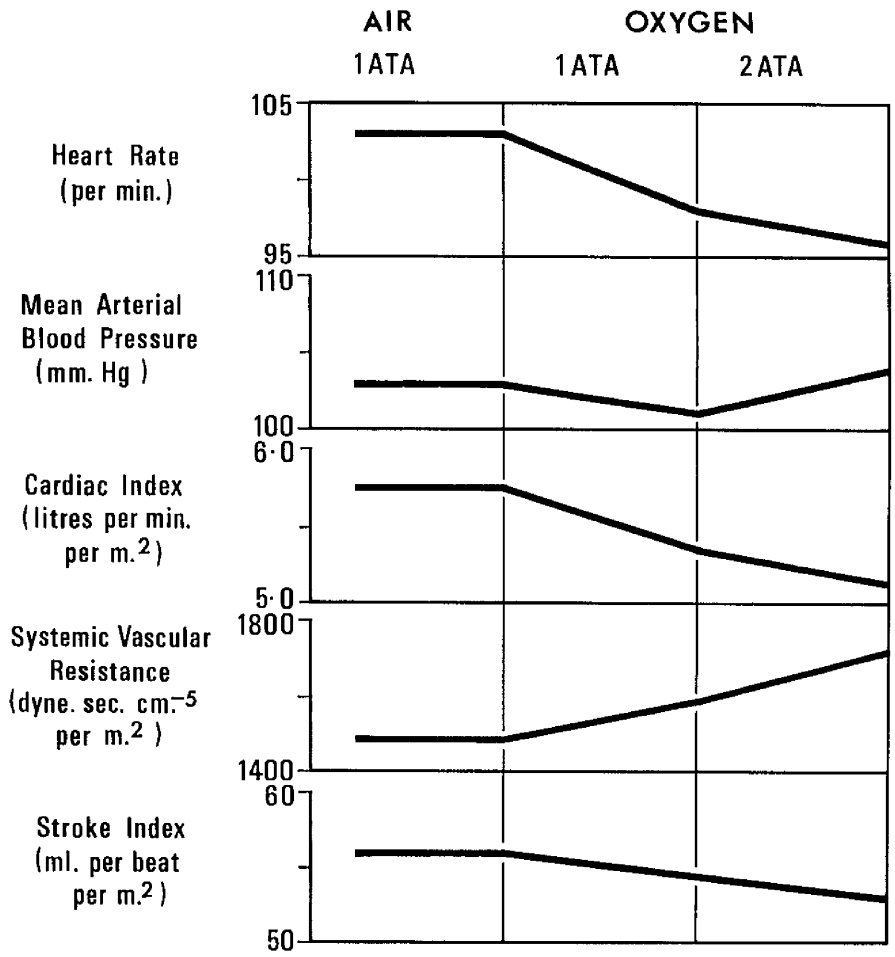


Fig. 8. Mean values for heart rate, arterial blood pressure, cardiac index, systemic vascular resistance and stroke index in 18 healthy subjects after 10 minutes exercise at 600 K.p.m. breathing air at one atmosphere, and 100 per cent oxygen at one and two atmospheres absolute pressure.

ATA = atmospheres absolute pressure

K.p.m. = Kilopond-metres per minute

was increased. The stroke index showed no significant change with oxygen at either one or two atmospheres pressure when compared with air at one atmosphere pressure.

The systolic, diastolic and mean arterial pressure did not change significantly when oxygen at one or two atmospheres pressure was inhaled, compared with the value for air at one atmosphere. When oxygen at two atmospheres was inhaled there was a small fall in systolic pressure compared with oxygen at one atmosphere and a small rise in diastolic pressure: the mean pressure however was not significantly altered by these changes.

The systemic vascular resistance rose significantly with oxygen at both one and two atmospheres ($P < 0.02$).

The calculated left ventricular work decreased when oxygen at one and two atmospheres pressure was inhaled. The fall with oxygen at one atmosphere was just significant ($P < 0.05$), but the further fall with oxygen at two atmospheres was not significant when compared with air.

Group 2

The detailed haemodynamic findings in the seventeen subjects for inhalation of air at one atmosphere, oxygen at one atmosphere and oxygen

at two atmospheres absolute pressure, while performing exercise at a rate of 1,500 K.p.m. are shown in Tables 8 and 9. The mean values for heart rate, arterial blood pressure, cardiac index and systemic vascular resistance are shown in fig. 9.

While there was a progressive fall in heart rate with oxygen at one and two atmospheres, the decrease was not significant when compared with air at one atmosphere. Cardiac index, on the other hand, also showed a progressive fall which became significant with oxygen at two atmospheres when compared with air at one atmosphere ($P < 0.005$). The decrease with oxygen at one atmosphere was, however, not significant. The stroke index also fell at each stage and reached significance when oxygen at two atmospheres was compared with air at one atmosphere ($P < 0.05$).

The systolic arterial blood pressure did not change significantly. The diastolic arterial blood pressure rose with oxygen inhalation and was significantly higher with oxygen at two atmospheres pressure than with air at one atmosphere ($P < 0.02$). The mean arterial blood pressure also rose with oxygen at one and two atmospheres, and the increase was significant

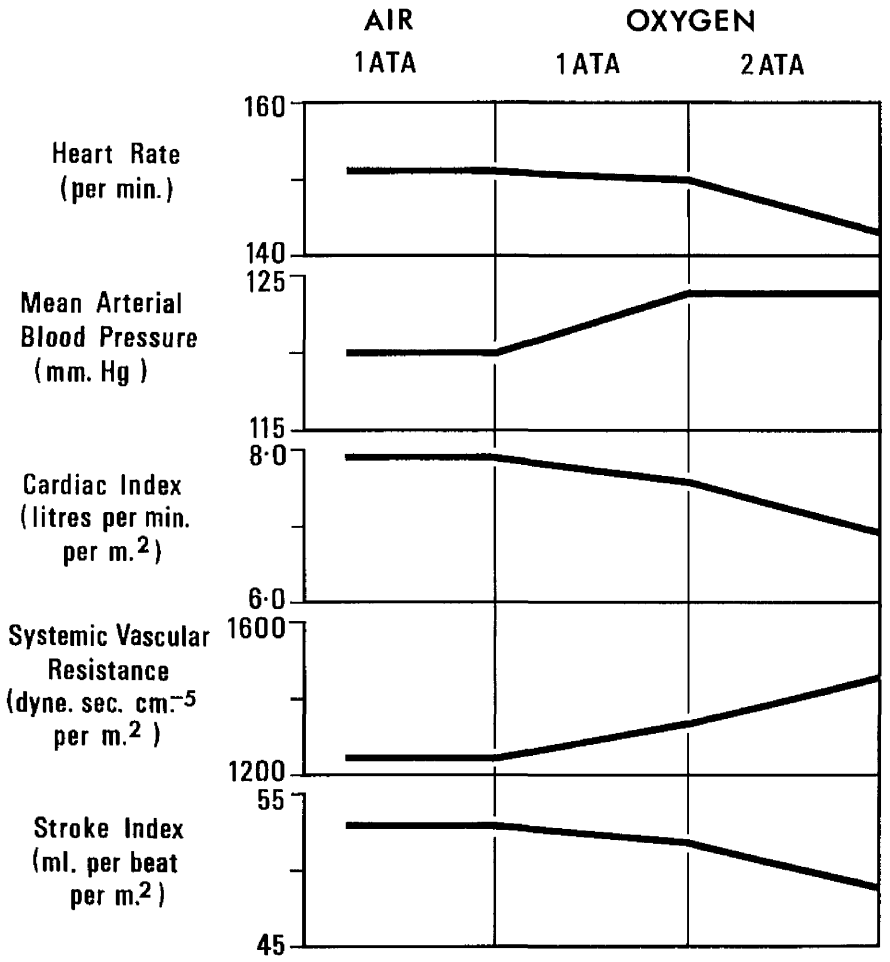


Fig. 9. Mean values for heart rate, mean arterial blood pressure, cardiac index, systemic vascular resistance and stroke index in 17 healthy subjects after 6 minutes exercise at 1,500 K.p.m. breathing air at one atmosphere, and 100 per cent oxygen at one and two atmospheres absolute pressure.

ATA = atmospheres absolute pressure

K.p.m. = Kilopond-metres per minute

when oxygen at two atmospheres was compared with air ($P < 0.05$).

The systemic vascular resistance showed a progressive rise with oxygen which was significant at both one and two atmospheres ($P < 0.02$) and in this case the difference between oxygen at one and two atmospheres was also significant ($P < 0.025$).

Left ventricular work fell with oxygen at both one and two atmospheres absolute pressure but in this instance the reduction was not significant. The difference in venous blood lactate levels before and after exercise are shown in Table 10. Although the mean value fell progressively with oxygen, the individual results were very variable and there was no statistically significant difference between the values for air and oxygen at either one or two atmospheres absolute pressure.

Conclusions

Group 1 showed changes similar to those obtained at rest when oxygen is inhaled. Namely, there is a fall in both heart rate and cardiac index during exercise which results in no significant change in stroke index. The arterial blood pressure is not significantly altered but there is a progressive rise in systemic vascular resistance. These changes are accompanied by a small fall in left ventricular work due largely to the reduction in cardiac output.

The changes noted in Group 2 with heavy exercise are somewhat different. In this case no significant change in heart rate took place, but despite this the cardiac output fell with oxygen due to a reduction in stroke volume. Thus in these circumstances, the fall in cardiac index is not entirely rate-dependent. Again, while there was no significant change in systolic or mean arterial pressures the diastolic pressure did show a small rise with oxygen at two atmospheres pressure. A progressive rise in systemic vascular resistance also took place and although there was a fall in left ventricular work, the decrease was not significant.

These results indicate that the circulatory effects of oxygen inhalation during light exercise are very similar to those obtained in the resting subject. On the other hand, during heavy exercise, the haemodynamic response appears to be altered and changes occur by a slightly different mechanism. In subjects both at rest and during light exercise the reduction in cardiac index is brought about largely by a reduction in heart rate, but after heavy exercise the reduction in cardiac index is due mainly to a fall in stroke volume and is not dependent on a change in heart rate. While there

were no striking changes in arterial blood pressure in either group, it is interesting to note that in Group 2 a small but significant rise in diastolic and mean arterial pressure occurred with oxygen at two atmospheres. This again may represent a different response to oxygen inhalation and may partly be due to the absence of a significant fall in heart rate in the presence of a rise in systemic vascular resistance. These findings also give support to the concept that oxygen may have a direct effect on the peripheral vasculature.

Discussion

Although there has been a large volume of previous work concerning the physiological circulatory responses to the inhalation of oxygen at atmospheric pressure, many of the results have been conflicting, and as yet the mechanism of these changes remains largely unknown. Much of the previous work associated with the inhalation of oxygen at increased pressures has been performed on experimental animals and has been carried out at much higher pressures than were used in this investigation. Even in the studies in which human subjects were used, the ambient pressure was often very high and the results may therefore have been affected by changes due to oxygen toxicity and for this reason some of the circulatory changes noted may not have been truly physiological. The effects of inhalation of oxygen at two atmospheres absolute, which as far as is known does not produce any toxic effect, is of particular interest, but information on this subject is meagre.

Benedict and Higgins (1911) were the first to demonstrate clearly that slowing of the heart rate could be produced by inhalation of oxygen at normal atmospheric pressures. In their carefully controlled experiments a fall in heart rate of four beats

per minute was obtained in six healthy subjects by breathing a gas mixture containing 90 per cent oxygen. Their results were confirmed by Parkinson (1912) who also showed a fall of three to four beats per minute when oxygen was inhaled for 30 minutes by 10 healthy subjects, using Mackenzie's polygraph to obtain accurate measurements. Many subsequent investigators described similar findings (Dautrebande and Haldane, 1921; Katz, Hamburger and Rubinfeld, 1932; Richards and Barach, 1934; Anthony and Kummel, 1939; Keys, Stapp and Violante, 1943; Whitehorn, Edelmann and Hitchcock, 1946; Otis et al., 1946) and it was later shown that the reduction in heart rate was statistically significant (Dripps and Comroe, 1947; Alveryd and Brody, 1948; Barrett-Boyes and Wood, 1958; Daly and Bondurant, 1962). The converse has also been repeatedly demonstrated: namely that inhalation of gas mixtures containing a low concentration of oxygen produced a significant rise in pulse rate (Bert, 1878; Dripps and Comroe, 1947; Evans, 1952).

The effects of oxygen at increased pressures was first described by Paul Bert (1878) in animals, when a fall in heart rate at increased atmospheric pressures was noted. The earliest hyperbaric investigation in man was carried out by

Dautrebande and Haldane (1921), who noted a drop in their own pulse rates of about five beats per minute when breathing 100 per cent oxygen at rest at normal barometric pressure and of eleven beats per minute at 2.08 atmospheres absolute. Marked slowing of the pulse on inhalation of oxygen at 3.7 atmospheres absolute was reported by Donald (1947). Similar bradycardia was observed by Lambertsen et al., (1953) in a comparative study of three groups of healthy men breathing air at one atmosphere, oxygen at one atmosphere and oxygen at 3.5 atmospheres absolute pressure. In the control group there was no change in pulse rate, but oxygen at one atmosphere produced a mean fall of pulse rate of seven beats per minute and oxygen at 3.5 atmospheres a fall of eight beats per minute. Only the fall at 3.5 atmospheres reached statistical significance, but it is worthy of note that this was the largest group, containing 12 subjects whereas the other groups contained only 8 subjects. Whalen et al., (1965) also found a fall in heart rate in a group of ten healthy subjects. Slowing of the heart took place progressively with inhalation of oxygen at 1 and at 3.04 atmospheres but only reached significance at the latter pressure.

There appears therefore to be a conflict between the results of earlier workers and those of Lambertson et al., (1953) and Whalen et al., (1965) in that the later workers found that bradycardia was produced only when oxygen was inhaled at increased atmospheric pressure. This investigation, however, supports the earlier findings that oxygen at one atmosphere pressure does indeed produce significant cardiac slowing, and increasing the pressure to two atmospheres produces further reduction in rate, although this additional reduction has not been found to be significant. It is difficult to account for the discrepancy between the present results and those of Lambertson et al., (1953) and Whalen et al., (1965). In all three studies the levels of arterial blood oxygen tension during air and oxygen breathing at one atmosphere were remarkably similar. It is very unlikely that the period of gas inhalation, which was 45 minutes in the present study compared with 20 - 30 minutes in that of Whalen et al., (1965) and with one hour at one atmosphere and 20 minutes at 3.5 atmospheres for that of Lambertson et al., (1953), has influenced the results since it has been shown that with inhalation of oxygen even at one atmosphere, the

slowing effect on the heart rate usually reaches its maximum within a few minutes (Dripps and Comroe, 1947; Alveryd and Brody, 1948). Perhaps therefore the explanation lies in the larger number of subjects in the present study. Moreover, it has been shown that a significant reduction in heart rate takes place during light exercise when oxygen is inhaled at atmospheric as well as at increased pressures. However, much of this effect is abolished when heavy exercise is performed possibly due to the reduction in vagal tone and increased sympathetic activities which occur in association with exercise (Evans, 1952).

Studies of the effects of inhalation of oxygen on the cardiac output have yielded conflicting results. It was originally suggested by Dautrebande and Haldane (1921) that the bradycardia produced by breathing high concentrations of oxygen indicated a general slowing of the circulation in response to the raised arterial blood oxygen tension and that this implied a drop in cardiac output. Further investigation of this hypothesis required accurate estimation of the cardiac output in man and this had to await the development of modern methods. Even so, many of the earlier workers used methods of

estimation of the cardiac output which are now generally regarded as unsatisfactory (Wade and Bishop, 1962). Thus, Grollman (1932), using the acetylene method found no significant changes in cardiac output in healthy individuals breathing oxygen at one atmosphere compared with air. Keys et al., (1943) using roentgenkymographic measurements, and several others employing ballistocardiographic techniques (Whitehorn et al., 1946; Otis et al., 1946; Dripps and Comroe, 1947) demonstrated a fall in cardiac output on inhalation of oxygen. However, even the advent of more accurate techniques has not brought agreement of results. Storstein (1952) in a careful investigation using the Fick principle did not find any significant reduction of cardiac output on inhalation of 97 per cent oxygen in 12 healthy individuals although he did observe a rise in cardiac output when low oxygen concentrations were inhaled. Barrett-Boyes and Wood (1958) could not detect any significant change in cardiac output after oxygen inhalation in healthy subjects. More recently, Daly and Bondurant (1962) using a dye dilution technique observed a significant reduction in the cardiac index in healthy subjects during inhalation of 100 per cent oxygen at one atmosphere. In the only

study so far reported on the effect of oxygen at increased atmospheric pressure, Whalen et al. (1965) also found a drop in cardiac output in healthy young men breathing oxygen at one and 3.04 atmospheres absolute. Again, however, as with their measurements of heart rate, the fall in cardiac output was only significant with oxygen at 3.04 atmospheres. The results of the present investigation are in agreement with those of Daly and Bondurant (1962) in demonstrating a significant decrease in cardiac output when oxygen at one atmosphere is inhaled but also show a further slight but consistent reduction at two atmospheres which is not significant. With light exercise, on the other hand, although a progressive fall in cardiac index took place with oxygen at one and two atmospheres, significance was only obtained with the value for 2 atmospheres. By contrast in the subjects performing heavy exercise a significant reduction in cardiac index took place even at one atmosphere.

There does, therefore, seem to be fairly convincing evidence that inhalation of oxygen is accompanied by a fall in cardiac output. The fall is, however, small in degree and therefore does not lie far outwith the experimental error inherent in present methods of measurement. It follows, therefore,

that it may only be detected when a relatively large number of subjects are studied. Thus the variance between the present results and those of Whalen et al. (1965) are probably related to the number of subjects studied and again it seems likely that a significant further reduction in cardiac output does occur with oxygen at two atmospheres as compared with oxygen at one atmosphere although this has not been clearly detected in the subjects while at rest.

The mechanism by which a reduction in cardiac output occurs after oxygen has also been the subject of controversy. Thus, while many of the earlier workers (Keys et al., 1943; Otis et al., 1946; Dripps and Comroe, 1947) concluded that the fall in cardiac output with inhalation of high concentrations of oxygen was due to the accompanying decrease in heart rate without a change in stroke volume, Whitehorn et al. (1946) considered that the reduction in cardiac output was secondary to a decrease in both heart rate and stroke volume. Their study was based on serial observations in healthy subjects breathing 100 per cent oxygen continuously for periods up to one hour and it was found that slowing of the heart rate accounted for the drop in output during

the first 10 minutes of oxygen inhalation, but thereafter reduction in stroke volume also took place and contributed a significant proportion of the total effect after 15 - 30 minutes. Daly and Bondurant (1962) found a rate-dependent decrease in cardiac index without any change in stroke index, but the duration of oxygen breathing for their subjects is not specifically mentioned. Similar results were obtained by Whalen et al. (1965) who found no change in stroke volume with oxygen at one atmosphere after 20 to 30 minutes and, while there was a slight increase at 3.04 atmospheres, it was felt that this was not significant and was likely to be associated with experimental error. These authors therefore also considered that the decrease in cardiac output was predominantly rate-dependent. The present study has shown that although there is a small fall in stroke index in healthy subjects at rest breathing 100 per cent oxygen for 45 minutes at either one or two atmospheres absolute pressure it is of insignificant degree and the reduction in cardiac index is therefore largely dependent on changes of heart rate in these conditions. On the other hand, during light exercise a progressive fall in stroke index occurred with oxygen at one and

two atmospheres pressure, although again this was not significant. With heavy exercise, however, the reduction in stroke index with oxygen at two atmospheres pressure did become significant. Thus it appears that oxygen can cause a reduction in cardiac index both by a reduction in heart rate and by a decrease in stroke volume.

Review of the previous work discloses much diversity of opinion regarding the effect of oxygen on the arterial blood pressure. Parkinson (1912) measured the blood pressure in five of his ten subjects before and after inhalation of oxygen at one atmosphere for half an hour and observed no change. Katz et al. (1932) also found no significant changes in the blood pressure of two healthy subjects who were exposed to an atmosphere containing 45 to 50 per cent oxygen over periods ranging from several hours to seven days and likewise Richards and Barach (1934) noted no consistent changes in the blood pressure in two normal men after a week's residence in a chamber with an atmosphere of 45 per cent oxygen or in 28 patients with cardiac or pulmonary disease exposed to oxygen for a similar period. Although Behnke et al. (1935) stated that no significant changes occurred in the blood pressure

of six subjects while inhaling 96 to 99 per cent oxygen, examination of their results shows, as Bean (1945) pointed out in a review of the subject, that there was a general tendency to a decrease in the systolic and pulse pressures and a consistent rise in diastolic pressure. On the other hand, a consistent slight rise in both systolic and diastolic pressures, but with a decrease in pulse pressure was noted by Keys et al. (1943) in seven healthy subjects breathing 100 per cent oxygen for 10 to 48 minutes. The fact that the length of exposure may affect the blood pressure response to oxygen was indicated by Whitehorn et al. (1946). In their experiments with serial measurements on sixteen subjects during inhalation of oxygen the systolic pressure fell slightly after 15 minutes exposure to oxygen, but thereafter showed a slight elevation; overall, however, there was no significant change. The diastolic pressure on the other hand rose from the start, but only became significant after 30 to 60 minutes. Corresponding results were obtained by Alveryd and Brody (1948) in fifteen healthy subjects after a shorter time of 30 to 40 minutes. While it might be suspected that the explanation for these differences lay in the inaccuracy of the blood

pressure recordings in the presence of small changes in blood pressure, recent results utilising intravascular pressure recordings have been by no means uniform. A slight but significant rise in mean arterial blood pressure was noted by Lambertsen et al., (1953) in eight men breathing oxygen at one atmosphere for one hour and this was also the experience of Daly and Bondurant (1962) in their ten subjects. In the investigation of Barrett-Boyes and Wood (1958) systolic and diastolic pressures were also measured intravascularly on twenty healthy individuals breathing 95 per cent oxygen. Although the period of oxygen inhalation was only 3 to 5 minutes a significant increase in systolic pressure averaging 6 mm.Hg. was noted and there were less significant increases in diastolic and mean pressures. On the other hand, Whalen et al. (1965) in their study of ten subjects during inhalation of 100 per cent oxygen at one atmosphere for periods of 20 to 30 minutes detected no significant changes in systolic, diastolic or mean arterial pressure. Equally conflicting results have been obtained in the relatively few studies which have been undertaken at increased ambient pressures. Thus Behnke et al. (1935) stated that there was no change in the arterial blood pressure

in several healthy men breathing 100 per cent oxygen at two, three and four atmospheres absolute for periods of three hours, two hours and forty-five minutes respectively. In a later report, however, (Behnke, Forbes and Motley, 1936) they stated that one of their subjects previously studied at four atmospheres had developed a rise in blood pressure immediately prior to the onset of symptoms of oxygen poisoning. Further studies of four men breathing oxygen at 3 atmospheres pressure led them to conclude that there was a rise of about 10 mm.Hg. in diastolic pressure during the first three hours of exposure and a further rise of systolic and diastolic pressures during the 4th hour coinciding with the symptoms of oxygen toxicity. Unfortunately they do not state the results actually obtained. Similar observations were reported by Donald (1947) in men breathing oxygen at 3.7 atmospheres who found a gradual rise of both systolic and diastolic pressures stabilising after 20 minutes at about 15 mm.Hg. above the normal levels. Just before the onset of acute symptoms of poisoning a further brisk rise of about 15 - 20 mm.Hg occurred. Lambertsen et al. (1953) using intravascular pressure measurements demonstrated a significant increase in mean arterial pressure

in eight men with inhalation of oxygen at 3.5 atmospheres for about 20 minutes without the occurrence of symptoms of oxygen toxicity. In contrast to these results, Whalen et al. (1965), also using intravascular pressure measurement, found no significant alteration in systolic, diastolic or mean arterial blood pressures in ten subjects breathing oxygen at 3.04 atmospheres for 20 to 30 minutes despite the fact that symptoms and signs of oxygen poisoning developed in two cases.

It is difficult to explain these inconsistent experimental findings but there are many variable factors which may affect the results including the level of ambient pressure, the concentration and method of administration of oxygen and its duration, the environmental conditions such as temperature, the number of subjects studied and the methods of measurement. Moreover, as the earlier investigators were unable to measure the arterial oxygen tension readily, critical appraisal of their results is difficult as the efficiency of oxygen administration must remain uncertain in many cases. In the present study it has been attempted to control these variables as accurately as possible. The results therefore support the opinion that inhalation of

100 per cent oxygen by healthy subjects at rest for periods of up to one hour at pressures of one and two atmospheres absolute causes a slight but insignificant rise in systolic, diastolic and mean arterial pressures. Inhalation of oxygen during light exercise gives similar results and it is only with heavy exercise that a small but significant rise is obtained in diastolic pressure. Since no evidence of oxygen toxicity was encountered it is not possible to comment on the problem of whether an abrupt rise in blood pressure heralds its onset.

The effect of oxygen on systemic vascular resistance has not been discussed in many of the previous reports. In these investigations in which it is considered, the results are once more at variance. With oxygen at one atmosphere Whitehorn and Bean (1952) considered that the slight increase in mean arterial pressure, in spite of a reduced cardiac output, must indicate an increased systemic vascular resistance although they point out that such an increase in total resistance does not yield information as to the condition of blood vessels in specific organs. Barratt-Boyes and Wood (1958) found variable changes in systemic vascular resistance, though a rise was obtained in

12 of 20 cases, while Daly and Bondurant (1962) obtained a significant rise. The only study at increased ambient pressures in which the systemic vascular resistance was calculated is that of Whalen et al. (1965) who found no significant change at one atmosphere pressure (although a small rise in mean value was recorded) but a significant increase at 3.04 atmospheres pressure. The results of the present investigation show a consistent rise in systemic vascular resistance with oxygen. While these findings in the subjects at rest are in agreement with those of Daly and Bondurant (1962) in showing an increase in vascular resistance with oxygen at one atmosphere and a further but not significant rise at two atmospheres, in the exercising subjects a rise was obtained at both stages and the increase which occurred between oxygen at one and two atmospheres pressure was also significant. While it is true that changes in total systemic resistance do not indicate changes in particular areas a general increase in resistance in the presence of a reduction in cardiac index presumably indicates that arterial vasoconstriction is occurring at least in some regions. Nevertheless, a progressive fall in the calculated left ventricular work has been

shown both in the resting and exercising subjects. This finding is in agreement with that of Keys et al. (1943) using indirect methods for the measurement of cardiac output and ventricular systolic and diastolic volumes, who noted a slight decrease in cardiac work with no significant change in heart size or efficiency in healthy subjects breathing high concentrations of oxygen at normal atmospheric pressure.

In conclusion, although there have been wide variations in the results obtained by individual investigators of the physiological effects on the circulation of inhalation of high concentrations of oxygen, a general trend is apparent. The heart rate tends to fall on inhalation of oxygen at normal and increased atmospheric pressure. This is accompanied in most instances by a fall in cardiac index which is largely secondary to the decrease in heart rate resulting in little change in stroke volume. Most workers have found small rises in arterial blood pressure with a rise in systemic vascular resistance. The present investigations largely confirm these findings and provide some further information. Inhalation of oxygen caused a fall in heart rate and cardiac index,

with no appreciable change in stroke index in resting subjects, but after heavy exercise there was a fall in stroke volume. While no significant changes in systolic, diastolic or mean blood pressure were recorded at rest, the mean values did rise slightly and a significant increase in diastolic pressure was found in subjects inhaling oxygen at two atmospheres pressure during heavy exercise. It has been confirmed that these changes produce an increase in systemic vascular resistance, but that there is no increase in left ventricular work and in some instances there is a fall.

It must be remembered, of course, that it is not only the statistical significance of results which is important but also the magnitude of the changes observed. If the results are considered in this light, it is seen that the maximum mean decrease in heart rate occurs with oxygen at 2 atmospheres pressure and amounts to about 5 beats per minute at rest and 8 beats per minute with exercise. While these changes may seem small they indicate a reduction of 300 and 480 beats per hour respectively and in twenty four hours there would be 7,200 fewer cardiac contractions at rest. These changes are therefore by no means negligible although at first sight they seem small.

In the case of cardiac index the mean reduction with oxygen at two atmospheres pressure when compared with air at one atmosphere pressure is 0.37 litres per minute in subjects at rest, and 0.63 litres per minute and 0.97 litres per minute during light and heavy exercise. Although these changes are small in absolute terms, they represent reductions in the cardiac index of 10 per cent, 11 per cent and 12 per cent respectively. On the other hand, the changes in arterial blood pressure are very small even on the occasions when statistical significance is found. Thus, while a statistically significant rise in diastolic blood pressure occurred in subjects inhaling oxygen at two atmospheres pressure during heavy exercise, the increase was only 6 mm.Hg. which is a rise of 7 per cent. Similarly the reduction in left ventricular work which occurred with oxygen at 2 atmospheres was also significant but only represented 7 per cent of the initial value whereas the systemic vascular resistance rose by 13 per cent. It is therefore probable that the most important changes are the reduction in heart rate and cardiac index and the rise in systemic vascular resistance. In healthy subjects, changes in arterial blood pressure,

if they do occur, are small in magnitude and are probably of little significance either statistically or in the wider sense.

The physiological mechanisms which underlie the haemodynamic changes are obscure, but they will be discussed in a later chapter (Chapter IV). It is probable, however, that the changes are part of the homeostatic mechanism and therefore represent a true physiological response. If this is so, it is likely that the overall haemodynamic effects of inhalation of oxygen in healthy subjects are neither advantageous nor disadvantageous but are simply a maintenance of the status quo. It remains to be seen, however, whether the same holds true in the diseased state and this will be studied in the next chapter.

# CHAPTER III

## Effects of inhalation of oxygen in patients with ischaemic heart disease

Introduction

Section A: Haemodynamic and metabolic effects of oxygen at pressures of one and two atmospheres absolute in patients with acute myocardial infarction

Section B: Effects of hyperbaric oxygen in chronic ischaemic heart disease

Introduction

Acute myocardial infarction is one of the most important causes of death in the population of this country at the present time and there are indications that its incidence may be increasing (Jones, 1970). It is a particularly distressing condition as it commonly attacks previously healthy men who are often still in the prime of life and may well be supporting a young family. As yet the basic cause of this disease remains unknown although the subject has received world-wide attention and there are many theories of its aetiology. The pathology of the condition has also, of course, been widely studied and while in the majority of cases the onset of clinical symptoms is due to the sudden occlusion of one of the main coronary arteries, this is by no means always the case. It is generally agreed, however, that the defect underlying the production of a myocardial infarction is the failure of blood supply by one means or another to the affected area of the myocardium with resultant local anoxia and subsequent death of the tissue. The overall

mortality of the condition is very difficult to determine as many variables may affect the results obtained (Schnur, 1953). Earlier figures for hospital deaths gave a mortality of 30 to 40 per cent, (Honey and Truelove, 1957; Wahlberg, 1963), but recent results in special coronary care units appear to have reduced the mortality to 14 to 20 per cent (Restieaux et al., 1967, Lawrie et al., 1967, Thomas, Jewitt and Shillingford, 1968). The true mortality is almost certainly higher than these figures suggest as the frequency of sudden death is inversely proportional to the time after onset of the infarct and many patients do not survive long enough to reach hospital (Kuller, Lilienfeld and Fisher, 1966).

There are three main types of complication which account for most of the deaths in this condition.

(1) Cardiac arrhythmias. Since the introduction of continuous electrocardiographic monitoring of patients with acute myocardial infarction it has been shown that the incidence of arrhythmias is very high and some form of abnormal rhythm occurs in over 80 per cent of patients (Lawrie et al., 1967). While the development of an arrhythmia does not necessarily disturb the patient, the potential danger

is great. Thus ventricular ectopic beats are the commonest disorder of rhythm and although usually innocent in nature, they may induce ventricular fibrillation if they occur at the vulnerable period of the cardiac cycle (Smirk, 1949). Ventricular fibrillation may also develop without a premonitory arrhythmia in these patients and the overall incidence of this potentially fatal complication lies between 8 and 10 per cent (Lawrie et al., 1968). Ventricular asystole is the other main cause of cardiac arrest and occurs in a further 6 per cent of cases. Other serious arrhythmias such as ventricular tachycardia, atrial tachycardia or fibrillation and heart block may promote cardiac failure with sudden or gradual deterioration of the condition of the patient.

(2) Left or right ventricular failure. Cardiac failure may develop from the onset of the illness and indeed the sudden development of left ventricular failure is a not uncommon mode of presentation. In other patients cardiac failure may develop over a period of days or weeks following the infarct and may result in a gradual down-hill course of the illness followed ultimately by death in many cases.

(3) Cardiogenic shock. This is an unsatisfactory term as it is used to describe different conditions by various authors. If, however, cardiogenic shock is

defined as a syndrome in which the patient is pale and sweating, has cold clammy extremities, a systolic blood pressure of less than 80 mm.Hg. a tachycardia in excess of 100 beats per minute and a diminution of consciousness accompanied by acute anxiety, then the condition is almost 100 per cent fatal. It occurs in about 5 per cent of cases of myocardial infarction and while it may indicate that the heart is failing as a pump, this is not always so, and inappropriate reflex activity, with peripheral vasodilatation and hypotension, may be responsible (Constantin, 1963).

At the present time effective treatment of the above complications of myocardial infarction is largely restricted to the first two categories. Thus it is possible to produce a reversion to sinus rhythm by electrical means in patients with ventricular fibrillation and the other arrhythmias are often amenable to drugs, cardioversion or electrical pacing. Similarly conventional drug therapy may be used with effect in patients with cardiac failure. As yet, however, there are few effective therapeutic measures available for the treatment of cardiogenic shock as defined above.

Perhaps more important than the treatment of these complications would be their prevention if this were

possible. In this respect there have been some recent claims for the efficiency of procaine amide or lignocaine in the prevention of ventricular arrhythmias (Jewitt, Kishon and Thomas, 1968; Chopra, Portal and Aber, 1969; Koch-Weser et al., 1969). This treatment is, however, not generally accepted as a prophylactic measure and is not without side-effects. Prophylaxis of cardiac failure or cardiogenic shock is even less satisfactory. As all these complications of myocardial infarction are the result of ischaemia of the myocardium it seems likely that anoxia may be partly responsible for their production and it has been shown in experimental animals that ventricular fibrillation may be more easily induced when the oxygen supply to the heart is reduced, (Burn and Hukovic, 1960). It seems reasonable to assume, moreover, that anoxia may further impair an already failing heart by interference with cell metabolism and thus an increase in the myocardial oxygen supply may well assist in the relief of cardiac failure. Barach, as early as 1931 described the use of oxygen in patients with myocardial infarction in the hope that it would relieve the pain secondary to ischaemia. In animal experiments, Smith and Lawson (1958 and 1962) observed an apparent protective effect of oxygen at 2

atmospheres absolute pressure in preventing death from ventricular fibrillation after experimental ligation of the circumflex branch of the left coronary artery in dogs. Cameron et al. (1965) performed the only controlled trial of the effects of hyperbaric oxygen in myocardial infarction which is currently available and found no difference in mortality between the control and the treated group. In recent years it has also been observed that myocardial infarction is frequently accompanied by a degree of arterial hypoxaemia, especially in the presence of left ventricular failure and cardiogenic shock (MacKenzie et al., 1964; McNicol et al., 1965; Valentine et al., 1966). The low arterial blood oxygen tension may be largely responsible for some of the serious metabolic abnormalities which take place and may also contribute to the production of hypotension. These findings, therefore, support the view which has long been advocated (Dunlop and Alstead, 1966; Friedberg, 1966) that oxygen should be administered in the treatment of myocardial infarction. There is, however, little objective evidence that such treatment is of definite value and moreover there is little information available concerning the effect of oxygen on the underlying circulatory derangements (McKenzie et al., 1964; Thomas, Malmcrona and

Shillingford, 1965). In particular the haemodynamic and metabolic effects of oxygen at increased pressures in patients with myocardial infarction has not previously been studied although it seems possible that oxygen might be more effective when administered in this manner.

Section A Haemodynamic and metabolic effects of oxygen at pressures of one and two atmospheres absolute in patients with acute myocardial infarction.

The object of the present investigation was to determine the haemodynamic and metabolic effects of the administration of oxygen in high concentrations at pressures of one and two atmospheres absolute to patients with acute myocardial infarction and to assess its therapeutic value.

Patients and Methods

Fifty-one men with acute myocardial infarction were studied in two groups. In Group 1, which consisted of sixteen patients, the effects of inhalation of 100 per cent oxygen at atmospheric pressure was initially investigated. In Group 2 the effects of inhalation of oxygen at both one and two atmospheres absolute pressure were studied in thirty-five patients.

The clinical details of the patients are summarised in Table 11. Patient nos. 1 - 16 formed Group 1, the remainder (nos. 17 - 51) forming Group 2. Their ages ranged from 33 to 77 years with a mean of 57.1 years. The following criteria were fulfilled in each case. The diagnosis was based on a history of a first attack of cardiac pain lasting for more than 30 minutes (Snow, Jones and Daber, 1956), of acute left ventricular failure or of unconsciousness. No patient had suffered a myocardial infarction in the preceding six months, but previous infarction at an earlier date did not exclude inclusion in the investigation. The clinical diagnosis was confirmed by electrocardiograms which showed Q waves and sequential ST-T wave changes. Investigations were restricted to patients admitted within 24 hours of

infarction and Table 12 summarises the time intervals elapsing between the onset of symptoms and the beginning of the investigations. Serial serum-glutamic-oxaloacetic transaminase (S.G.O.T.) estimations were carried out and the maximum values obtained are shown in Table 13.

The patients were admitted to a special unit with facilities for coronary care and investigation located in the Gardiner Institute, Western Infirmary, Glasgow. After initial clinical assessment, fine intravascular polythene catheters were introduced percutaneously under local anaesthesia, by a modified Seldinger technique (Seldinger, 1953). A Cournand needle was used to puncture the vessel and a nylon thread replaced the conventional guide wire. Separat catheters were positioned in a brachial artery and antecubital vein and the tips were advanced until they lay in the region of the aortic arch and superior vena cava respectively. In twelve patients of Group 2, using a modification of the technique described by Bradley (1964) a fine polythene catheter was introduced into an antecubital vein through a wide-bore cannula (fig. 1). The catheter was advanced and the tip was allowed to float onwards into the right ventricle or pulmonary artery where

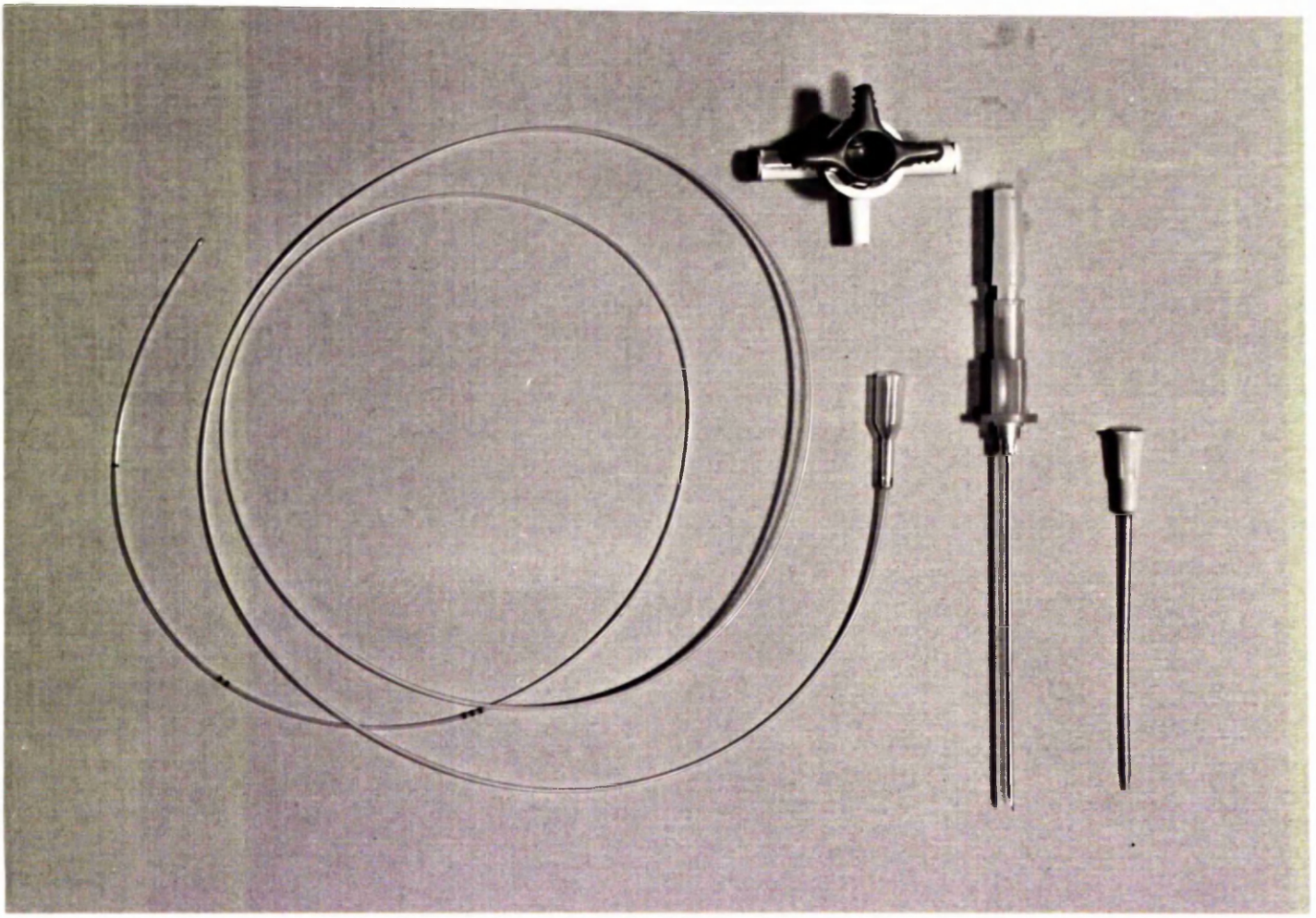

Fig. 1. Catheter used for measurement of pulmonary artery pressure together with cannula for percutaneous insertion.

its situation was determined by recording the pressure through the catheter. The intravascular pressures were recorded using strain-gauge transducers and a Devices direct-writing recorder. The electrocardiogram was also recorded on the latter and both the pressures and the electrocardiogram were monitored continuously on an oscilloscope. Cardiac output was measured by a dye-dilution technique following the procedure previously described for healthy subjects (Chapter II, page 26). The indicator used was Coomassie blue which was injected into the superior vena cava from a calibrated syringe, the average dose being 40 mg. The concentration of dye in the plasma of a sample of venous blood withdrawn three minutes after the initial injection was estimated as before. The cardiac output was measured in duplicate at each stage and the mean of the results was taken.

Blood gas tensions and pH values were measured with an Instrumentation Laboratory Inc. system (Model I.L. 113). The arterial oxygen tension was measured with a Clark electrode. The carbon dioxide tension was measured with a Severinghaus electrode and the pH with a glass electrode. The system was calibrated with known gas samples and carefully tonometered blood. Specimens of arterial blood for these estimations were obtained from the in-dwelling arterial cannula

in heparinised syringes and transferred directly to the measuring apparatus at the bedside.

Samples of arterial blood (10 ml.) were also obtained in most patients for estimation of lactate and pyruvate levels. The blood was withdrawn in dry syringes and was immediately mixed with 10 per cent ice-cold perchloric acid. Blood lactate and pyruvate concentrations were then measured using enzymatic methods (Varley, 1962) with the aid of Boehringer preparations.

In view of the difficulty in obtaining accurate values for the height and weight of severely ill patients, the cardiac index and stroke index were not calculated in this investigation. For this reason the results in this chapter are expressed as cardiac output (litres per min.) and stroke volume (ml.). The systemic vascular resistance was calculated from the formula:

$$\text{Systemic vascular resistance (dynes sec. cm}^{-5}\text{)} = \frac{\text{mean arterial pressure (mm.Hg.)} \times 80}{\text{cardiac output (litres per min.)}}$$

Left ventricular work was calculated from the formula:

$$\text{Left ventricular work (kg. m. per minute)} = \frac{\text{mean arterial pressure (mm.Hg.)} \times \text{cardiac output (litres per min.)}}{1{,}000}$$

Oxygen was administered by means of a close-fitting facemask connected to a humidifier and

low-resistance demand valve (fig. 2) which has previously been described (Chapter II). When connected to the oxygen supply this delivers a concentration of inspired gas in excess of 80 per cent as measured by direct sampling at the mouth (McDowall et al., 1965).

Investigation of the patients in Group 1 was undertaken as a pilot study to assess the haemodynamic effects of inhalation of oxygen at one atmosphere pressure and was carried out in the special unit in the Gardiner Institute. Initial observations were made with the patient breathing air. The patient was then connected to the oxygen supply and after one hour the measurements were repeated. Oxygen administration was continued for 48 hours.

In the patients of Group 2, the haemodynamic and metabolic effects of oxygen at one and two atmospheres pressure were studied. Clinical assessment of the patients on admission and preliminary procedures, including the insertion of arterial and venous catheters, was carried out in the Gardiner Institute. A special bed was used which could be transferred to the pressure chamber in the Department of Surgery, Western Infirmary, without further disturbance of the patient. As soon as the initial procedures had been

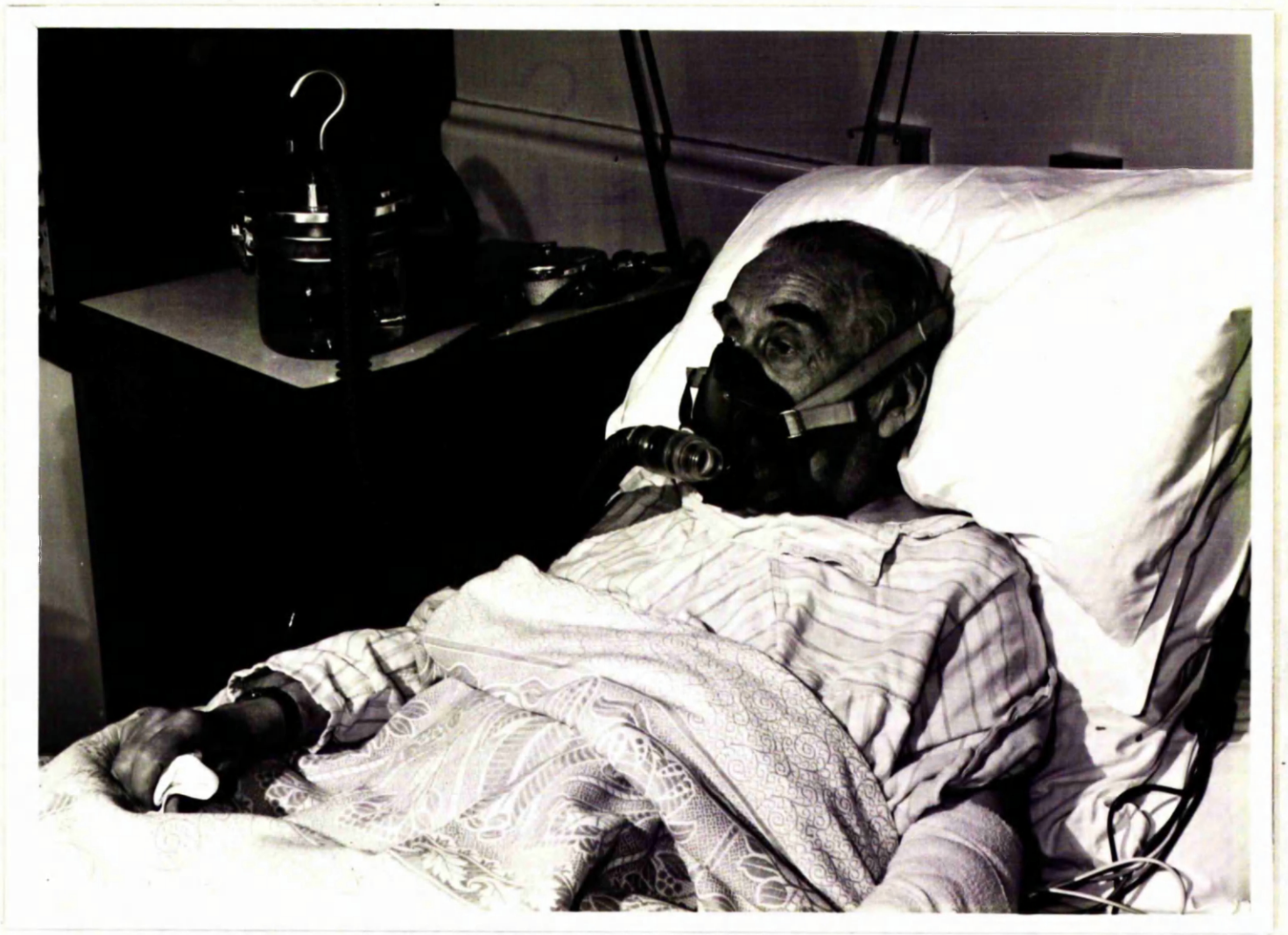

Fig. 2. Oro-nasal mask used for administration of oxygen. The humidifier and demand valve are seen lying on the bedside table.

completed the bed was moved to the chamber and a short period of about 30 minutes was allowed for stabilisation of the patient and preparation of apparatus. Thereafter initial observations were made and the patient was then connected to the oxygen supply (fig. 3). After one hour the measurements were repeated. The pressure in the chamber was then increased to two atmospheres absolute over a period of 10 - 15 minutes with the patient continuing to breathe oxygen through the facemask. An hour later a third set of measurements was made. During the course of hyperbaric treatment the facemask was removed for 30 minutes to facilitate nursing procedures and in 9 patients the opportunity was taken to repeat the observations with the patient breathing air at two atmospheres. The facemask was reapplied and treatment with hyperbaric oxygen was continued for a further hour. In 9 patients the measurements were again repeated at the end of this period. The chamber was then decompressed slowly over 15 - 20 minutes and a final set of readings was obtained in the same 9 patients one hour after returning to atmospheric pressure, the patient meanwhile continuing to breathe oxygen. Following these procedures, all the patients were returned to

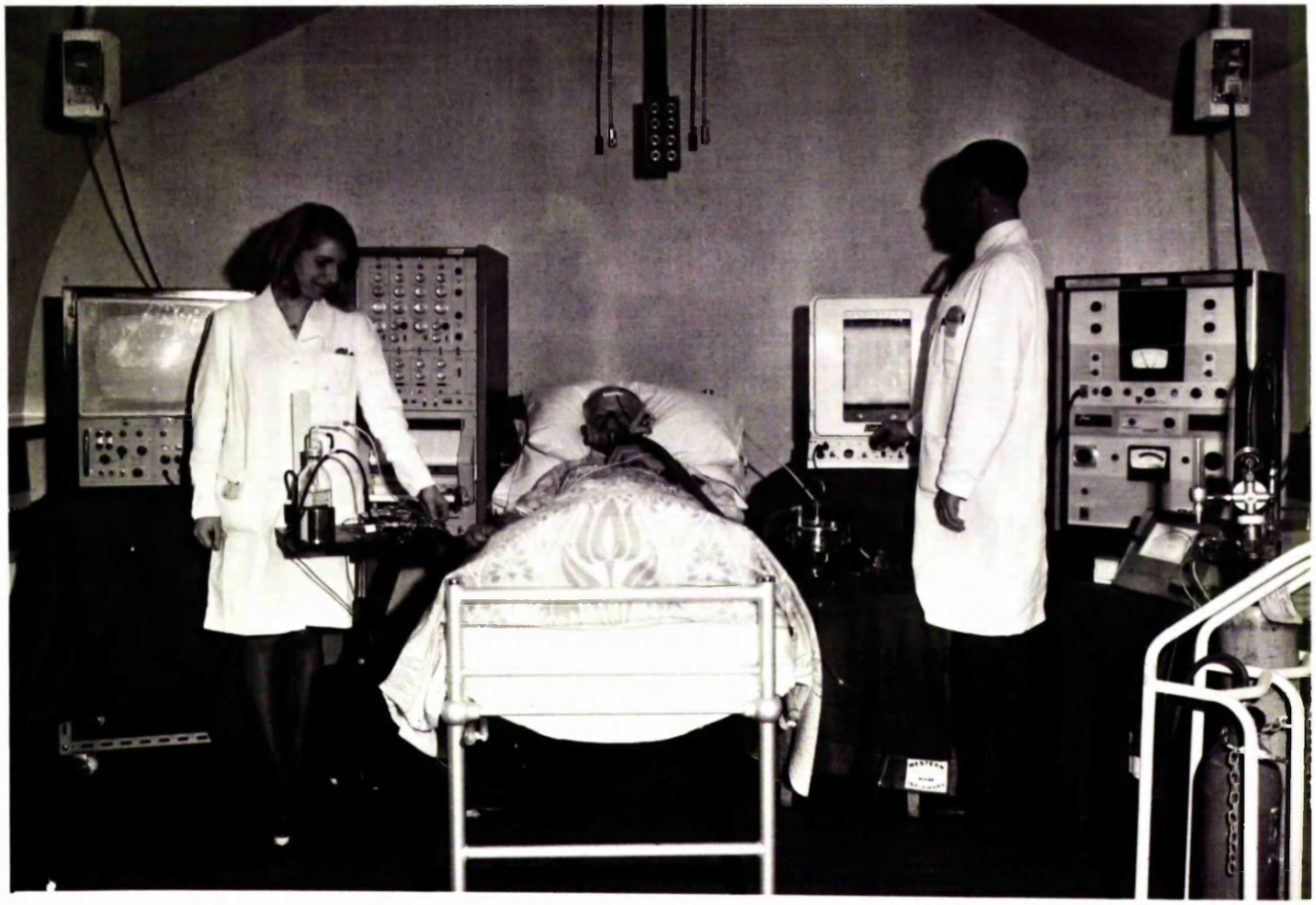

Fig. 3. Photograph of patient and attendants within the hyperbaric chamber. Apparatus for measurement and monitoring of the arterial blood pressure and the electrocardiogram is seen on the left, while the cardiac output recorder, defibrillator and blood gas analysis apparatus is seen on the right of the bed.

the intensive care area in the Gardiner Institute where in addition to standard therapy oxygen administration was continued for a further 48 hours.

During the period of investigation in both Groups 1 and 2 no drugs were required by the patients except in case no. 39, and the detailed management of this patient is given later in this section.

The results were treated statistically using Student's paired t test, $\chi^2$ test and the Wilcoxon test where applicable (Fisher, 1954, Forrester and Ury, 1969).

## RESULTS

### Group 1.

The haemodynamic findings in the 16 patients while breathing air and oxygen are given in Tables 14 and 15. The arterial blood oxygen and carbon dioxide tensions and pH are detailed in Table 16.

The response of the heart rate to inhalation of oxygen was variable and the mean value did not change significantly. The cardiac output fell in 12 of the 16 patients. The mean value decreased by 0.51 litres per minute when oxygen was inhaled and the change in the group as a whole was statistically significant ($P < 0.05$). The mean value for stroke volume fell by 9 ml. per beat and the overall result was significant ($P < 0.05$). The systolic, diastolic and mean arterial blood pressure increased in 13 of the 16 patients following treatment with oxygen and the mean values rose by 6, 4 and 7 mm.Hg. respectively ($P < 0.05$). The systemic vascular resistance showed a mean rise of 207 dyne. sec. $cm^{-5}$, and in this case although the changes were less consistent, a rise being obtained in only 11 cases, the increase in mean value was nevertheless significant ($P < 0.05$).

The mean arterial oxygen tension was 67 mm.Hg. while breathing air and rose six-fold to 422 mm.Hg.

after oxygen. There was no significant change in the mean arterial carbon dioxide tension or pH value.

CONCLUSIONS

The results of this investigation indicate that inhalation of oxygen at atmospheric pressure by patients with acute myocardial infarction causes a rise in systolic, diastolic and mean arterial blood pressure. These changes are accompanied by a significant fall in stroke volume and cardiac output. Other workers (MacKenzie et al., 1964, Thomas et al., 1965) have noted similar changes in arterial pressure and cardiac output, but they also found a reduction in heart rate and therefore no marked change in stroke volume. In this investigation, changes in heart rate were, however, very variable. In view of the discrepancy between these results and those of previous authors a larger series of patients was investigated with inhalation of oxygen at both one and two atmospheres absolute pressure and this constitutes the next section of this chapter.

## RESULTS

### Group 2.

The detailed haemodynamic findings in the 35 patients breathing air at one atmosphere absolute pressure, oxygen at one atmosphere absolute pressure and oxygen at two atmospheres absolute pressure are shown in Tables 17 and 18 and the mean values for heart rate, mean arterial blood pressure, cardiac output, systemic vascular resistance and stroke volume are illustrated in fig. 4. Arterial blood oxygen and carbon dioxide tensions and pH are given in Table 19 and lactate and pyruvate values in Table 20.

Heart rate altered little with oxygen at either one or two atmospheres pressure. With oxygen at one atmosphere, there was a fall in heart rate in 14 patients, a rise in 14 and no change in 7, and with oxygen at two atmospheres, compared with air, a fall occurred in 19 patients, a rise in 12 and no change in 4 patients. Although the mean value fell with oxygen at one and two atmospheres, the differences were not significant.

There was a general tendency for the cardiac output to fall after oxygen. At one atmosphere the cardiac output decreased in 26 patients and after oxygen at two atmospheres a fall occurred

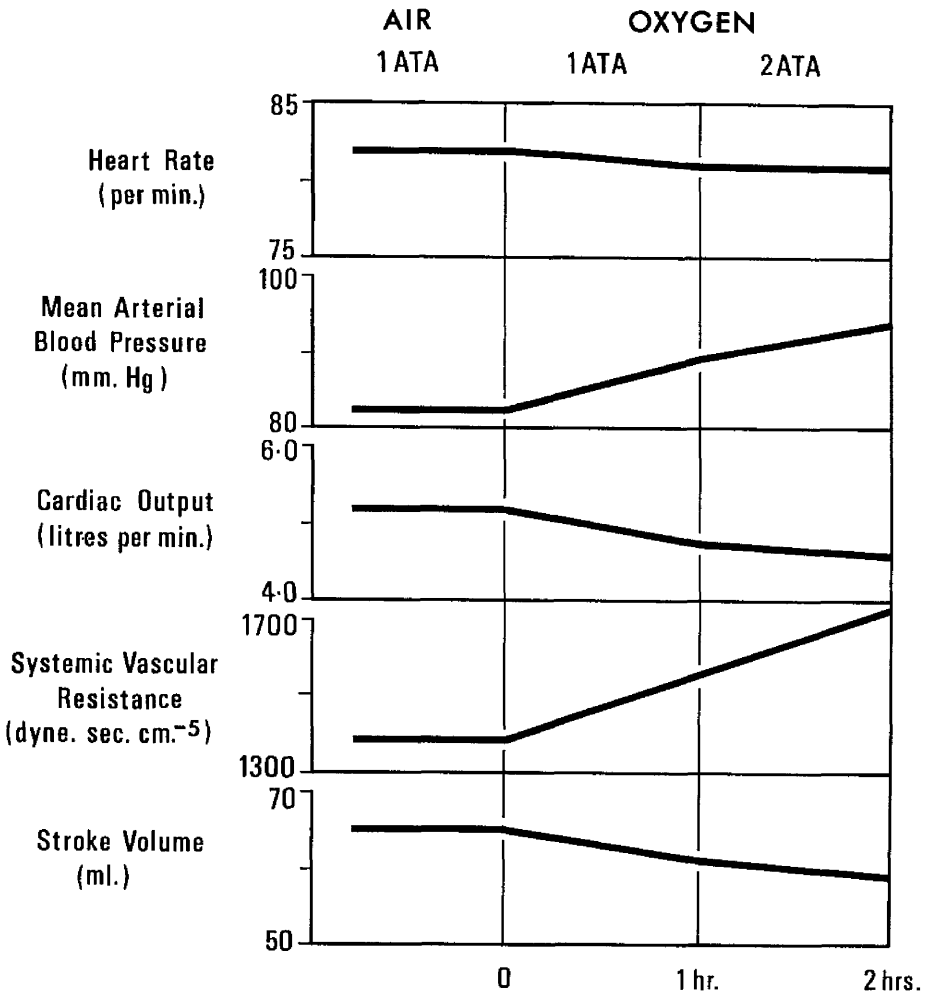


Fig. 4. Mean values for heart rate, arterial blood pressure, cardiac output, systemic vascular resistance and stroke volume in 35 patients with acute myocardial infarction breathing air at one atmosphere and 100 per cent oxygen at one and two atmospheres absolute pressure.

ATA = atmospheres absolute pressure.

in 29 patients compared with air at one atmosphere. The mean value showed a significant reduction between air at one atmosphere pressure and oxygen at one atmosphere pressure ($P < 0.001$) and a further fall at two atmospheres which was significant both when compared with air ($P < 0.001$) and when compared with oxygen at one atmosphere ($P < 0.05$). In 26 of the patients the initial cardiac output was greater than 4 litres per min. and a fall occurred in 23 of these with oxygen at one atmosphere and in 25 patients at two atmospheres pressure. On the other hand, in the 9 patients whose initial cardiac output was less than 4 litres/minute, a fall occurred in only 3 instances at one atmosphere and in 4 cases with oxygen at two atmospheres. The difference in response of these two groups was statistically significant. ($P < 0.01$).

There was a progressive fall in the mean value for stroke volume with oxygen at one and two atmospheres pressure ($P < 0.05$). The individual values fell in 24 patients with oxygen at one atmosphere and in 23 patients with oxygen at two atmospheres. The initial stroke volume was greater than 60 ml. in 23 patients, between 40 - 60 ml. in 9, and less than 40 ml. in 3 patients.

Arterial blood pressure rose progressively with oxygen. The systolic pressure rose with oxygen at one atmosphere in 24 patients, fell in 7 patients and showed no change in 4 patients. With oxygen at two atmospheres a further rise occurred in most patients and in all but 7 patients the value was above the initial value breathing air. A mean rise in systolic pressure of 8 mm.Hg. and 15 mm.Hg. occurred with oxygen at one and two atmospheres respectively compared with air at one atmosphere. The diastolic pressure rose in 21 cases with oxygen at one atmosphere and fell in 10 with no change in 4 patients. With oxygen at two atmospheres, the diastolic pressure was above the initial value in 24 patients. A progressive rise in the mean value for diastolic pressure occurred with oxygen: by 4 mm.Hg. at one atmosphere and 8 mm.Hg. at two atmospheres. The mean arterial pressure showed similar changes. Thus, a rise occurred in 26 patients with oxygen at one atmosphere and in 29 patients at two atmospheres. At two atmospheres, moreover, a fall occurred in only 2 patients and in 4 patients the value was unchanged from the initial findings. The increases in systolic, diastolic and mean arterial blood pressure were all statistically significant with

oxygen at both one and two atmospheres absolute pressure when compared with air at one atmosphere ($P < 0.001$). In addition the further increase in pressure which occurred at two atmospheres was also significant when compared with oxygen at one atmosphere ($P < 0.001$).

Arterial hypotension was present in 11 patients initially. On admission, 6 had a systolic pressure between 81 and 100 mm.Hg. and in 5 of these a rise occurred with oxygen at one atmosphere and in all at two atmospheres. A further 5 patients were severely hypotensive with a systolic pressure of 80 mm.Hg. or less: in 3 of these a rise occurred after oxygen while in 2 there was a fall.

Oxygen increased the systemic vascular resistance in 29 patients at one atmosphere and in all but one patient at two atmospheres pressure. For the whole group, the mean rise was progressive: by 169 dynes sec. $cm^{-5}$ at one atmosphere and 337 dynes sec. $cm^{-5}$ at two atmospheres. The difference was significant between air and oxygen at one atmosphere ($P < 0.02$) and between oxygen at one and two atmospheres ($P < 0.001$).

While there were some variations in the left ventricular work after oxygen in individual patients, the mean figures for the group showed no

statistically significant change.

The arterial blood oxygen tension was initially reduced (less than 80 mm.Hg.) in 28 patients, the mean value being 65 mm.Hg. The mean value rose to 441 mm.Hg. with oxygen at one atmosphere and to 996 mm.Hg. with oxygen at two atmospheres. This represents an increase over the initial value by a factor of 6.8 and 15.3 respectively. It is noteworthy that a substantial elevation of the arterial oxygen tension was obtained even in those patients in whom the initial value was very low. Before treatment was commenced the arterial carbon dioxide tension was within normal limits in most patients. With oxygen at one atmosphere there was a very small increase which was just significant but at two atmospheres there was no significant change from the initial value. The mean values for arterial blood pH were not significantly altered after oxygen at either one or two atmospheres pressure.

The arterial blood lactate level was initially raised in 19 patients (normal range 0.999 - 1.776 m.moles/litre). Although there was a tendency for the lactate value to fall with oxygen at one atmosphere returning to normal in 8 cases, after

oxygen at two atmospheres raised levels were found in 16 patients. The changes, however, produced by oxygen were highly variable. Some of the patients who had a high initial arterial blood lactate level showed a progressive fall with oxygen at one and two atmospheres: in others, however, the decreaae which occurred with oxygen at one atmosphere was reversed by oxygen at two atmospheres: in yet others, with normal initial lactate values a rise to abnormal levels occurred with oxygen. The mean value showed a significant fall in oxygen at one atmosphere ($P < 0.001$) but rose again with oxygen at two atmospheres. The value obtained at two atmospheres lay between that obtained for oxygen and air at one atmosphere and did not differ significantly from either.

The value for arterial blood pyruvate was raised (normal range 0.045 - 0.068 m.moles/litre) in only 4 patients while breathing air and there was no significant change with oxygen at either one or two atmospheres absolute pressure.

When the mask was removed in the pressure chamber so that the patient was breathing air at 2 atmospheres absolute pressure (equivalent to 40 per cent oxygen at one atmosphere) the following results were obtained in the 9 patients in whom measurements were made. (Tables 21 to 27). The

heart rate showed little change. The cardiac output rose in all patients, the mean increment being 0.66 litres per minute which was significant ($P<0.01$). The stroke volume rose in all patients by a mean value of 9 ml. per beat ($P<0.01$). The systolic arterial pressure fell in 7 patients, the diastolic in 5 patients and the mean arterial pressure in 5 patients. These changes were not significant. The systemic vascular resistance, however, fell in all patients by a mean of 276 dynes. sec. $cm^{-5}$ and this was significant ($P<0.01$). When the mask was reapplied so that the patient was again breathing oxygen at two atmospheres absolute pressure, the cardiac output, arterial blood pressure and systemic vascular resistance reverted to their previous levels. The mean values of these responses are shown diagramtically in fig.5.

The detailed results for right ventricular or pulmonary arterial systolic pressure in 12 patients breathing air, oxygen at one atmosphere pressure and oxygen at two atmospheres pressure are shown in Table 28. In 7 patients the tip of the catheter was in the pulmonary artery and in 5 patients in the right ventricle. The changes in right ventricular or pulmonary artery systolic pressure were variable. With

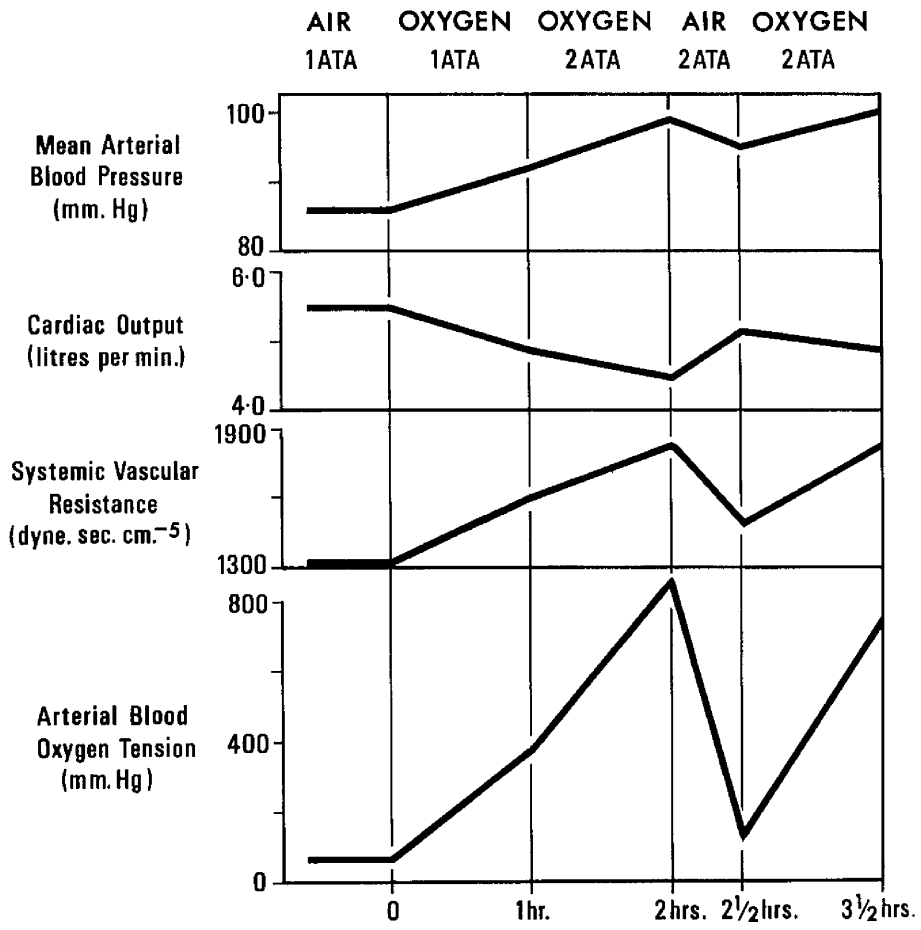


Fig. 5. Mean values for arterial blood pressure, cardiac output, systemic vascular resistance and arterial oxygen tension in 9 patients with acute myocardial infarction breathing air and oxygen at one and two atmospheres absolute pressure.
ATA = atmospheres absolute pressure.

oxygen at one atmosphere a fall in pressure occurred in 6 patients, there was no change in 2 and there was a rise in 4. The mean value showed a small fall which was not significant. With oxygen at two atmospheres the results were also variable. Although a rise occurred in 8 patients and the mean value showed a small rise, this was not significant. Only 2 patients had a raised pressure initially and in these patients a fall occurred with oxygen at one atmosphere and a slight rise again at two atmospheres.

Throughout the period of oxygen administration in both Groups 1 and 2, ectopic beats were noted in some patients but there were no serious arrhythmias. There was no noticeable change in the frequency of ectropic beats during air or oxygen inhalation. The electrocardiogram did not show any constant changes during administration of oxygen and in particular there was no evidence of any change in atrio-ventricular conduction (Table 29). No symptoms or signs of oxygen toxicity were observed in any patient.

Eight patients died during the period of admission to hospital, but only two deaths (cases 24 and 43) occurred in the first 48 hours, while oxygen was being given continuously. No deaths

took place during the period of hyperbaric oxygen treatment. Cases 24 and 43 had persistent hypotension and cardiac failure, and died shortly after discontinuing hyperbaric treatment. Primary ventricular fibrillation as defined by Melzer and Kitchell (1966) did not take place in any patient while oxygen was being administered. In view of the small numbers involved the significance of this is doubtful.

Selected case histories.

A descriptive account is given here of the effects of administration of hyperbaric oxygen in three patients of Group 2.

(a) Patient No. 39

This patient, a 54 year old machine-setter, was admitted as an emergency with a two hour history of severe crushing retrosternal pain accompanied by sweating and dyspnoea. He had a past history of myocardial infarction 6 years previously and had suffered from angina of effort for the past 3 years. On admission he was pale with peripheral cyanosis but was not dyspnoeic at rest. Jugular venous pressure was elevated. Pulse was 80 per minute, regular. B.P. 100/70 mm.Hg. The heart sounds were soft and triple rhythm was present. There were bilateral basal crepitations. The electrocardiogram showed sinus rhythm with a P.R. interval of 0.20 sec., and left bundle branch block. Chest X-ray revealed bilateral pulmonary oedema.

He was considered a suitable patient for inclusion in the investigation and after preliminary procedures had been undertaken he was transferred to the hyperbaric chamber. After initial measurements had been performed he was given 100 per cent oxygen

at atmospheric pressure for one hour. Compression of the chamber to two atmospheres pressure was carried out and after one hour of hyperbaric treatment the measurements were repeated and oxygen administration was continued for a further one hour period. Although there were clinical signs of left ventricular failure on admission, his general condition remained fairly good, and his colour improved with oxygen treatment. He was fully conscious and free of pain and made no complaints. He was initially hypotensive but his blood pressure rose with oxygen and he achieved a high level of arterial blood oxygen tension. In view of his satisfactory general condition it was decided to return him to the Gardiner Institute and decompression of the chamber was carried out slowly, the patient continuing to breathe oxygen. Immediately on return to atmospheric pressure, however, while still in the pressure chamber he became acutely dyspnoeic, tore off the oxygen mask and began to produce copious white frothy sputum. He was in obvious pulmonary oedema and produced about one litre of frothy white sputum in a very short period. Treatment with sedation, intravenous diuretics and digoxin was given, but there was little improvement in his condition. He was still very dyspnoeic

and tolerated the oxygen mask with difficulty and there seemed no alternative but to return to two atmospheres pressure at once. The chamber was recompressed and his condition improved dramatically. Production of sputum ceased and the dyspnoea disappeared. After a further 3 hours of hyperbaric oxygen treatment the pressure in the chamber was cautiously reduced over a longer period of time. On this occasion no untoward symptoms occurred and he was returned to the ward. Subsequent progress was uneventful and acute left ventricular failure did not recur. A few days after admission conduction on the electrocardiogram returned to normal and changes of a recent antero-lateral myocardial infarction were apparent. Serial S.G.O.T. estimations confirmed the diagnosis.

(b) Patient No. 24

The patient, a 72 year old retired switchboard attendant, was admitted with a three hour history of gripping retrosternal chest pain radiating to his left arm. The pain was accompanied by sweating and nausea. He felt faint and his wife commented on the pallor of his face. He was not dyspnoeic. He had a past history of a myocardial infarction 2 years previously and had suffered from angina of effort since that time.

On admission he had marked pallor and was sweating profusely. His lips and fingers showed cyanosis. The jugular venous pressure was elevated. The pulse was regular at a rate of 100 beats per minute. B.P. 80/60 mm.Hg. The heart sounds were very soft. Fine crepitations were present at both bases.

The electrocardiogram showed the presence of a recent antero-lateral myocardial infarction with sinus rhythm. This was subsequently confirmed by the S.G.O.T. level which was elevated to 570 Frankel units per ml.

He was transferred to the hyperbaric chamber shortly after admission and after initial measurements had been made he was treated with oxygen at one atmosphere pressure for one hour and oxygen at two atmospheres pressure for a further two hours.

Following administration of oxygen there was improvement in the general condition of the patient. The blood pressure rose and the cardiac output fell slightly. The systemic vascular resistance which was low on admission increased with oxygen. The initial arterial oxygen tension was very low at 24 mm.Hg., and rose to 127 mm.Hg. at one atmosphere and 458 mm.Hg. at two atmospheres. The arterial

lactate value was elevated initially and fell progressively with oxygen.

Following the period of hyperbaric treatment the chamber was decompressed slowly while the patient continued to breathe oxygen. He was transferred back to the Gardiner Institute where treatment with oxygen was continued. His condition remained much better than on admission, but on the following day he complained of further chest pain and suddenly collapsed due to ventricular asystole. Resuscitative measures were unsuccessful. Post mortem examination showed the presence of a recent extensive myocardial infarction in the lateral wall of the left ventricle and the presence of widespread atheroma of the coronary arteries.

(c) Patient No. 43

This patient, a 51 year old drill-setter, was admitted as an emergency with a history of severe chest pain of six hours' duration. He had previously suffered two episodes of myocardial infarction 3 years and 3½ years before. He had made a good recovery from these illnesses and had recently been well.

On admission he had an ashen pallor and looked extremely ill. His skin was cold and clammy and he

was sweating profusely. He had peripheral and central cyanosis. His pulse rate was 120 per min. and of small volume. His blood pressure was approximately 50/30 mm.Hg. by sphygmomanometry. Both heart sounds could be detected but were very soft. There was no clinical evidence of congestive cardiac failure or of left ventricular failure.

The electrocardiogram showed sinus tachycardia. There were changes of a widespread anterior myocardial infarction with a minor intraventricular conduction defect.

After initial assessment he was transferred to the hyperbaric chamber and treated for one hour with oxygen at one atmosphere pressure and then two hours at two atmospheres pressure. During this treatment, although his colour improved, the blood pressure showed little change and his general condition did not alter. The cardiac output, however, increased slightly with an increase in stroke volume. The initial systemic vascular resistance was raised and fell with oxygen. The arterial oxygen tension rose from 54 mm.Hg. on admission to 480 mm.Hg. at two atmospheres. The arterial lactate concentration which was high initially continued to rise

progressively despite oxygen therapy. After three hours' inhalation of oxygen at two atmospheres pressure there was still little evidence of any improvement with the treatment and the chamber was decompressed slowly. On return to atmospheric pressure the patient's condition deteriorated further and he died a few minutes later, before recompression could be carried out.

Post mortem examination showed the presence of an extensive myocardial infarction involving the apex and the posterior and lateral walls of the left ventricle with occlusion of the interventricular branch of the left coronary artery.

Conclusions

In patients with acute myocardial infarction administration of oxygen at one atmosphere pressure causes a significant fall in cardiac output and the use of hyperbaric oxygen at two atmospheres causes a further fall which is significant but of lesser magnitude. In contrast to the findings in healthy subjects the fall in cardiac output is not accompanied by a decrease in heart rate and there is therefore a reduction in stroke volume. These changes are accompanied by a rise in systolic, diastolic and mean arterial blood pressure which is progressive as the oxygen tension is increased and a similar rise occurs in systemic vascular resistance. Despite these alterations in the circulation, left ventricular work is not appreciably altered, and in particular it is not significantly increased. Oxygen administration appears to have no consistent effect on the pulmonary arterial systolic pressure although there was a tendency for the pressure to be reduced by oxygen at one atmosphere and to be increased by oxygen at two atmospheres.

The results of this investigation confirm that a low arterial oxygen tension is frequently present

in patients with acute myocardial infarction even in those in whom cardiac output and blood pressure are well maintained. By administration of high concentrations of oxygen at one or two atmospheres pressure it is possible to raise the arterial oxygen tension considerably in excess of normal values even in those patients with very low initial values.

A raised arterial blood lactate has been shown to be a common finding in patients with acute myocardial infarction although the pyruvate level remained normal. Oxygen at one atmosphere causes a significant fall in arterial lactate but oxygen at two atmospheres produces variable effects. Arterial blood carbon dioxide levels and pH values are little affected by oxygen administration.

The selected case histories illustrate the effect of oxygen at increased pressure in individual patients. In the first patient there seemed little doubt that administration of oxygen at increased pressure assisted in the relief of left ventricular failure. The other two patients both exhibited features of "cardiogenic shock" but the mechanism of hypotension was different. In one, the cardiac output was within normal limits but the systemic

vascular resistance was low, accounting for the low blood pressure, whereas in the other it was the low cardiac output which was responsible for the hypotension which occurred despite a raised vascular resistance. In the patient with a normal cardiac output administration of oxygen produced some general improvement and the blood pressure rose due to a rise in systemic vascular resistance. In the last patient, however, oxygen did not result in any apparent improvement. These findings suggest that if hypotension is due to inappropriate peripheral vasodilatation with a low peripheral resistance but a normal output, oxygen may be beneficial, but when hypotension is due to "pump failure" with a raised systemic vascular resistance it is of less apparent benefit, although a slight rise in cardiac output did occur in this patient.

No conclusions regarding the effect of oxygen inhalation on the mortality of this condition can be drawn from this series in view of the relatively small number of cases.

## Discussion

The use of oxygen is widely recommended in patients with myocardial infarction. By this means it is hoped that arterial hypoxia will be relieved and in addition that the oxygen supply to the marginal ischaemic zone around the infarcted area will be increased. There is indeed some experimental work in support of this (Sayen et al., 1951), while the relief of cardiac pain (Barach, 1931, Boland, 1940) and apparent clinical improvement following the use of oxygen (Levy and Barach, 1930) also lends credance to this concept. Nevertheless very few detailed studies of the circulatory effects of oxygen in patients with myocardial infarction have been carried out. The information that is avilable, apart from the results of the present investigation, is based on the observation of small numbers of patients. At the present time, as far as can be ascertained, haemodynamic studies of the effects of oxygen at atmospheric pressure have been reported in only three series in a total of 34 patients, (MacKenzie et al., 1964, Thomas et al., 1965, Foster, Casten and Reeves, 1969). These investigations have, moreover, used different concentrations of oxygen for different periods of

time and administered by different means. There is even less information concerning the effects of oxygen at increased atmospheric pressure. The first investigation of the use of hyperbaric oxygen in myocardial infarction took the form of a controlled clinical trial of its effects on mortality (Cameron et al., 1965) and haemodynamic studies were not carried out. Only two other studies are available (Moon, Williams and Hopkinson, 1964; Ashfield and Gavey, L969) and neither give details of the haemodynamic effects. There have, of course, been many studies of the effects of hyperbaric oxygen in experimental myocardial infarction in laboratory animals. Kuhn et al. (1965) using oxygen at three atmospheres pressure, demonstrated a reduction in early and late mortality in dogs after experimental coronary embolisation. A protective effect of oxygen at two atmospheres against the development of ventricular fibrillation after coronary artery ligation has also been reported (Smith and Lawson, 1958, 1962; Gage et al., 1965). Unfortunately the results of such work is not directly referable to the clinical situation.

The present investigation, therefore, extends the information which is available in man concerning

the circulatory effects of oxygen at atmospheric pressure and is the only report so far available of the haemodynamic effects of oxygen at two atmospheres pressure in patients with myocardial infarction.

One of the first reports of the use of oxygen in myocardial infarction described the effects of inhalation of 40 to 50 per cent oxygen in 4 patients and it was observed that this treatment was followed by slowing of the heart rate (Levy and Barach, 1930). In the study by MacKenzie et al. (1964), a high flow rate of oxygen was inhaled for a period of 30 minutes by fifteen patients. The effect on the heart rate was found to vary with the clinical state of the patient. While no significant change was found in six patients with "cardiogenic shock" and a systolic blood pressure less than 100 mm.Hg., a fall in heart rate took place in all but one of the nine patients who were not hypotensive. Thomas et al.,(1965) studied six patients whose blood pressures varied from severely hypotensive to mildly hypertensive levels using approximately 40 per cent oxygen administered by "polymask". They found that the heart rate was lower in 16 of the 19 comparisons when oxygen was

breathed, even in patients with hypotension and low cardiac output. In the only study in which more than one concentration of oxygen has been used (Foster et al., 1969) a variable effect of oxygen on the heart rate was found depending on the clinical state of the patient. In 16 patients with a cardiac index above 2.5 litres per min. per $m^2$ there was a small but significant decrease in heart rate that was linearly related to the concentration of oxygen inhaled and a similar relationship was observed in 5 normal subjects. On the other hand, in six patients with a cardiac index less than 2.5 litres per min. per $m^2$ little change was noted in the heart rate with oxygen. It should also be noted that the magnitude of change in heart rate in all three studies is very small: the mean value in the study by MacKenzie et al., (1964), decreased by 2 beats per minute while Foster et al., (1969), also obtained a fall of 2 beats per minute in their patients compared with a fall of 5 beats per minute in normal subjects. In the present study, no significant change was noted in the heart rate with oxygen at either one or two atmospheres absolute pressure although the mean value showed a slight fall. There was moreover no obvious correlation between

changes in heart rate and the degree of hypotension or the level of cardiac output. This discrepancy between the present study and the findings of other workers is not readily explained. It has already been pointed out, however, that even where a significant fall in heart rate did occur in previous studies, the decrease was very small and the number of subjects studied was not great. It seems possible therefore that the findings in this larger series is more representative of the overall effect of oxygen inhalation in patients with myocardial infarction.

Investigation of the effects of oxygen on the cardiac output has also given variable results. Thus a small but statistically significant fall in cardiac output after oxygen was found by MacKenzie et al., (1964) in six of nine patients without cardiogenic shock. In their six shocked patients the cardiac output either remained unchanged or was slightly decreased, although in the patient with the lowest cardiac output of all, a slight increase was recorded. A significant decrease in cardiac output was also found in all six patients studied by Thomas et al., (1965), even in the presence of a low initial output. On the other hand, Foster et al., (1969)

found no significant change in cardiac index in patients with myocardial infarction as the concentration of oxygen inhaled was increased, although a significant fall was noted in healthy control subjects. Although their results did not attain statistical significance, examination of the published figures shows a small but consistent fall in cardiac index in patients with an initial value above 2.5 litres per min. per $m^2$ as the inhaled oxygen percentage increased, whereas a small progressive rise occurred in those whose initial index was less than 2.5 litres per min. per $m^2$. In the present investigation it has been confirmed that administration of oxygen to patients with myocardial infarction results in a significant fall in cardiac output which becomes more pronounced at two atmospheres absolute pressure. While the further reduction in cardiac output which occurs at two atmospheres is also significant statistically, it is to be noted that it is relatively less in degree, the mean value falling by 8.5 per cent with oxygen at one atmosphere when compared with air and by only a further 2.9 per cent with oxygen at two atmospheres absolute pressure. On the other hand, in this investigation it has been shown that the response to oxygen may be different if the initial cardiac output

is very low and indeed a rise has been noted in many patients in these circumstances. This finding is in keeping with that of Foster et al., 1969, and if it represents a true difference in response,is obviously of considerable clinical importance.

More consistent changes in arterial blood pressure have been found following inhalation of oxygen. Both in patients with cardiogenic shock and in those without shock an increase in mean arterial blood pressure has been noted (MacKenzie et al., 1964), although significance was reached only in the latter group. Thomas et al., (1965) also found consistent increases in systolic, diastolic and mean arterial pressures when their patients were breathing oxygen even when the initial blood pressure was very low. In the study of Foster et al., (1969) the mean aortic pressure rose significantly with increasing levels of oxygen in the inspired air in patients with both high and low initial cardiac indices. In the latter study the increase in arterial pressure was brought about largely by a rise in systolic pressure, the diastolic pressure showing relatively little change. The results from the present investigation are in line with previous

work and show a progressive increase in systolic, diastolic and mean arterial pressure with oxygen at one and two atmospheres absolute pressure. The rise which occurred as the oxygen was increased from one to two atmospheres pressure was almost as great as the initial rise with oxygen at atmospheric pressure. An increase in blood pressure was found both in hypotensive patients and in those with a relatively normal blood pressure on admission. There is little doubt, therefore, that administration of oxygen to patients with myocardial infarction will result in most cases in a rise of arterial blood pressure to an extent which may well be of value in the treatment of this condition.

As a result of these changes in arterial pressure, the calculated systemic vascular resistance is increased. A consistent rise was found by MacKenzie et al., (1964) in both shocked and non-shocked patients. A similar rise in peripheral resistance was observed by Thomas et al., (1965) in all their patients, and Foster et al., (1969) also recorded a rise in patients with both high and low initial vascular resistance. The present study has confirmed these findings, and the values obtained with oxygen at two atmospheres were significantly

higher than those with oxygen at one atmosphere. It should be remembered that the systemic vascular resistance is calculated from the cardiac output and arterial blood pressure and changes in resistance simply reflect changes in the two measurements. Nevertheless, a rise in systemic vascular resistance in these circumstances probably does indicate arterial vasoconstriction although it does not, of course, give any information about changes in the blood supply to individual regions of the body. In addition alterations in resistance must be considered along with the original values. Thus in a subject with an initial high systemic vascular resistance, a further increase could well be disadvantageous whereas a similar increase in a subject who has an inappropriately low resistance might be beneficial. In this series there were seven patients with abnormally low results and these all increased to within normal limits with oxygen at either one or two atmospheres pressure. Conversely there were eight subjects with abnormally high initial resistance and these patients also showed a rise with oxygen.

It might be expected that the rise in arterial pressure and systemic vascular resistance which follows the administration of oxygen would result in

an increased work-load for the heart. In view of the fall in cardiac output which takes place at the same time it is possible that the contrary is the case. Thus MacKenzie et al., (1964) stated that the measurements of left ventricular work showed no significant change after oxygen. In this study there was also no significant change in left ventricular work with oxygen at either one or two atmospheres pressure, although the mean value showed a slight fall at one atmosphere. The absence of a significant rise in cardiac work means that if the other haemodynamic and metabolic changes such as the rise in arterial pressure and oxygen tension are indeed beneficial, they have been achieved at little expense to the patient.

Recent studies of the circulatory disturbances associated with myocardial infarction have shown that there is frequently a reduction in arterial oxygen tension especially in the presence of left ventricular failure and cardiogenic shock (MacKenzie et al., 1964; McNicol et al., 1965; Valentine et al., 1966; Valencia and Burgess, 1969; Fillmore, Shapiro and Killip, 1970).

While there is agreement that a reduction in arterial oxygen tension is a frequent occurrence in patients with myocardial infarction it is clear that

the underlying mechanisms are still not fully explained. There are four possible ways in which a low arterial oxygen tension can occur in a subject breathing air at normal pressure. Firstly, it could be due to general hypoventilation of the lungs. If this were so, an increase in arterial carbon dioxide tension would also be found, and it is generally agreed that the carbon dioxide tension remains normal in this condition. Secondly, it could be the result of abnormality of the ventilation-perfusion ratio with reduced ventilation of alveoli which continue to be normally perfused. Thirdly, it may be due to direct shunting of blood from the right side of the circulation to the left without coming into contact with gas-filled alveoli. Finally, it may be due to a decreased diffusing capacity in the lungs. Evidence in support of all the last three mechanisms has been produced.

In a study of 73 patients with myocardial infarction, McNicol et al., (1965) found that in those patients who did not have pulmonary congestion or cardiogenic shock, the mean arterial oxygen tension was 73 mm.Hg. whereas in patients with evidence of these complications the mean value was 57 mm.Hg., and that a rise in arterial oxygen tension followed intravenous diuretics. The effect of inhalation of

100 per cent oxygen was also investigated in these patients and it was shown that in some cases the arterial blood oxygen tension remained low. These authors considered that pulmonary congestion secondary to left ventricular failure was the cause of the hypoxaemia with shunting of blood through underventilated alveoli. On the other hand Valentine et al., (1966) studied the blood-gas changes in 19 patients after acute myocardial infarction. They also found a reduction in arterial blood oxygen tension in nearly all patients which, although it was more pronounced in patients with pulmonary oedema, was also present in patients without evidence of this complication. After administration of 100 per cent oxygen the arterial blood oxygen tension increased and the calculated venous-admixture effect was greatly reduced. These workers therefore concluded that significant anatomical shunting of venous to arterial blood does not occur and that the hypoxia following myocardial infarction is principally due to alteration in ventilation-perfusion ratios. They conceded, however, that none of their patients was seriously hypotensive and that anatomical shunting may still occur if cardiogenic shock is present, as claimed by MacKenzie et al., (1964).

In a careful study of respiratory function in seventeen male patients following myocardial infarction and in a control group of 12 patients, it has been shown that defective gas exchange is present after myocardial infarction (Higgs, 1968). In this investigation it was demonstrated that inhalation of 100 per cent oxygen resulted in a relatively greater increase of arterial blood oxygen tension in the patients than in the control group, indicating that disturbance of the ventilation-perfusion ratio was present. In addition, a voluntary increase in tidal volume was shown to produce a rise in arterial blood oxygen tension with a reduction of alveolar-arterial gradient. This suggests that the airways in some parts of the lung had been closed and that shunting of blood past groups of atelectatic alveoli had also taken place. The conclusion reached, was, therefore, that there is a combination of ventilation-perfusion imbalance and intrapulmonary shunting. Valencia and Burgess (1969) measured the arterial oxygen tension in three groups of patients with coronary insufficiency, myocardial infarction without left ventricular failure and myocardial infarction with left ventricular failure. It was found that the mean arterial oxygen tension in the

second group was significantly less than in patients with coronary insufficiency, but that a still greater degree of hypoxaemia occurred when left ventricular failure was present, although there was no correlation between cardiac index and arterial oxygen tension. In all patients the response to breathing 100 per cent oxygen fell short of the expected value indicating a right to left shunt-like effect. However, they also found that a significant increase in arterial blood oxygen tension occurred after three voluntary deep breaths, but to no greater extent that in normal subjects, indicating only a mild degree of maldistribution of ventilation. There was also a reduction in pulmonary diffusing capacity which correlated significantly with arterial blood oxygen tension. There workers concluded, therefore, that while arterial hypoxaemia in myocardial infarction may be due to left ventricular failure it can also be associated with abnormalities in the distribution of ventilation and a reduced pulmonary diffusing capacity. However, in a recent study of 39 patients with acute myocardial infarction it has been found that the arterial blood oxygen tension and also the increment which was obtained on inhalation of 28 per cent oxygen correlated well with clinical severity as judged by the presence and degree

of left ventricular failure or shock (Fillmore et al., 1970).

In this investigation a reduction in arterial oxygen tension has also been found. The arterial carbon dioxide tension remained within normal limits and therefore general alveolar hypoventilation is excluded. While the greatest reduction in oxygen tension occurred in the most severely ill patients low values were also obtained in patients in whom cardiac output and blood pressure were well maintained. There was no good correlation between arterial oxygen tension and cardiac output or arterial blood pressure. It follows that hypoxaemia is not entirely related to the development of left ventricular failure. Moreover, with the methods of oxygen administration used in this study it has been possible to raise the arterial oxygen tension considerably in excess of normal values even in those patients with very low initial levels. It is noteworthy, however, that the levels achieved remained lower than those obtained in healthy subjects (Chapter II). This would seem to indicate that while a degree of right-to-left shunting may be occurring in the lungs, alterations of ventilation-perfusion ratio play the major role. While the pulmonary diffusing capacity was not measured, the

arterial oxygen tension increased approximately linearly with the increase in inspired oxygen tension. If there was a significant block to diffusion, one might have expected a relatively greater increase in arterial oxygen tension as the alveolar oxygen tension increased. It is likely, therefore, that the mechanism underlying arterial hypoxaemia is complex and the resultant of several factors. Abnormalities of ventilation-perfusion ratio and shunting of blood through alveoli which are either fluid-filled or atelectatic probably occurs concomitantly. Nevertheless, it has been shown in the present study, that administration of oxygen in high concentration results in a correction of arterial hypoxia in all patients and is sufficient to restore the arterial blood oxygen saturation to normal values.

Raised arterial lactate levels are generally accepted as evidence of increased anaerobic metabolism (Best and Taylor, 1961). Elevation of arterial lactate values has been observed in patients with severe hypotension and cardiogenic shock by MacKenzie et al., 1964, but these workers found normal values in patients with uncomplicated myocardial infarction. Fillmore et al., (1970)

also found that arterial lactate levels increased with clinical severity, although abnormal levels were only found in patients with pulmonary oedema or cardiogenic shock. In this study a raised arterial blood lactate was a surprisingly common finding, although the pyruvate level remained normal. While very high lactate levels were found in association with the syndrome of hypotension, hypoxia and low cardiac output, raised values were often present in patients with less pronounced circulatory disturbances. Similar observations have been made by Foster et al., (1969) who found the arterial lactate level to be significantly increased in patients with myocardial infarction compared with a control group of healthy subjects. They found that while the highest arterial lactate values occurred in patients with a very low cardiac index, an increased value was also obtained in patients with a high cardiac index. It seems likely therefore that tissue hypoxia is present in many patients even although it may not be clinically apparent. Inhalation of high concentration of oxygen at one atmosphere caused a reduction of arterial lactate levels in most cases in the present investigation and this was also the finding of

Foster et al., (1969) although these workers observed that the arterial lactate concentration was linearly related to the duration of oxygen breathing rather than the concentration of oxygen in the inspired air. It is to be noted, however, in the present work that inhalation of oxygen at two atmospheres did not cause a further fall in arterial lactate levels but instead produced a rise in the mean values. These results seem to indicate that while improved tissue oxygenation occurs following oxygen inhalation at one atmosphere, despite the reduction in cardiac output, the same is not necessarily true of hyperbaric oxygen.

The therapeutic effects of the changes which accompany the inhalation of oxygen in patients with myocardial infarction are difficult to assess. For example, the reduction in cardiac output which is the usual response to oxygen might be undesirable and a decrease in coronary arterial blood flow would be particularly disadvantageous. It is known, however, that in the presence of myocardial ischaemia the coronary arteries are maximally dilated and blood-flow is largely pressure-dependent (Gorlin et al., 1959). Despite the fall in cardiac output, therefore, the accompanying rise in arterial pressure should result

in improved coronary perfusion and this is achieved without any significant increase in left ventricular work. On the other hand, in many of those patients with initially very low cardiac outputs oxygen caused a rise which could well be beneficial.

In addition to the local anoxia at the site of the infarction it has been shown that generalised hypoxia is often present. However, the availability and amount of oxygen delivered to the tissues obviously depends not only on the arterial oxygen tension and thus the blood-tissue oxygen gradient, but also on the regional blood flow. Direct measurement of blood flow to individual parts of the body is difficult in severely ill patients, but indirect information regarding the adequacy of perfusion of the tissues can be obtained by study of the products of metabolism. In any such investigation it is essential that simultaneous measurement of lactate and pyruvate levels should be made (Huckabee, 1958). It has been seen from the results presented in this chapter that the indications are that tissue oxygenation is indeed improved by oxygen inhalation at one atmosphere despite the haemodynamic changes. Diffusion of oxygen from haemoglobin to cell mitochondria is

dependent on a gradient of partial pressure. While it might be expected that the increase in this gradient produced by hyperbaric oxygenation would improve tissue oxygenation, it has also been shown that this is not necessarily the case and it may be that the metabolic benefits of hyperbaric oxygenation are overcome by the increased haemodynamic effects which have been described.

There are no clear indications whether oxygen should be used routinely in the treatment of myocardial infarction. Clearly many factors have to be taken into account apart from the changes in arterial oxygen tension. Further studies of the mechanism of the haemodynamic effects of oxygen and in particular the effect of oxygen on the coronary circulation itself are described in a later chapter and the clinical indications for oxygen in myocardial infarction will be further discussed thereafter.

SECTION B

Effects of hyperbaric oxygen in chronic ischaemic heart disease.

It is generally accepted that the symptoms of angina pectoris are due to myocardial hypoxia resulting from an inadequate myocardial blood supply (Wood, 1956, Gorlin, 1965). It has also been shown that inhalation of low concentrations of oxygen can induce anginal pain and typical electrocardiographic changes in patients with this condition (Stewart and Carr, 1954). It seems reasonable to assume therefore that if myocardial hypoxia could be prevented, the symptoms of angina will be reduced. For this reason, a study of the effects of hyperbaric oxygen in patients with angina seemed worthy of trial, as a method of assessing indirectly whether myocardial oxygen availability is increased thereby. Studies of the effects of therapy in angina are, however, notoriously difficult to perform in view of their dependence on subjective findings. Recently, however, it has been suggested (Sowton et al., 1967) that the "anginal threshold" can be readily established with the use of atrial pacing and that the method is safe and does not trouble

the patient unduly. It was decided, therefore, to attempt to measure the "anginal threshold" of patients with chronic ischaemic heart disease while breathing air, oxygen at one atmosphere and oxygen at two atmospheres in order to establish if the anginal threshold was raised by this means.

Patients and Methods

Three male patients aged 56, 58 and 62 years with chronic ischaemic heart disease were studied. All had severe angina pectoris which was provoked by mild exertion and required treatment with an average of 10 glyceryl trinitrate tablets per day. The clinical details of the three subjects are given in Table 30.

The studies were carried out within the hyperbaric chamber at the Western Infirmary. Attempts were made to measure the anginal threshold in each patient while breathing air at one atmosphere absolute pressure and oxygen at two atmospheres absolute pressure. Air or oxygen was administered by means of a close-fitting face-mask as previously described (Chapter II).

Under local anaesthesia a Zucker bipolar electrode catheter was inserted via an antecubital vein into the right atrium. The tip was advanced under

radiographic control using an image intensifier until it lay on the lateral wall of the atrium at the junction with the superior vena cava. The catheter was manipulated until a position was found at which stable atrial pacing was obtained with a current of less than 2 volts. A fine polythene catheter was also introduced percutaneously under local anaesthesia into a brachial or femoral artery for measurement of arterial blood pressure and withdrawal of arterial blood. The arterial pressure was measured using strain gauge transducers and Devices recording apparatus. The cardiac output was estimated using a dye dilution technique. Indocyanine green dye in an average dose of 5 mg. was injected from a calibrated syringe into the right atrium through the Zucker catheter and flushed in with saline. Arterial blood was withdrawn via the arterial cannula through a Beckman cardio-densitometer by means of a Harvard constant rate withdrawal pump (fig. 6). Cardiac output measurements were made in duplicate and the mean of the results was taken. Samples of arterial blood were taken before the first injection of dye for calibration purposes. Three standard dilutions of dye in whole blood were prepared and a calibration slope was constructed by

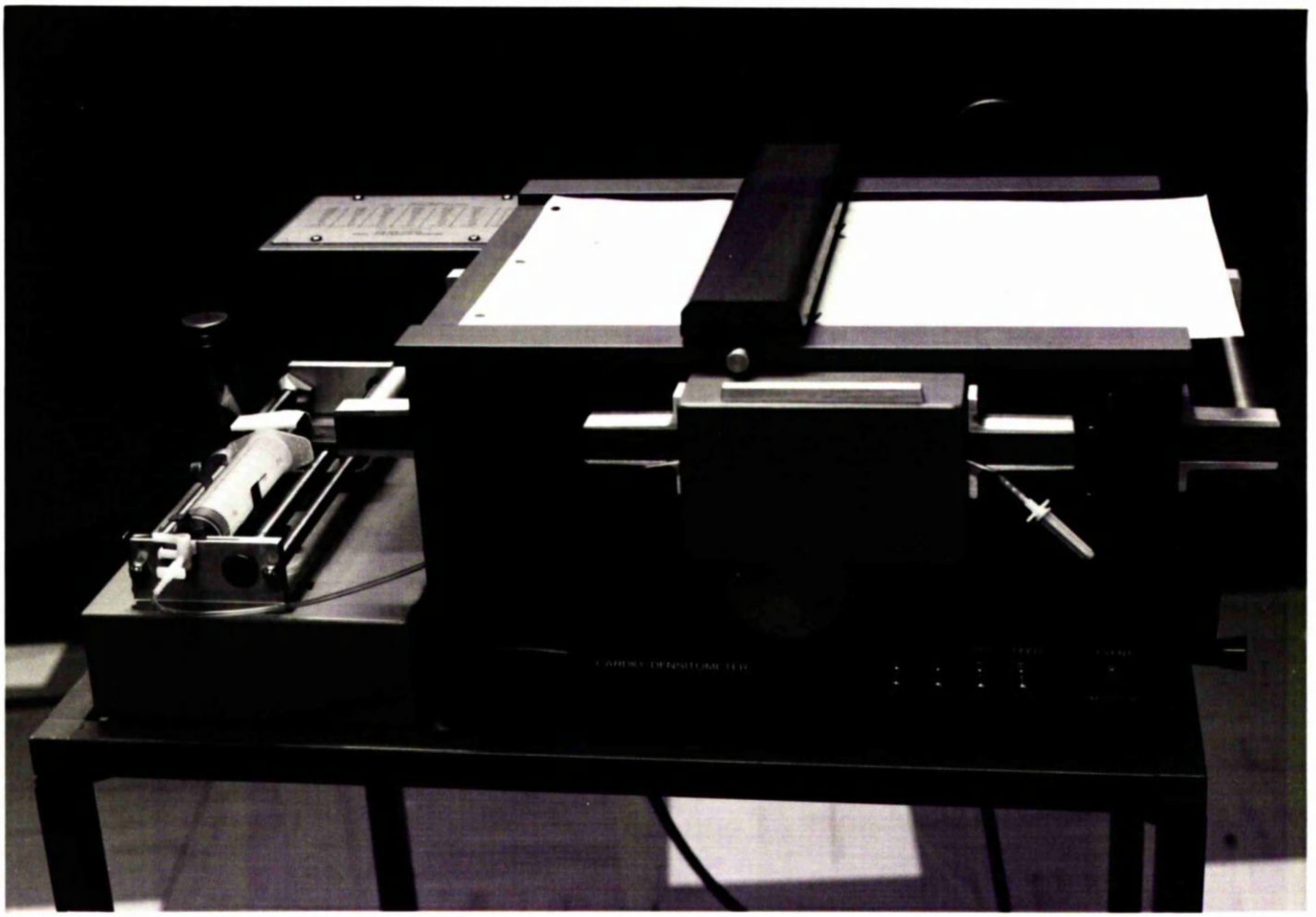

Fig. 6. Beckman cardio-densitometer for recording dye dilution curves. The Harvard withdrawal pump used to pull arterial blood through the densitometer cuvette as seen on the left.

passing these blood samples through the densitometer at the end of the investigation. The electrocardiogram was monitored continuously on an oscilloscope and the heart rate was measured from a recording of the tracing. The oxygen tension of samples of arterial blood was measured using an Instrumentation Laboratories Inc. blood-gas analysis system as previously described.

The pacing catheter was connected to a Devices external pacemaker unit which has a maximum rate of 140/min. and the anginal threshold was measured following the method of Sowton et al., 1967. The heart rate was increased by atrial pacing starting approximately 5 beats per min. above the resting heart rate. The rate was then increased by increments of 5 to 10 beats per min. to a maximum of 135 - 140 beats per min. Each rate was maintained for a period of at least 120 secs. Pressure recordings were taken at the end of each pacing period and the cardiac output was measured initially and then with a heart rate of 90, 120 and 135 beats per minute. After these measurements were made with the subject breathing air, the patient was connected to the oxygen supply and the pressure in the chamber was increased to two atmospheres. After a period of 20 - 30 mins. to allow stabilisation of the patient, the procedure was repeated.

Results

In each case the heart rate was increased to a maximum of 140/min. while breathing air at one atmosphere absolute pressure and oxygen at two atmospheres absolute pressure. No chest pain or electrocardiographic changes were experienced by any of the three patients during this procedure and therefore the "anginal threshold" could not be measured.

An interesting occurrence did, however, take place with patient No. 2. He experienced no chest pain during the preliminary procedures or during atrial pacing at rates up to 140/min. while breathing air at one atmosphere. 100 per cent oxygen was given and pressurisation was commenced uneventfully. Five minutes are compression to two atmospheres had been achieved while the patient was resting quietly in sinus rhythm at 72 beats/min. he suddenly experienced severe chest pain accompanied by striking electrocardiographic changes of myocardial ischaemia (fig. 7). At this time his arterial pressure was only slightly increased above the level obtained while breathing air and the cardiac output was moderately reduced. The arterial blood oxygen tension was 1017 mm.Hg. After the commencement of

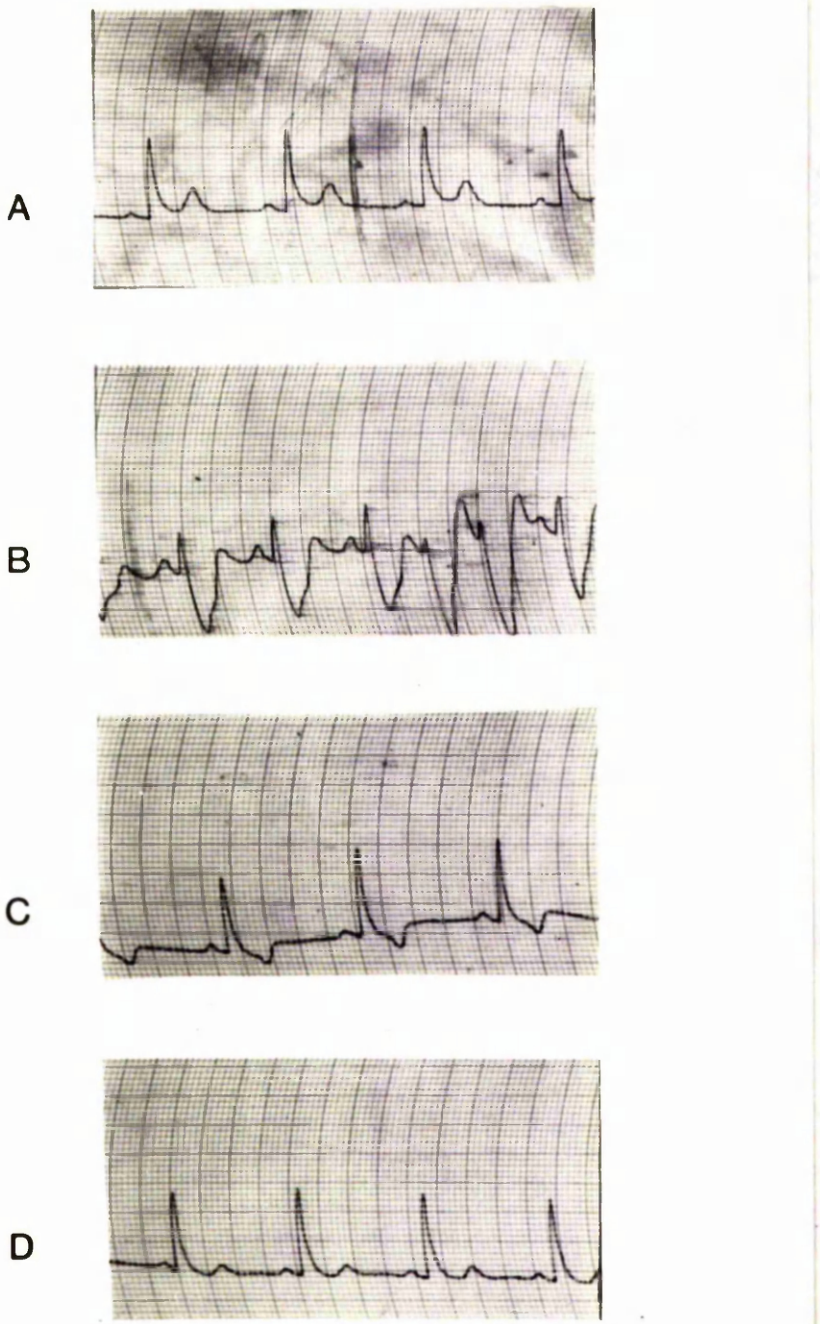


Fig. 7. Electrocardiogram of patient No. 2.

A. Breathing air at one atmosphere.

B. Breathing oxygen at two atmospheres pressure during cardiac pain.

C. Breathing air at two atmospheres pressure: pain lessening.

D. Breathing oxygen at two atmospheres pressure after sublingual glyceryl trinitrate.

chest pain the arterial pressure rose considerably, but the onset of pain occurred before the rise in pressure took place. At this stage the patient insisted on removal of the face-mask and took 0.6 mg. glyceryl trinitrate sublingually and the chest pain rapidly disappeared while the electrocardiogram reverted to the previous pattern. After a period for recovery the patient again breathed oxygen through the face-mask and the procedure continued uneventfully. No further chest pain was experienced despite atrial pacing up to a rate of 140/min. with oxygen at two atmospheres pressure.

The haemodynamic and blood gas findings in the three patients breathing air and oxygen at two atmospheres pressure shown in Tables 31 and 31A Haemodynamic studies could not be completed in patient No. 3 due to blockage of the arterial catheter, but atrial pacing was continued.

Conclusions

It is difficult to account for the failure to obtain an "anginal threshold" in these patients especially as they were selected for study on account of the severity of their symptoms. It may be that the rate at which they were paced was not high enough, as it was limited in this study to a maximum of 140 beats per min. by the apparatus used. On the other hand, Sowton et al., (1967) report that angina pectoris was induced in 13 out of 17 patients with pacing rates of between 83 and 152/min. and with a mean value at the onset of pain of 117 beats/min. Lau et al., (1968) also obtained a positive pacing test in 23 of 25 patients with angina pectoris at paced heart rates usually between 120 - 140 beats/min. It seems strange, therefore, that chest pain was not produced in at least one of the patients investigated. Once again, it should be repeated that the reason for the small number was due to the careful selection of patients with very severe symptoms of angina as it was only felt justifiable to perform this investigation in patients where the possibility of surgical treatment was being considered.

The episode of chest pain experienced in

patient No. 2 is interesting. It occurred at a time when the oxygen supply to the heart might be expected to be increased and certainly in the presence of a high arterial oxygen tension. While too much weight should not be placed on the result of one experiment, the occurrence of an episode of cardiac pain with electrocardiographic changes indicative of myocardial ischaemia during hyperbaric exposure suggests that the oxygen supply to the myocardium may in fact be decreased by this procedure and not augmented as might be hoped. In other words this incident could be explained on the basis of coronary arterial vasoconstriction following the inhalation of oxygen at two atmospheres pressure and subsequent pain may have been prevented by the ingestion of trinitrate. This occurrence certainly seems to point to the need to investigate the effects of inhalation of oxygen on the coronary circulation as constriction of the coronary arteries would obviously be undesirable in the treatment of patients with myocardial infarction.

# CHAPTER IV

Studies of the mechanism underlying the haemodynamic changes produced by inhalation of oxygen.

Section A: Effects of atropine on the haemodynamic changes induced by inhalation of oxygen.

Section B: Haemodynamic effects of inhalation of oxygen at two atmospheres pressure after administration of atropine in healthy subjects.

Section C: Haemodynamic effects of inhalation of oxygen in subjects with a fixed heart rate.

There have been several attempts to elucidate the mechanism whereby oxygen produces haemodynamic changes. Dautrebande and Haldane (1921) originally put forward the hypothesis that slowing of the blood-flow through the tissues is part of the homeostatic mechanism designed to maintain a constant internal environment and thus protect against the toxic effects of excess oxygen. It has been shown in dogs that while the early bradycardia associated with inhalation of oxygen is dependent on the integrity of the vagal cardiac fibres, a delayed slowing of the heart rate can still take place in the totally denervated heart (Whitehorn and Bean, 1952). Confirmation of the importance of the vagal effect in man was provided by Daly and Bondurant (1962) who found that atropine could largely abolish the effects of oxygen at one atmosphere absolute pressure on heart rate, cardiac index and vascular resistance. They were careful to state, however, that the possibility of a subsidiary myocardial effect could not be excluded and furthermore, since the blood pressure still rose significantly after atropine, that a reflex or direct vascular effect of increased arterial blood oxygen tension could not be ruled out. While the

effects of oxygen on healthy subjects observed in Chapter II are largely in keeping with these findings, it is of interest that in patients with acute myocardial infarction, the haemodynamic changes take place without a significant alteration of heart rate (Chapter III). In view of this discrepancy, it was decided to carry out some experiments in order to determine whether the haemodynamic effects of oxygen in healthy subjects are wholly dependent on changes in heart rate mediated by vagal action. The results of these investigations are described here.

Section A Effects of atropine on the haemodynamic changes induced by inhalation of oxygen at two atmospheres absolute.

It was decided initially to observe if the haemodynamic effects of oxygen inhalation at 2 atmospheres pressure in healthy subjects could be reversed by the administration of atropine.

Method. Three healthy male medical students were investigated while breathing air at one atmosphere absolute pressure and after a period of 45 minutes breathing oxygen at two atmospheres absolute pressure. They were then given an intramuscular injection of 0.6 mg. atropine sulphate and continued to breathe oxygen at two atmospheres pressure for a further 30 minutes when the measurements were repeated. The age, height, weight and body surface area of the three subjects are given in Table 32 (Subjects A1 - 3).

The experimental conditions were similar to those described for the investigation of healthy subjects. Oxygen was administered by a close-fitting mask and the heart rate, cardiac output and blood pressure were estimated in the same manner as before (Chapter II).

Results The detailed haemodynamic findings in the three subjects during inhalation of air at one

atmosphere and during inhalation of oxygen at 2 atmospheres before and after atropine are shown in tables 33 and 34. The heart rate fell in 2 of the 3 subjects following oxygen, but rose in all three subjects after atropine. The heart rate after atropine was greater than the heart rate breathing air in each case (fig. 1). The cardiac index fell in each case with oxygen but rose again with atropine. Changes in stroke index were variable as were the changes in systolic arterial pressure. The diastolic blood pressure and the mean arterial pressure rose in all three subjects after oxygen and the rise was maintained after atropine. The systemic vascular resistance, on the other hand, rose with oxygen but the effect was reversed after atropine. Conclusions. The results indicate that the bradycardia produced by oxygen can be reversed by atropine. Moreover, it appears that the reduction in cardiac output induced by oxygen can also be abolished by atropine. In the third subject, however, it is noted that although the heart rate after atropine is higher than the initial value the cardiac index remained lower than the initial value. In the other two subjects, the heart rate after atropine is considerably above the initial value and it may be

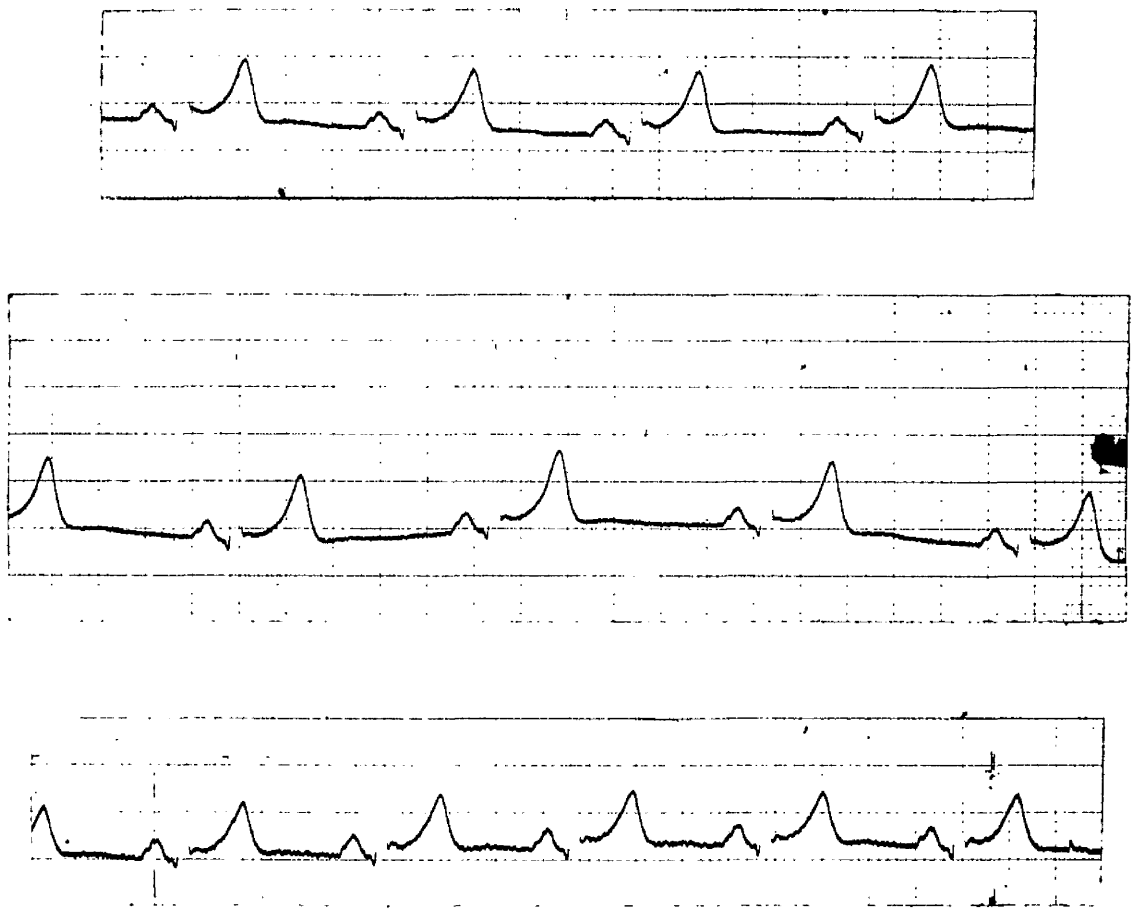

Fig. 1. Electrocardiogram of subject No. 2 showing bradycardia after 100 per cent oxygen at two atmospheres reversed by administration of atropine.

A. Breathing air at one atmosphere.

B. Breathing oxygen at two atmospheres.

C. Breathing oxygen at two atmospheres after atropine 0.6 mg. I.M.

that the increase of the cardiac index in these subjects is related mainly to the tachycardia which has been produced. In other words, if the heart rate after atropine had simply increased to the initial value, the corresponding cardiac index might have remained lower than the value breathing air. The rise in diastolic and mean blood pressure occurring with oxygen is maintained after atropine, but there is a fall in systemic vascular resistance.

Section B. Effects of inhalation of oxygen at two atmospheres pressure after administration of atropine in healthy subjects.

Following the observation that the haemodynamic effects of oxygen could be reversed by giving atropine (Section A) it was decided to investigate if the haemodynamic effects could be prevented by the prior administration of atropine. The age, height, weight and body surface area of the three subjects are given in Table 32 (Subjects A4 - A10).

Method. Seven healthy male volunteers were studied. The experimental conditions were similar to those described in Chapter II for the investigation of healthy subjects. Initial measurements were made with the subjects at rest breathing air. An intramuscular injection of 1.2 mg. atropine sulphate was then given and after a period of 45 minutes the measurements were repeated. Oxygen was then inhaled while the ambient pressure was increased. Pressurisation took 15 minutes and a third set of measurements was made shortly after reaching 2 atmospheres pressure. The subjects continued to breathe oxygen at 2 atmospheres and 30 minutes later the observations were repeated.

The heart rate, cardiac index, arterial blood

pressure, stroke index and peripheral vascular resistance were estimated as previously described. The results were analysed statistically using the Wilcoxon test (Forrester and Ury, 1969).

Results. The detailed haemodynamic findings in the seven subjects are shown in Tables 35 and 36 and the mean values for heart rate, cardiac index, stroke index and arterial blood pressure are illustrated in fig. 2.

After atropine there was a significant rise in heart rate acoompanied by an increase in cardiac index. There was a slight fall in systolic arterial pressure and a rise in diastolic pressure. There was little change in stroke index or in mean arterial pressure, but the systemic vascular resistance showed a fall.

When oxygen was given at 2 atmospheres pressure there was no significant change in heart rate and indeed, the mean value rose slightly. The cardiac index, however, showed a significant fall compared with the value obtained after atropine while breathing air ($P < 0.05$). The fall in cardiac index recorded five minutes after compression took place, without any decrease in heart rate. Although the further fall in cardiac index obtained 30 minutes later was accompanied

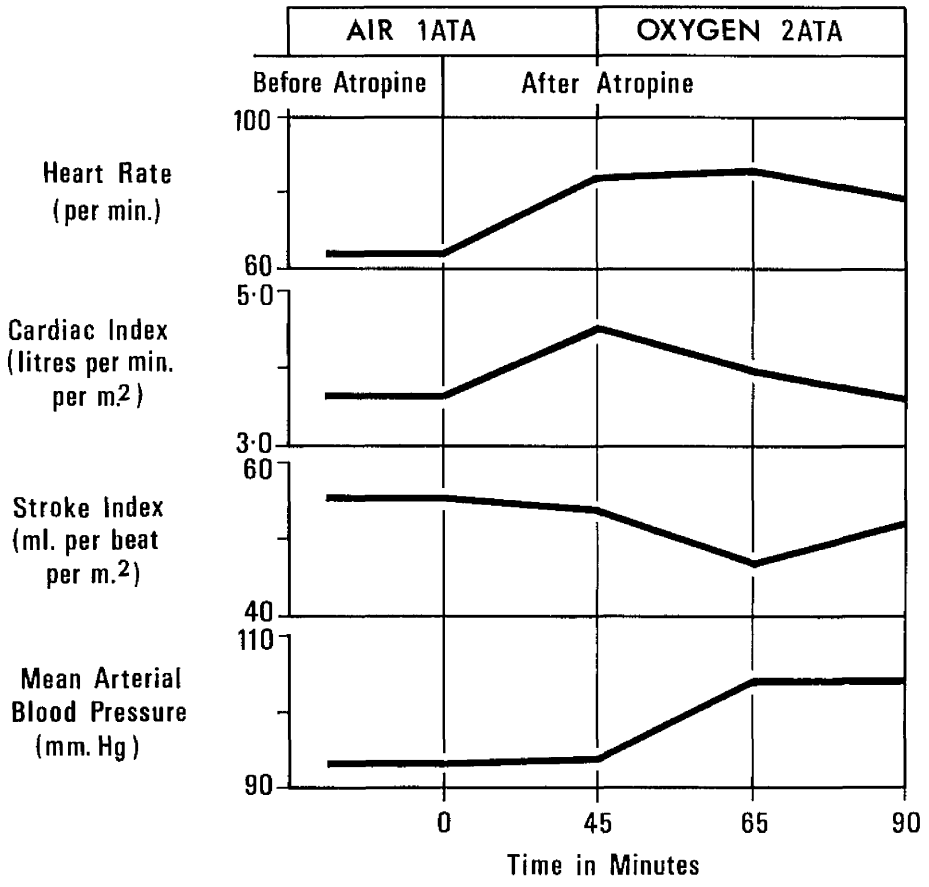


Fig. 2. Mean values for heart rate, cardiac index, storke index and mean arterial blood pressure in 7 healthy subjects breathing air at one atmosphere and 100 per cent oxygen at two atmospheres absolute pressure before and after administration of atropine.

by a small reduction in heart rate, the latter was still significantly higher than the rate before atropine was given ($P<0.02$). The mean value for cardiac index, on the other hand, was less than the pre-atropine value although the difference was not significant.

Consequently, the stroke index fell significantly when oxygen was breathed ($P<0.05$).

The systolic, diastolic and mean arterial blood pressure all rose significantly after oxygen ($P<0.05$) and there was an increase in the systemic vascular resistance.

Conclusions. These results indicate that the haemodynamic changes which accompany inhalation of high concentrations of oxygen are not entirely due to the fall in heart rate which occurs in healthy subjects. This is contrary to the findings of Daly and Bondurant (1962) who found that the haemodynamic effects of oxygen could be abolished by atropine. The explanation for this difference may be the fact that the present study utilised oxygen in higher concentration and at an increased ambient pressure, whereas earlier workers have studied the effects of oxygen at atmospheric pressure. A criticism of the present investigation might be that the dose of atropine was

small and was given by the intramuscular route rather than intravenously (Chamberlain, Turner and Sneddon, 1967). However, the object of this experiment was not to produce complete parasympathetic blockade but to reduce vagal tone sufficiently to secure a persistent increase in heart rate and it can be seen that this was indeed achieved. It has been shown, therefore, that inhalation of oxygen can produce a fall in stroke volume in healthy subjects and the resultant fall in cardiac output can be independent of a bradycardia induced by vagal action.

In addition to the changes in heart rate and cardiac output, the rise in arterial pressure and in systemic vascular resistance which is obtained in healthy subjects after inhalation of oxygen, was apparently accentuated by previous injection of atropine. Daly and Bondurant (1962) also observed that the blood pressure of atropinised subjects rose substantially during oxygen breathing. These findings support the concept of a direct effect of oxygen on the peripheral vasculature.

Section C. Haemodynamic effects of inhalation of oxygen at two atmospheres absolute pressure in subjects with fixed heart rate.

In order to study further the relationship between the haemodynamic effects produced by inhalation of oxygen and the heart rate the opportunity was taken to investigate the effects of oxygen inhalation in subjects who were being artificially paced for chronic complete heart block and in whom, therefore, the heart rate was maintained at a constant fixed rate.

Method. Five male patients with chronic complete heart block were studied. Four had a permanent fixed-rate endocardial pacemaker and generator implanted prior to the present investigation. The fifth was studied before implantation while he had a temporary transvenous endocardial pacing catheter in position; in this patient it was therefore possible to alter the heart rate at will, by changing the setting of the external pacing generator.

The patients were studied at rest breathing air and after inhalation of 100 per cent oxygen at two atmospheres absolute pressure in the hyperbaric chamber. Oxygen was administered via a close-fitting oro-nasal mask as previously described (Chapter II). In the fifth patient measurements were made breathing

air and oxygen at six different heart rates.

The heart rate was measured from the electrocardiogram which was monitored continuously. Using the Seldinger technique (Seldinger 1953), a fine polythene cannula was inserted percutaneously under local anaesthesia into a femoral or brachial artery for withdrawal of blood samples and estimation of arterial blood pressure. The latter was measured using strain-gauge transducers and a Devices recorder. The cardiac output was estimated using a dye dilution technique. A second fine polythene cannula was inserted percutaneously into an antecubital vein and advanced until the tip lay near the superior vena cava. Indocyanine green dye in an average dose of 5 mg. was injected from a calibrated syringe into the venous catheter and rapidly flushed in with saline. Arterial blood was then withdrawn via the arterial cannula through a Beckman cardio-densitometer, by means of a Harvard pump, at a rate of 39 ml. per minute and an indicator dilution curve obtained. Cardiac output measurements were made in duplicate and the mean of the results was taken.

The stroke volume and the systemic vascular resistance were calculated as previously described (Page 72). The results were analysed statistically

using Students paired t test (Fisher 1954).

Results. The heart rate was maintained constant for each set of measurements breathing air and oxygen at 2 atmospheres absolute pressure as described above. The detailed haemodynamic results are given in Tables 37 and 38 and the mean values for cardiac output, stroke volume, arterial blood pressure and systemic vascular resistance are illustrated in fig. 3.

The cardiac output fell in every instance when oxygen was inhaled and the fall in mean value was highly significant ($P < 0.001$). As a result, the stroke volume showed a significant mean fall ($P < 0.001$).

The systolic, diastolic and mean arterial blood pressure all rose significantly after oxygen ($P < 0.001$). The calculated systemic vascular resistance also increased in all cases when breathing oxygen ($P < 0.001$).

The initial arterial oxygen tension was within normal limits and rose by a factor of 12.9 when oxygen at two atmospheres pressure was inhaled.

Conclusions. These results indicate clearly that a fall in cardiac output may be obtained without a change in heart rate when oxygen is inhaled in high concentrations. It follows that the reduction

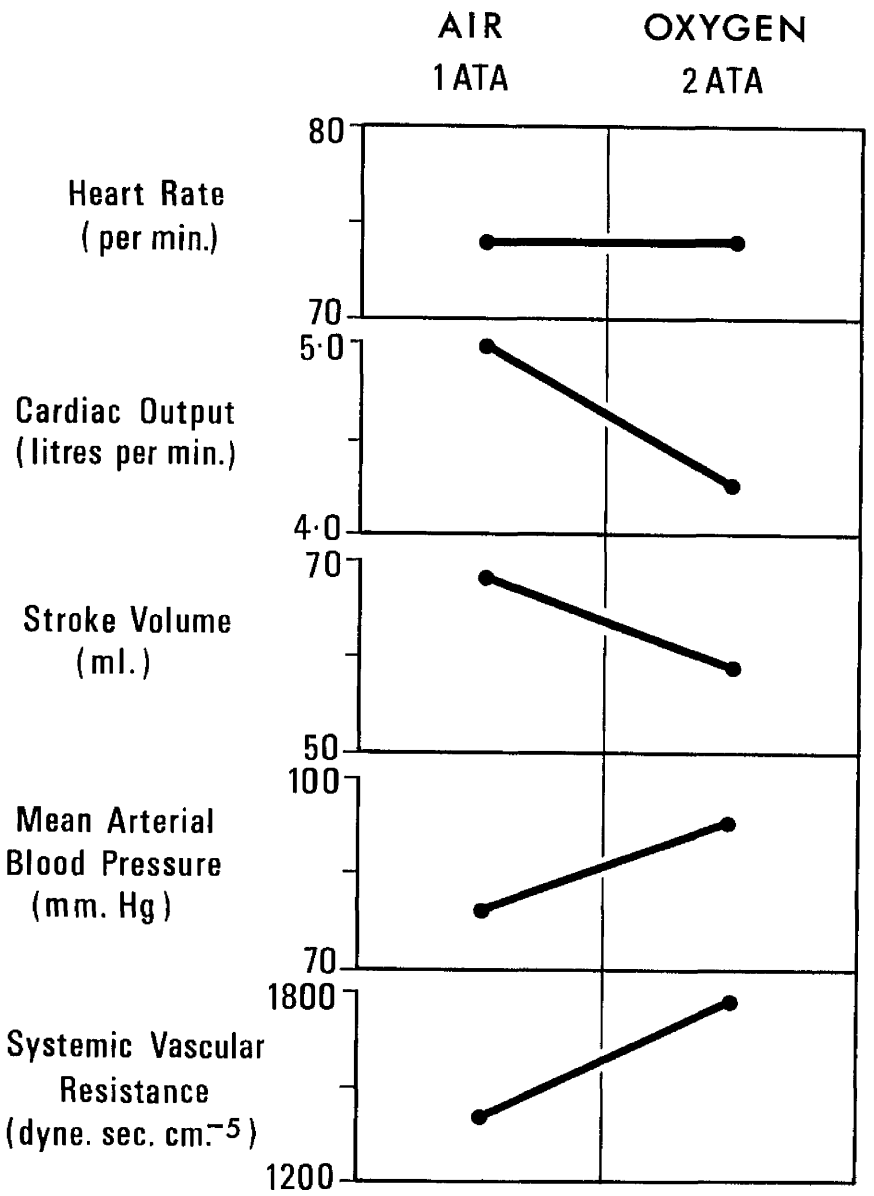


Fig. 3. Mean values for cardiac output, stroke volume, arterial blood pressure and systemic vascular resistance in 10 comparisons of subjects breathing air at one atmosphere and oxygen at two atmospheres while the heart rate was maintained constant by artifical pacing.

in cardiac output in these circumstances takes place by means of a decrease in stroke volume. It has been found moreover that maintenance of a fixed heart rate does not prevent the rise in arterial blood pressure and systemic vascular resistance which commonly occurs when oxygen is inhaled.

Discussion

Inhalation of oxygen by healthy subjects results in a slowing of the heart rate together with a fall in cardiac output (Chapter II). Earlier workers have shown that the bradycardia is normally dependent on vagal activity and can be eliminated by administration of atropine (Daly and Bondurant, 1962). It has also been found in animals, however, that slowing of the totally denervated heart can still take place with oxygen at increased pressure although the onset of the bradycardia is greatly delayed (Whitehorn and Bean, 1952). The experiments in this chapter have confirmed that the effect of oxygen on the heart rate of healthy subjects can be reversed or prevented by the use of atropine and this lends support to the concept that the slowing of the heart is normally due to vagal action.

Previous workers have also considered that the reduction in cardiac output which occurs on oxygen inhalation is secondary to the bradycardia (Daly and Bondurant, 1962, Whalen et al., 1965). It has, however, been shown in the present study that in patients with acute myocardial infarction, a fall in cardiac output can occur independently of changes in heart rate and a similar reduction in cardiac index

was noted in healthy subjects following heavy exercise without a corresponding bradycardia. The experiments in this chapter have confirmed these findings and have shown clearly that following inhalation of oxygen a reduction in cardiac output due to a fall in stroke volume can occur if the heart rate is held constant or if the slowing of the heart is prevented by the use of atropine. This means that while the normal mechanism for reduction of cardiac output in the presence of a raised arterial blood oxygen tension may well be by a reduction in heart rate it is not necessarily so. In this study a rise in arterial blood pressure and systemic vascular resistance was also a marked feature and it seems likely that a raised arterial oxygen tension has a direct or reflex action on the systemic circulation causing vasoconstriction. It is therefore possible that the fall in cardiac output is the result of reflex activity secondary to the changes in the peripheral vessels but a direct effect of oxygen on the myocardium itself is a possibility. Recent work has shown that hyperbaric oxygenation may result in a decrease of myocardial contractility (Kioschos et al., 1969) and it has been suggested that this is a manifestation of oxygen toxicity at a cellular level (Jacobs, Williams and

Schenk, 1970). These findings, however, refer to animals inhaling oxygen at 3 - 4 atmospheres absolute pressure. In the present study there was no evidence of oxygen toxicity and the pressure was not increased above 2 atmospheres: it seems unlikely, therefore, that the fall in cardiac output represents a toxic effect. It may nevertheless indicate that oxygen at high pressure has a negative inotropic effect and if so this could well be of importance in the treatment of patients with heart disease.

Overall, it seems likely that Dautrebande and Haldane (1921) were correct in their hypothesis that the changes in circulation produced by oxygen are a protective phenomenon. From the present study it appears that if slowing of the circulation is prevented in one manner, the body makes other adjustments to the circulatory system in order to maintain a constant internal environment. The mechanism by which these changes are brought about is complex but involves changes both in the working of the heart and in the peripheral circulation.

# CHAPTER V.

## Effects of Inhalation of Oxygen on Myocardial Blood Flow and Metabolism in Man.

In a previous chapter it was shown that the arterial oxygen tension is commonly reduced in patients with acute myocardial infarction. While inhalation of oxygen in high concentration usually results in the correction of the systemic arterial hypoxia, this does not necessarily mean that the supply of oxygen to the tissues is increased. Indeed there is some indirect evidence from metabolic studies to show that under certain circumstances the reverse may be the case. For example, in the investigations which have been performed on the effects of hyperbaric oxygen on patients with myocardial infarction a rise in arterial lactate frequently occurred with oxygen at two atmospheres suggesting that tissue oxygenation in general may have been adversely affected despite elevation of the arterial oxygen tension. Part of the rationale for the use of oxygen in myocardial infarction is the belief that the oxygen supply to the myocardium and in particular to the ischaemic zone round the infarct will be increased. Again, there is some indirect evidence which suggests that this may not occur. It has recently been shown in subjects with coronary artery disease that inhalation of 100 per cent oxygen results in abnormal lactate production by the myocardium in some cases suggesting paradoxically that increased tissue hypoxia has occurred with this treatment

(Bourassa et al., 1969). In another study of 19 patients with chronic ischaemic heart disease (Neill, 1969) it has been observed that inhalation of 100 per cent oxygen at atmospheric pressure did not cause a decrease in coronary venous lactate/pyruvate concentration ratio as would have been expected if the oxygen supply to the myocardium had increased. At the same time there was widening of the coronary arterio-venous oxygen difference and, if it is assumed that the myocardial oxygen consumption has not changed, this indicates a reduction of myocardial blood flow with oxygen. In view of these findings it was decided to investigate directly the effect of inhalation of oxygen on myocardial blood flow and metabolism in man in order to determine whether in fact myocardial oxygen availability and utilisation is increased thereby.

Patients and Methods

Ten patients with rheumatic or congenital heart disease who were being assessed for surgery were studied. The clinical findings are shown in Table 39. In five cases the cardiac rhythm was sinus and in the others, atrial fibrillation. Measurements were made with the patients breathing room air and then after inhalation of 100 per cent oxygen for 10 minutes through a scuba-type mouthpiece connected to a demand valve system.

A No. 7 Goodale-Lubin catheter was passed from a right arm vein into the coronary sinus. The tip of the catheter was placed in an intermediate site and the exact position confirmed by injection of a small amount of radio-opaque contrast medium through the catheter (fig. 1). Trans-septal cardiac catheterisation was then carried out via the right femoral vein using the Brockenbrough technique and the tip of the catheter was manipulated across the mitral valve into the left ventricle. Retrograde aortic catheterisation was performed percutaneously via the femoral artery with a Gensini catheter and the tip was positioned in the descending aorta (fig. 2).

The aortic pressure was measured using strain gauge transducers (Consolidated Electrodynamics) calibrated directly with a mercury manometer, and a

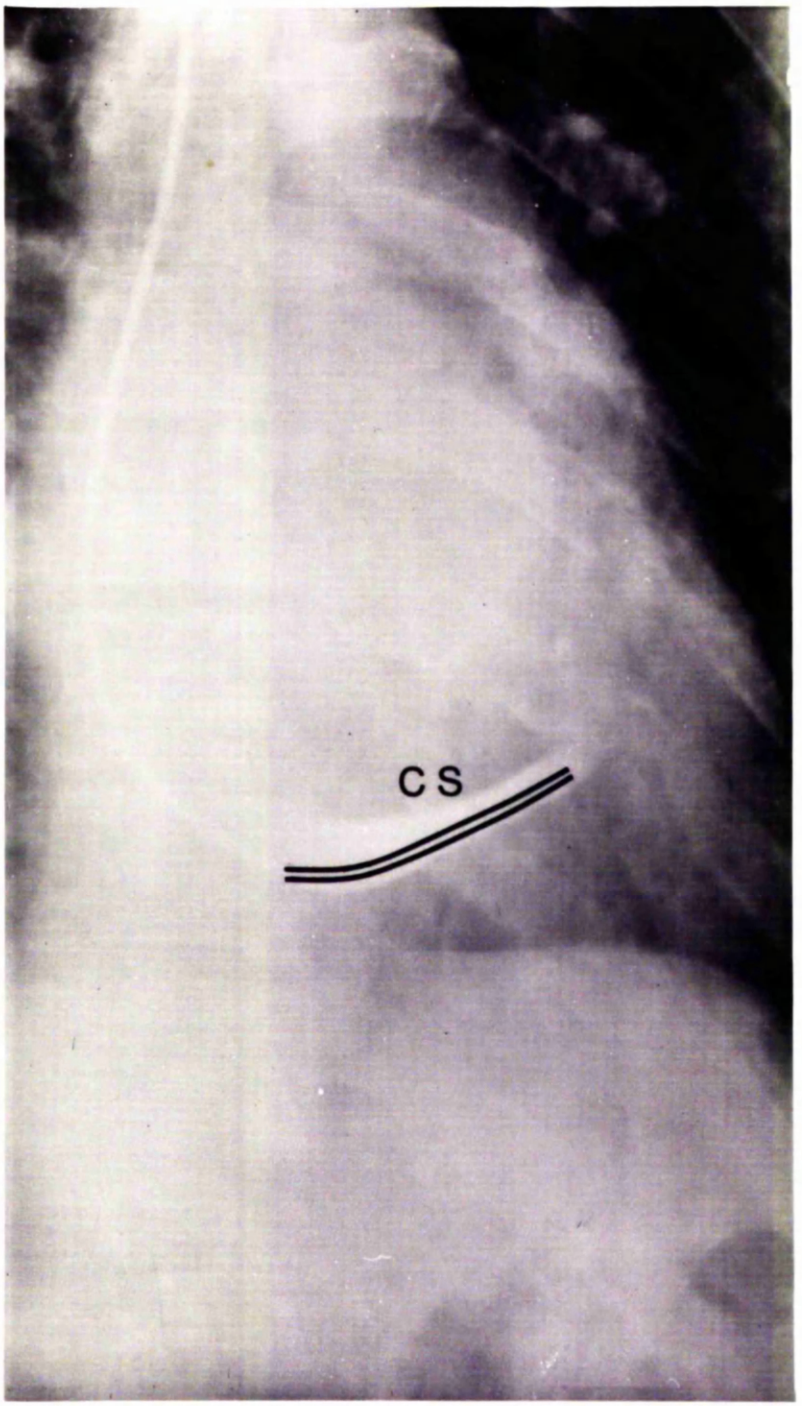


Fig. 1. A Goodale-Lubin catheter in the coronary sinus with the tip in the intermediate position which was used for sampling of blood. The coronary sinus has been opacified by the injection of a few mls. of contrast medium through the catheter.

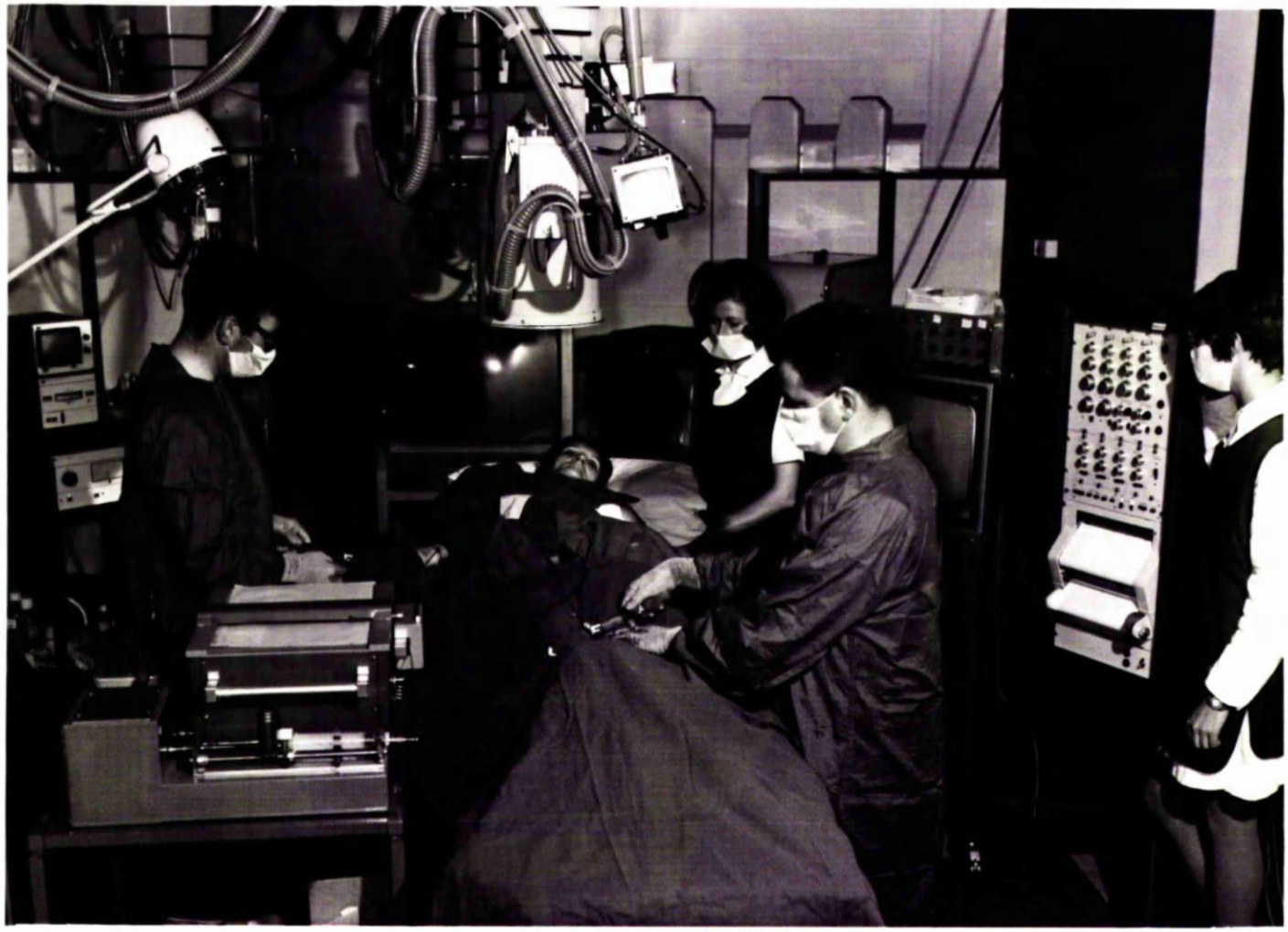

Fig. 2. Photograph of patient with cardiac catheters in position. The trans-septal and retrograde arterial catheters can be seen entering the right groin and the coronary sinus catheter is shown in the right antecubital fossa.

Devices recorder. The mean pressure was obtained by electronic integration. The heart rate was obtained from the electrocardiogram which was monitored continuously. Cardiac output was measured by the indicator dilution method using a Beckman Cardio-densitometer. Indocyanine green dye in an average dose of 5 mg. was injected into the left ventricle from a calibrated syringe and arterial blood was withdrawn from the descending aorta. Duplicate measurements were made at each stage and the mean of the results was taken.

Using a modification of the technique of Cohen, Elliott and Gorlin (1964) myocardial blood flow was measured by the rapid injection of 5 ml. of Xenon-133 solution through the trans-septal catheter into the left ventricle (fig. 3). The Xenon-133 solution was flushed in immediately with saline. Thereafter, six consecutive 5 ml. samples of arterial and coronary venous blood were withdrawn at 30 sec. intervals. The syringes were rapidly capped and were counted without further blood transfer in a fixed geometry over an end-window counter. A semilogarithmic plot of these activities with time was made. A typical graph is shown in fig. 4.

Samples of arterial and coronary venous blood were analysed for oxygen saturation. Aliquots of

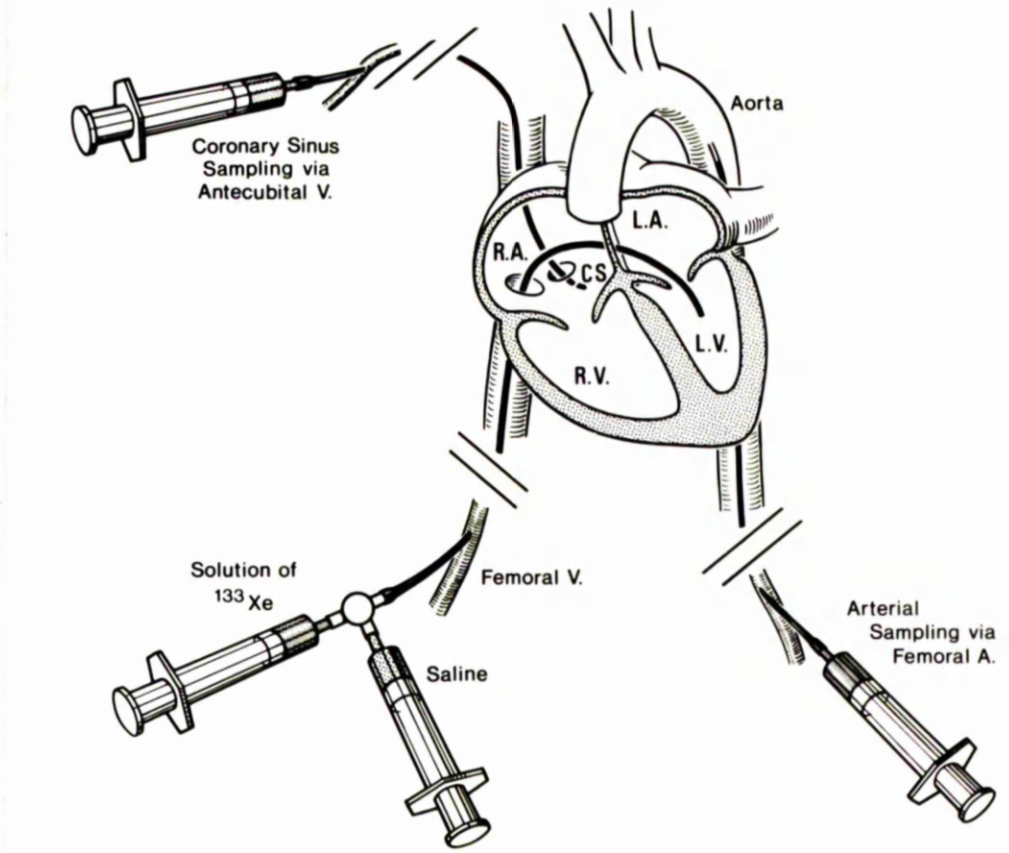


Fig. 3. Position of cardiac catheters for measurement of myocardial blood flow. Xenon-133 is injected through the trans-septal catheter into the left ventricle and flushed in rapidly with saline. Blood samples are then taken from the aorta and coronary sinus at intervals of 30 seconds for a period of 3 minutes.

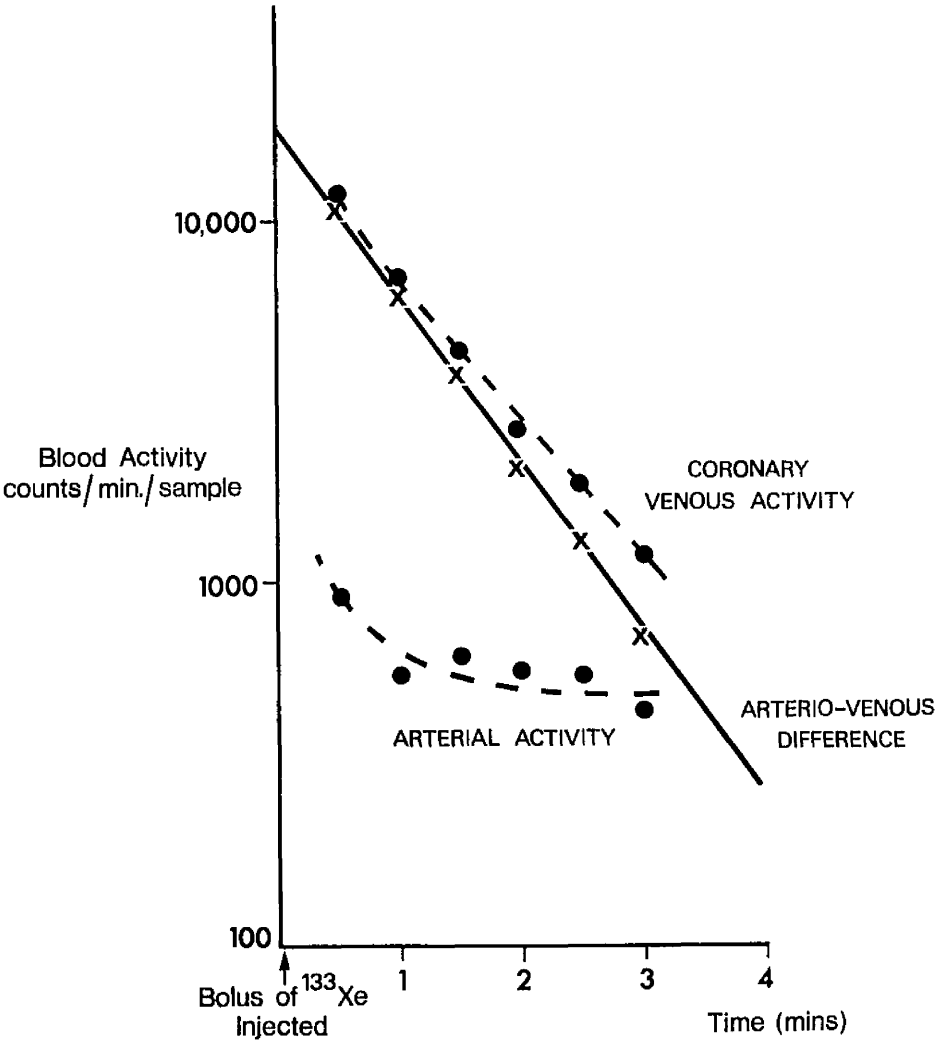


Fig. 4. A typical graph of the activities in arterial and coronary venous blood after injection of Xenon-133 into the left ventricle. Note exponential decrease in coronary venous activity with practically constant recirculating arterial activity.

arterial and coronary venous blood were also taken for estimation of lactate and pyruvate levels. The blood was withdrawn rapidly and immediately mixed with ice-cold 10 per cent perchloric acid. The levels were then estimated by Boehringer enzymatic methods.

The following calculations were carried out on data obtained. Cardiac output was derived from the indicator dilution curves using the manual semilogarithmic replot technique and the conventional formula. The systemic vascular resistance was calculated from the formula:

$$\text{Systemic vascular resistance (dynes sec. cm}^{-5}) = \frac{\text{mean arterial pressure (mm.Hg)} \times 80}{\text{cardiac output (litres/min.)}}$$

Left ventricular work was determined from the formula:

$$\text{Left ventricular work (kg. m/min.)} = \frac{13.6 \times \text{mean arterial pressure (mm.Hg)} \times \text{cardiac output (litres/min.)}}{1{,}000}$$

The measurement of blood flow using radioactive inert gases has been considered theoretically by several workers (Lassen, 1967). They have shown that blood flow, f, is given by:

$$f = \frac{100\ k\lambda}{\rho}\ \text{ml./100g/min.}$$

where k is the exponential decay constant of the

venous blood activity; $\rho$ is the density of the myocardium (1.05); and $\lambda$ is the partition coefficient of Xenon-133 between blood and myocardium (0.72) (Conn, 1961). This expression is strictly only valid when the venous activity decreases monoexponentially over its early stages and the recirculating arterial activity remains constant. The results indicated that these conditions were met experimentally.

Blood oxygen content was derived from the formu

oxygen content (vols.%) = oxygen capacity (vols.%) x % saturation of Hb. + $PO_2$ x 0.0031

where oxygen capacity (vols.%) = Hb. content (g./100 ml.) x 1.34

$PO_2$ = blood oxygen tension (mm.Hg)

0.0031 = ml. of oxygen physically dissolved in 100 ml. blood per mm.Hg partial pressure of oxygen.

Blood oxygen tensions were not measured in this study, but the factor ($PO_2$ x 0.0031) is negligible while breathing air. When 100 per cent oxygen was inhaled an arterial oxygen tension of 600 mm.Hg was assumed. This value is near the theoretical maximum and was probably not achieved in most patients, but it was chosen in order to prevent underestimation of the arterial oxygen content when oxygen was inhaled.

The myocardial oxygen uptake (ml./100g./min.) was calculated from the product of myocardial blood flow (ml./100g./min.) and the coronary arterio-venous oxygen content difference (vols.%). Myocardial oxygen availability (ml./100g./min.) was obtained from the product of arterial oxygen content and the myocardial blood flow. The myocardial lactate extraction ratio was expressed as a percentage of the coronary arterio-venous difference of lactate divided by the arterial concentration. In normal subjects this ratio is usually between 20% and 50%, and a value below 10% is considered indicative of myocardial ischaemia (Herman, Elliott and Gorlin, 1967).

The results were examined statistically using the Wilcoxon test for paired differences (Forrester and Ury, 1969).

Results

The detailed haemodynamic findings and the mean values while breathing air and oxygen are given in Tables 40 and 41 and the values for arterial and coronary venous oxygen saturation and content along with the calculated myocardial oxygen uptake are shown in Tables 42 and 43. Arterial and coronary venous blood lactate and pyruvate levels, myocardial lactate extraction ratios and coronary venous lactate/pyruvate ratios are shown in Tables 44 and 45.

Haemodynamic Findings

After administration of oxygen there was a significant fall in heart rate averaging 7 beats per minute ($P < 0.025$). At the same time, the cardiac output fell slightly and the stroke volume rose, but these changes were not significant. There was a significant increase in systolic blood pressure ($P < 0.025$) and in diastolic blood pressure ($P < 0.025$) but the mean arterial pressure did not rise significantly. The systemic vascular resistance increased ($P < 0.05$) but the calculated left ventricular work was unchanged.

Myocardial Blood Flow

After oxygen there was a fall in myocardial blood flow in seven patients, a very small rise in one patient and no change in two patients (fig. 5). The mean value for all ten patients showed a significant fall ($P < 0.01$) averaging 12.7% although in some cases the reduction was as much as 33%.

Metabolic Results

Both the arterial and the coronary venous blood oxygen content rose significantly ($P < 0.005$) following inhalation of oxygen. The increase was greater in the arterial blood than in the coronary venous blood and thus the arterio-venous oxygen difference rose ($P < 0.005$). Nevertheless, the calculated

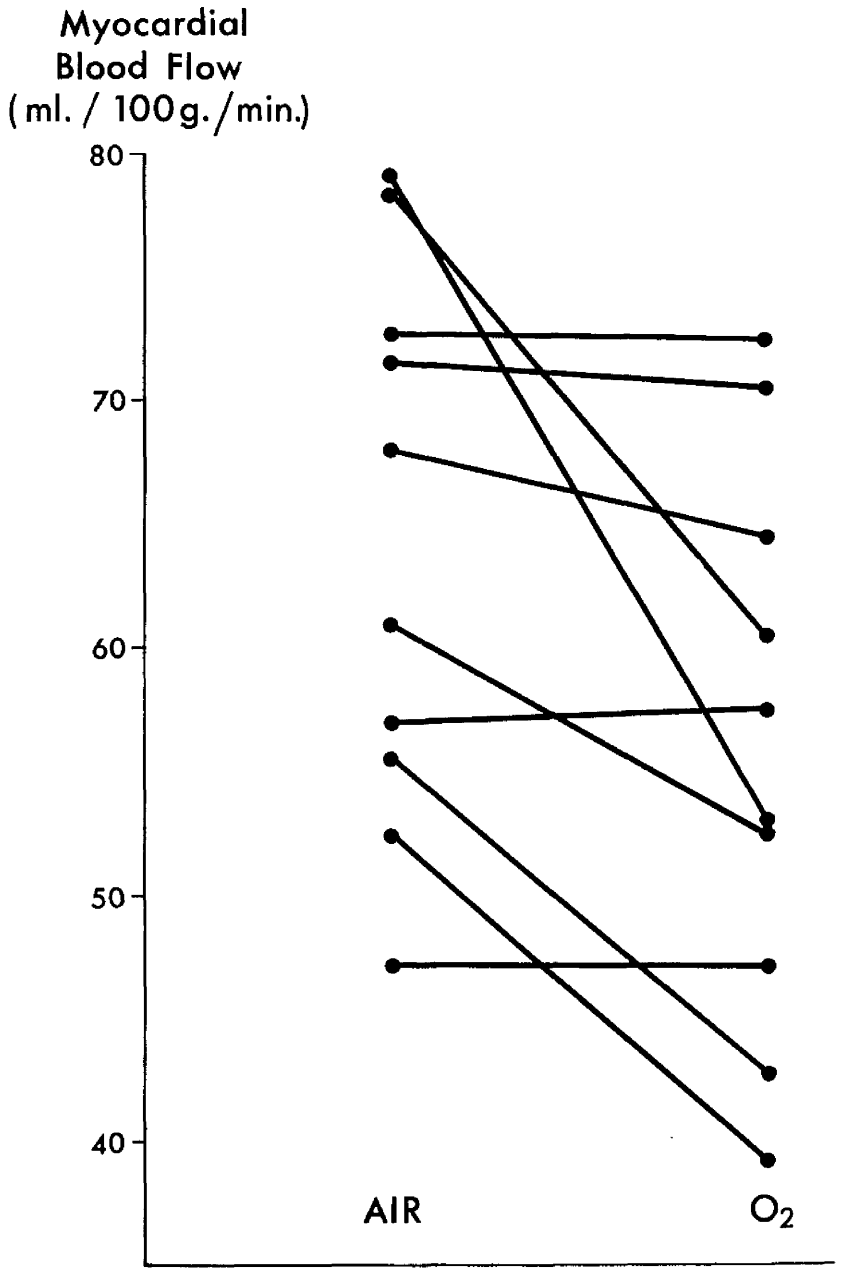


Fig. 5. Values for myocardial blood flow in 10 patients while breathing air and after inhalation of 100 per cent oxygen.

myocardial oxygen uptake showed no significant change and the myocardial oxygen availability was not increased.

Arterial blood lactate was within normal limits (normal value $<1.776$ m.-moles per litre) in all patients while breathing air and the mean value fell after oxygen ($P<0.025$). The coronary arterio-venous lactate difference fell ($P<0.01$) but the myocardial lactate extraction ratio showed no significant change. Moreover there were no significant changes in pyruvate levels or in lactate/pyruvate ratios.

Discussion

The effects of inhalation of oxygen in healthy subjects was described in Chapter II. It was shown that a fall in heart rate occurs with no appreciable change in arterial pressure and stroke volume. On the other hand, when oxygen is given to patients with myocardial infarction (Chapter III) there is little effect on the heart rate although there is still a fall in the cardiac output and in addition a rise in arterial pressure and systemic vascular resistance. These changes become progressively more marked as the oxygen tension is increased. Theoretically, coronary perfusion should not be greatly altered because the rise in arterial pressure should compensate to some extent for the fall in cardiac output. In the present investigation the outstanding finding was a significant reduction in myocardial blood flow and since there was no obvious correlation with the other haemodynamic findings it is unlikely that this is a secondary effect. It follows, therefore, that it must be due directly or indirectly to changes in coronary vascular resistance. It has previously been shown in man that inhalation of high concentrations of oxygen causes vasoconstriction in various regions. Behnke et al., (1936) noted

constriction of the visual fields after inhalation of oxygen at three atmospheres absolute pressure suggestive of retinal ischaemia and constriction of the small arterioles of the retina with oxygen at two atmospheres pressure has been observed (Dollery et al., 1964). A reduction of cerebral blood flow accompanied by an increased vascular resistance indicative of cerebral vasoconstriction has been found following inhalation of oxygen in concentrations of 85 - 100% at atmospheric pressure in healthy young men (Kety and Schmidt, 1948). A decrease in renal blood flow which was greater than the fall in cardiac output has also been observed after oxygen and this demonstrates that vasoconstriction occurs in the kidney in these circumstances (Aber, Harris and Bishop, 1964). There is also some experimental animal evidence that the coronary arteries may be similarly affected. Thus Eckenhoff, Hafkenschiel and Landmesser (1947), using a bubble-flow meter in open-chest dogs was the first to demonstrate that coronary arterial blood flow was consistently reduced after inhalation of 100 per cent oxygen without any significant change in blood pressure or heart rate. Confirmation of these results in open-chest dogs was carried out by

Sobol et al., (1962) who found that the reduction in myocardial blood flow produced by inhalation of 100 per cent oxygen resulted in a small though not significant decrease in oxygen transport to the myocardium. The effects of oxygen at increased pressure on myocardial blood flow has also been investigated in open-chest dogs by measurement of coronary sinus blood flow (Meijne and Straub, 1966) and by the myocardial clearance rate of directly injected Xenon-133 (Weglicki et al., 1969). Experiments have also been performed without thoracotomy in dogs at three atmospheres absolute pressure (McBride, Vance and Ledingham, 1969). These studies have all shown a reduction in myocardial blood flow with oxygen at increased pressure and in two studies a reduction in oxygen uptake was also found (Weglicki et al., 1969, McBride et al., 1969). It is thought that the reduction in oxygen uptake is largely secondary to changes in blood flow rather than to changes in myocardial metabolism.

The mechanism by which these changes in regional blood flow take place is not finally determined. However, as reduction in flow to various organs is often out of proportion to the overall reduction in cardiac output it is likely that the changes arise

from a direct effect of oxygen on arterioles. This concept is supported by investigations (Carrier, Walker and Guyton, 1964) which have shown that in isolated arterial segments from the dog, a decrease in vascular resistance always occurred when the oxygen tension of the perfusate was lowered and an increase when it was raised. It is suggested, therefore, that oxygen plays an important role in the autoregulation of blood flow. The results of the present study indicate that similar changes may occur in the coronary arteries in man and therefore arterial oxygen tension may be an important factor in determining the state of the coronary circulation. If this is so, hypoxaemia should result in coronary vasodilation, (and such vasodilation was indeed found to occur by Eckenhoff et al., (1947) in dogs duration inhalation of 10 per cent oxygen), but elevation of the arterial oxygen tension to normal or above will be followed by vasoconstriction.

Following the inhalation of oxygen there is a rise in arterial oxygen content which is due to further saturation of haemoglobin and a slight increase in the amount of oxygen in simple solution in the plasma. The latter becomes important only

when high concentrations of oxygen are inhaled at normal or increased ambient pressures. It has been shown in this study that along with the rise in arterial oxygen content, the coronary venous oxygen content is also increased but to a lesser degree. This explains the increased coronary arterio-venous oxygen difference shown in these results, which is, of course, consistent with a reduction in myocardial blood flow. As a result of diminished coronary blood flow the calculated myocardial oxygen uptake is virtually unchanged. Furthermore, the increased arterial oxygen content is counterbalanced by the reduction in flow so that there is no increase in myocardial oxygen availability.

In this study an attempt has also been made to assess some of the metabolic effects of oxygen inhalation on the heart. It has been shown that inhalation of oxygen causes a fall in arterial blood lactate. This is in accord with the previous findings in patients with myocardial infarction (Chapter III) and with the findings of Meijne and Straub (1966) in dogs. On the other hand the coronary venous lactate level showed little change and the arterio-venous lactate difference therefore showed a significant fall. It is known, however, that myocardial lactate

utilisation is directly related to the arterial blood lactate level (Krasnow et al., 1962). In the patients studied in the present work, the myocardial lactate extraction ratio was not significantly altered and it is likely that the decreased arterio-venous difference was largely, if not entirely, accounted for by the fall in arterial blood lactate. Nevertheless, it is of interest that although there was no overall change in the lactate extraction ratio after oxygen, it was increased in those cases where the initial value was low (Patients No. 2, 5, 6, 8) and in fact reached a normal level in three instances. There were no significant changes in arterial or coronary venous pyruvate levels or in coronary venous lactate/pyruvate ratio. No evidence has, therefore, been found to suggest that myocardial lactate metabolism was consistently altered by inhalation of oxygen.

The results obtained seem to indicate that giving oxygen to patients does not necessarily result in an increased oxygen supply to the myocardium. Myocardial oxygen availability depends not only on the coronary blood flow but also on the oxygen content of the perfusing blood. In the patients in this study it has been shown that an increase in arterial oxygen content is counterbalanced by a reduced myocardial blood

flow and there is no net gain in oxygen supply to the heart muscle. It seems likely, therefore, that a homeostatic mechanism is in force which maintains a near-constant oxygen transport to the myocardium, and this investigation once more lends support to the hypothesis postulated many years ago by Dautrebande and Haldane (1921).

# CHAPTER Vl

## Hazards of Oxygen Therapy

Oxygen therapy involves many potential hazards expecially when it is employed at increased ambient pressures. A consideration of these risks is necessary in any appraisal of its therapeutic effects.

While oxygen is essential for the continuance of life, it is also highly toxic if breathed at very high pressures. This effect is known as oxygen poisoning and may be encountered in two classical syndromes, namely, (1) neurological disturbances culminating in sudden convulsions, and (2) lung damage of more gradual onset leading to respiratory failure.

Knowledge that oxygen at high pressure is highly poisonous dates from the experiments of Paul Bert (1878). He demonstrated that birds exposed to air at 15 to 20 atmospheres pressure convulsed and finally died. Bert also discovered that the important factor was the partial pressure of oxygen in the inspired air and not the overall atmospheric pressure to which the animals were exposed. The use of high pressure atmospheres in the construction of tunnels and in underwater diving during peace and war stimulated further investigation of the toxic effects of oxygen, and a large background of experience has accumulated. Thomson (1935) reported that two naval officers both experienced twitching of the facial muscles while breathing oxygen at 3

atmospheres after exposures of only 13 and 16 minutes. In one the convulsion ceased on changing to air while still at increased pressure, but in the other the convulsion progressed into clonic spasms with loss of consciousness despite changing to air breathing. Behnke et al., (1935) reported that convulsions or syncope occurred in both their subjects who were exposed to oxygen at 4 atmospheres pressure, after about 45 minutes, but that inhalation of oxygen at 1 to 3 atmospheres for periods up to three hours was without serious neuromuscular effects in healthy subjects. Haldane (1941) also reported the sudden onset of convulsions after exposure to oxygen at 7 atmospheres for less than 5 minutes. Donald (1947) showed that the changes of oxygen poisoning were much greater than had been supposed and that the susceptibility to the symptoms of poisoning was greatly increased in subjects breathing oxygen under water. He demonstrated that pure oxygen was unsafe at as low a pressure as two atmospheres absolute in these circumstances and convulsions occurred in two of his subjects within two hours. In a recent report (Whalen et al., 1965) it has been shown that oxygen toxicity can also occur above water at lower pressures than was previously considered likely (Behnke et al., 1935). In Whalen's

study 10 healthy subjects were exposed to 100 per cent oxygen at 3.04 atmospheres pressure and two of these developed signs of oxygen toxicity, in one case progressing to a grand mal attack. As far as can be ascertained, however, there are no reports of oxygen toxicity occurring at or below 2 atmospheres absolute pressure except in Donald's underwater experiments.

The cause of the neuromuscular effects of oxygen poisoning remains obscure, although several possibilities exist. Thus oxygen convulsions may be due to a direct toxic action of high oxygen tensions on the tissues of the central nervous system, and it has been demonstrated that depression of respiration of tissue-slices of rat brain rapidly occurs after exposure to high oxygen tensions, (Dickens, 1946). Alternatively poisoning of the central nervous system could be due to an accummulation of carbon dioxide in the cells as a result of the breakdown of the normal transport function of haemoglobin, the venous blood being "over-loaded" with oxygen in these circumstances. However, it is difficult to see how this could account for oxygen poisoning at two to three atmospheres pressure, as in these circumstances the venous blood is not saturated and is therefore still capable of removal

of carbon dioxide. This problem was investigated by Lambertson et al., (1953) who found that significant accumulation of carbon dioxide in the brain did not occur during inhalation of oxygen at 1 or 3.5 atmospheres absolute pressure. The third possibility is that the symptoms of oxygen poisoning may be secondary to changes in cerebral blood flow. There is considerable evidence that oxygen at increased pressures causes peripheral vasoconstriction and a rise in arterial pressure is frequently noted just before the onset of symptoms of oxygen poisoning (Behnke et al., 1936, Donald, 1947) which would be in keeping with such a mechanism. However Lambertson et al., 1953 demonstrated that while cerebral vasoconstriction with a reduction in cerebral blood flow of the order of 25 per cent occurred with oxygen at 3.5 atmospheres pressure, this was not sufficient to account for oxygen poisoning in man.

The general conclusion is that a direct toxic effect of oxygen on nerve cells remains the most likely explanation of the neurological effects of oxygen, but as yet there is no direct evidence to support this concept in man.

While the occurrence of oxygen convulsions is very grave in the situation of deep sea diving, most of the reports stress the complete recovery which takes

place following the return to a normal atmosphere. Moreover, as has been discussed, oxygen convulsions appear to occur only at pressures in excess of 2 atmospheres absolute. For these reasons, while it is obviously essential to consider the possibility of this complication and take steps to prevent its occurrence, this form of poisoning is unlikely to present a serious hazard to patients undergoing treatment with oxygen unless the ambient pressure is greatly increased.

On the other hand, the occurrence of lung damage following inhalation of oxygen could present a greater threat to the patient especially as this manifestation of oxygen toxicity may be more insidious in onset and could well masquerade as part of the illness for which treatment is being given. Lorrain-Smith (1899) was the first to demonstrate that damage to the lungs of animals took place after breathing oxygen at high pressure over prolonged periods and resulted in respiratory failure. Congestion of the alveolar capillaries together with haemorrhagic exudation and consolidation were found by Bean (1929) in dogs after prolonged exposure to oxygen at 3 to 5 atmospheres pressure. Behnke et al., (1934) observed pulmonary congestion and atelectasis in anaesthetised dogs following oxygen at increased pressure, but no evidence of exudation. In view of these animal

studies it is surprising that evidence for the "Lorrain-Smith effect" in man is remarkably sparse. Some of the subjects of Behnke et al., (1935) complained of substernal pain and a dry cough on inhalation of oxygen but there is little other reference to pulmonary complications in man. However, in a recent study (Nash 1967) pulmonary congestion, alveolar oedema, intra-alveolar haemorrhages and fibroblastic proliferation were noted in the lungs of patients who had received prolonged artifical ventilation with 90 per cent oxygen. These effects were ascribed to the high concentration of oxygen used in treatment, but the evidence for this is not certain. Changes in pulmonary function have also been recorded and it has been shown that exposure to 98 per cent oxygen at atmospheric pressure for 2 to 3 days resulted in a decrease of vital capacity and pulmonary diffusing capacity (Caldwell et al., 1966). Several investigations have indicated that oxygen inhalation may reduce the flow of mucus and act on the pulmonary surfactant (Laurenzi, Yin, and Guarneri, 1968; Giammona, Kerner and Bondurant, 1965). It seems likely that oxygen inhalation at high pressures does result in some pulmonary changes although the clinical importance of these is doubtful, and man appears more resistant than animals to these

complications.

In the present investigation there was no evidence of oxygen poisoning of the central nervous system or of the lungs in any of the healthy subjects or in the patients with myocardial infarction. The healthy subjects breathed 100 per cent oxygen for at least 90 minutes and for half this time at a pressure of two atmospheres absolute, with arterial blood oxygen tensions often in excess of 1,000 mm.Hg. The patients with myocardial infarction were exposed to oxygen at two atmospheres pressure for periods of 2 hours or more and at one atmosphere for a further 48 hours, although the level of arterial oxygen tension was considerably lower than in the healthy subjects. A similar absence of signs of oxygen poisoning has been found in patients with myocardial infarction exposed to hyperbaric oxygen at 2 atmospheres absolute for intermittent 2 hour sessions over a period of four days (Ashfield & Gavey, 1969). It seems fairly certain, therefore, that the administration of 100 per cent oxygen at a pressure of two atmospheres absolute for periods of several hours is a tolerably safe procedure, although, of course, it would be unwise to discount altogether the existence of individual susceptibility which might only become evident with longer exposures.

There are, however, other hazards in the use of oxygen therapy although many of these can be avoided by careful management. For example, oxygen from a hospital pipe-line is free of moisture and it is important that adequate humidification of the gas is carried out before it is inhaled by the patient. If this is not done there will be resultant irritation and disturbance of ciliary action leading to an increased risk of lung infections (Sara, 1965). In the present investigation a special humidifier was used throughout in order to lessen this problem.

The use of ambient pressures greater than atmospheric also involves risks not only to the patient but to the medical and nursing staff. It is well known that workers exposed to increased pressure are liable to develop symptoms of "decompression sickness" on returning to atmospheric pressure. Symptoms of this condition vary from a transient joint pain to an irreversible paraplegia. In most cases the symptoms are due to the release of bubbles of dissolved nitrogen in the blood and tissues. The nitrogen, which is held in solution at the higher pressure, is freed by the lowering of pressure and symptoms are caused by the production of bubbles which block small blood vessels or expand

within tissues. Inhalation of 100 per cent oxygen largely removes nitrogen from the body and renders decompression illness very unlikely as bubbles of oxygen diffuse more rapidly and moreover enter into chemical combination in the tissues more easily. For this reason the patient undergoing hyperbaric oxygen therapy is largely protected from the dangers of decompression illness and it is the attendant personnel who are mainly at risk as they continue to inhale air at increased pressure. While this hazard usually occurs following exposure to pressures greater than two atmospheres, great care was taken in this study to conform to standard rates of decompression. No symptoms of decompression illness were noted in patients, healthy subjects or staff throughout this investigation. A long-term risk of work at increased pressure is the subsequent development of avascular necrosis of bone which may later develop insidiously without initial symptoms of decompression sickness. This condition has not been encountered in this investigation.

A further problem of the use of oxygen, especially at high pressures, is the greatly increased fire risk. In the present study the risk was minimal as air was used for compression. The risk rises steeply when oxygen is used as the compressing gas

as in single-man pressure chambers. In such an environment even the static electricity produced by movement of clothing material can induce fire which, of course, then spreads with fearful rapidity. Strict precautions are therefore necessary in these circumstances and it is this danger which argues most strongly against using oxygen as the compressing gas.

A relatively minor complication of the use of increased atmospheric pressure is the difficulties which may occur due to pressure inequalities in the para-nasal sinuses. Several of the patients and healthy subjects experienced pain in the ears and nasal sinuses during compression of the chamber. The symptoms were readily relieved by temporarily stopping compression and resuming again slowly once the pain had cleared. In no case were the symptoms severe enough to prevent the investigation being continued and there were no after-effects.

In summary, therefore, no morbidity was found in relation to the use of oxygen in the present investigation. Throughout the work the risks were fully appreciated and great care was exercised in the various aspects of safety in order to prevent harm to patients or attendants. While most forms of medical treatment are associated with side-effects which may be detrimental to the patient the potential

hazards of oxygen therapy are particularly numerous. It is therefore important that the indications for this treatment should be well defined and that benefit should be apparent prior to the routine administration of oxygen especially at pressures above one atmosphere.

# CHAPTER V11

## Conclusions concerning the indications for oxygen therapy in cardiac disease.

In these investigations it has been shown that variation of the tension of oxygen in the inspired air results in important and complex changes in the circulation in both healthy subjects and patients with cardiac lesions. Some of these effects may be beneficial while others could well be disadvantageous or even dangerous to the patient. The overall assessment of the value of such treatment is therefore very difficult. At first sight the best approach to solve this problem would be a controlled trial of the effects of oxygen on mortality in patients with myocardial infarction. On closer examination, however, such a project is fraught with many difficulties and pitfalls. In the first place, from the information which is already available (Cameron et al., 1965) it is apparent that the use of oxygen in myocardial infarction does not markedly affect the course of the disease in most patients. In consequence in order to obtain evidence of a beneficial effect if it exists, a very large number of patients would have to be studied with an equally large control group. One is then immediately confronted with all the perplexities of a controlled trial in patients with myocardial infarction, as occurred following the introduction of anticoagulant therapy, when widely divergent results were obtained from different centres (Report of

the Working Party on anticoagulant therapy, 1969). Many of the obstacles arise from the nature of the condition itself, which can vary widely in severity and course of illness. Strict criteria must therefore be followed in selection and assessment of patients and there is much difficulty in obtaining a well-matched control group, which is essential if a true comparison of different therapeutic regimes is to be undertaken. The amount of oxygen received by the patient is also hard to control and variability of results could well stem from this factor in the same way that different levels of anticoagulant dosage have caused so much controvery. At the present time, moreover, the optimal concentration of oxygen is still unknown and a trial would have to consider the effects of different oxygen concentrations. All in all, therefore, while a satisfactory controlled trial of oxygen therapy is obviously desirable, it would require to be carried out on a large-scale basis, possibly in several centres, and it was considered impractical during the present investigation due to the large number of patients required. It was therefore rendered necessary to approach the problem by a study of the objective effects of oxygen in order to deduce from these results whether or not the use of oxygen was

rational and likely to be of benefit to patients with cardiac disease.

In adopting this approach the physiological effects of oxygen in healthy subjects were first considered. It might be supposed that by increasing the oxygen in the air breathed and thus the oxygen content of the arterial blood that the work of the respiratory and circulatory systems would be reduced and the capacity for muscular exercise increased. This was indeed the view of the early physiological workers in this field (Hill et al., 1908) who attempted to improve the performance of athletes by inhalation of oxygen. An increase in the inspired oxygen content, however, represents a change in the external environment which is resisted by the organism in order to maintain a constant internal environment. Moreover, it has been shown that oxygen at increased pressures may be toxic and this is an added reason for protective mechanisms to be brought into play. This point was propounded many years previously by Claude Bernard (1878) in his book *"Lecons sur les Phénomènes de la Vie"* which was published shortly after his death. In this work he states: *"Il faut de plus que cet oxygène soit dans des proportions fixées jusqu'à un certain point dans le milieu intérieur: une quantité trop faible, une*

*quantité trop forte, sont également incompatibles avec le fonctionnement vital".*

It has been shown in this study that as a result of the physiological responses to the inhalation of oxygen there is a reduction in the heart rate and cardiac output and a rise in systemic vascular resistance with little or no change in arterial pressure. In effect, therefore, the physiological changes are directed towards a maintenance of the status quo as far as the delivery of oxygen to the tissues is concerned. Thus, although the oxygen content of the arterial blood is increased there is a reduction in blood flow accompanied by vasoconstriction both of which will tend to decrease the amount of oxygen transported to the tissues in unit time. This mechanism will moreover tend to reduce the possibility of a toxic action on the tissues. Even following inhalation of oxygen at increased pressures, the venous blood returning from the brain is not fully oxygenated and this means that the above mechanisms reduces blood flow sufficiently to prevent a very marked rise in oxygen tension at the cellular level (Lambertson 1953). Support to these arguments is given by finding that the overall oxygen consumption of the body is unchanged at increased pressures of oxygen (Telfer and Jennett, 1965). It is also known that the storage

capacity of the body for oxygen is relatively sm (Harris, 1969) and administration of oxygen will result in only a minor increase in total body oxygen content. While a small reduction in left ventricular work was found during oxygen inhalation, the above factors mean that any "beneficial" effect in healthy subjects must be small as the homeostatic mechanisms come into play and prevent as far as possible an increase of oxygen transport to the tissues.

In pathological conditions, however, the position may well be altered. In the presence of a low arterial blood oxygen tension homeostatic mechanisms also come into operation in this case in an attempt to increase the oxygen supply to the tissues. Some of these changes, for example the tachycardia which is produced, may well be undesirable in the presence of a cardiac lesion such as myocardial infarction. Administration of oxygen in these circumstances might be expected to restore a degree of normality to the situation and thus relieve the load on the heart. It has been shown in this study that it is indeed possible in most cases to raise the arterial oxygen tension to normal limits in patients with myocardial infarction. Although the oxygen tension achieved often falls short of the theoretically expected figure the

increase is sufficient to bring about full saturation of the arterial haemoglobin. This is accompanied by a rise in arterial pressure without a significant increase in left ventricular work. Such an effect must usually be advantageous as many of these patients are initially hypotensive and restoration of the arterial pressure should increase tissue perfusion. Support for this concept is found in the lowering of arterial blood lactate level which follows treatment with oxygen at atmospheric pressure.

On the other hand several changes are produced by oxygen therapy which appear undesirable. Thus cardiac output is decreased in most patients often in the presence of an already reduced cardiac output. At first sight this seems undesirable, but it can be argued that if the cardiac output can be decreased and at the same time an adequate oxygen delivery to the tissues is maintained, this is indeed of benefit as the pumping activity of the heart is thereby diminished. Similarly a rise in systemic vascular resistance could be interpreted as a contraindication to the use of oxygen. However it should be remembered that in many patients with myocardial infarction the vascular resistance is below normal limits and a rise represents a return towards normal conditions. As long as the rise in vascular resistance does not

increase the work of the heart it should not be deleterious.

In patients with myocardial infarction one of the main reasons for using oxygen apart from improving the oxygenation of the body generally, is to attempt to relieve the hypoxia in the ischaemic zone round the infarct. It is obviously important moreover that the blood supply to the heart should be maintained and if possible improved. It has been suggested (Chapter III) that the blood flow in the coronary arteries is largely pressure dependent in these circumstances and therefore the rise in arterial pressure following the use of oxygen should result in an improved myocardial blood flow. However, the rise in arterial pressure appears to be brought about by a generalised vasoconstriction, and from the study which has been carried out on myocardial blood flow (Chapter V) it seems that the coronary arteries also take part in the vasoconstriction. If this is so it means that administration of oxygen will actually reduce the blood supply to the heart and not increase it as might be hoped. It may be, of course, that reflex activity from the hypoxic zone around an infarct will maintain vasodilatation in these circumstances, but from the evidence which is available it seems that a major factor in the control of the coronary vessels

is the degree of oxygenation of the blood passing through them. An increase of arterial oxygen tension will therefore result in vasoconstriction.

Hypoxia may also lead to general depression in tissue respiration which will eventually result in cellular failure. As a consequence there may be further circulatory deterioration especially if the myocardium itself is involved and a vicious cycle may be set up whereby left ventricular failure induces further hypoxia which in turn promotes further circulatory failure. For this reason, prevention of hypoxia by oxygen administration is indicated as a prophylactic measure.

There is good experimental evidence that anoxia and metabolic acidosis may predispose to ventricular fibrillation (Burn and Hukovic, 1960; Gerst, Fleming and Malm, 1966). Since it has been found in the present work that the arterial blood lactate is frequently raised and that this can be at least partially corrected by administration of high concentrations of oxygen, it might be hoped that by this means such arrhythmias might be prevented. As reported in Chapter III primary ventricular fibrillation did not occur in any of the patients while they were receiving oxygen therapy. On the other hand, treatment with oxygen did not markedly reduce the frequency of ventricular ectopic beats when they were present.

There is therefore no definite evidence that oxygen was of prophylactic value against ventricular fibrillation and the infrequency of this complication in the present series may simply have been due to the small sample studied. Ashfield and Gavey (1969) have however claimed that hyperbaric oxygen was of benefit in the treatment of both atrial and ventricular arrhythmias in their patients, but they did not have a control series of observations.

The relative merits of oxygen at increased atmospheric pressure compared with atmospheric pressure have also been studied. It has been shown that the haemodynamic effects of oxygen at 2 atmospheres pressure are of the same nature as at one atmosphere absolute pressure. While the effects were somehwat more marked at two atmospheres the additional changes were relatively small compared with the large elevation of arterial oxygen tension. There is thus little haemodynamic evidence of any substantial benefit from the use of increased ambient pressures, but at the same time there were no strikingly adverse effects. The metabolic studies on the other hand did seem to show that some of the apparent benefit obtained in tissue oxygenation by treatment with oxygen at one atmosphere was reversed with increased pressures.

Unfortunately it was not possible to measure the effect of hyperbaric oxygen on myocardial blood flow, but previous animal work has shown that an even greater degree of coronary artery constriction takes place than with oxygen at atmospheric pressure. On balance, therefore, there is little objective evidence in favour of hyperbaric oxygen in the treatment of acute myocardial infarction. Nevertheless, there is no doubt that very high arterial oxygen tensions can be achieved in these patients by this means. It is possible therefore that the haemodynamic effects on the systemic and coronary circulation might be outweighed by the steep rise in blood-tissue gradient which may result in an increase of diffusion of oxygen into the ischaemic zone. This could explain the improved cardiac function which was noted after oxygen in some of the patients with hypotension and a low cardiac output. Similarly high alveolar oxygen tensions allow better oxygenation of the blood in patients with severe left ventricular failure and the vicious cycle previously mentioned, will be broken.

What, therefore, is the place of oxygen in the treatment of cardiac disease? The final answer to this question must still remain uncertain but now various guide-lines are available. In patients in whom the arterial oxygen tension is lowered with

desaturation of the arterial blood, there can be little doubt that a return of blood oxygen tension to normal limits is of value. It does seem from the present study, however, that increase of arterial oxygen tension above these limits is unlikely to result in an increased delivery of oxygen to the tissues in view of the circulatory changes which then take place. On the other hand, some of the circulatory effects such as elevation of the blood pressure may be desirable on their own account. Hyperbaric oxygen may be valuable in selected cases but its benefits must only spring from the increased diffusion gradient and not from the increased quantity of oxygen in the blood. The cases most likely to benefit from oxygen at increased pressure are those with cardiogenic shock or severe left ventricular failure and there is no evidence at present to suggest that the routine use of hyperbaric oxygen in all cases of myocardial infarction is of value.

The indications are therefore that routine treatment of cardiac patients whose arterial oxygen tension is below normal limits should be carried out with oxygen at atmospheric pressure in a concentration sufficient to elevate the arterial oxygen tension to normal limits. This can usually be achieved by administration of 60 to 100 per cent

oxygen by face-mask but care should be taken by blood gas analysis to prevent excessively high arterial oxygen tensions being produced. In those cases in which these measures fail to raise the oxygen tension to normal limits there may be a place for the use of hyperbaric oxygen, but such cases are uncommon. If this regime is adopted it should ensure that the patient receives the optimum benefit from oxygen treatment with a minimum of discomfort while the inherent disadvantages will be avoided.

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## Publications and Communications based on the work of this thesis

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# HAEMODYNAMIC AND METABOLIC STUDIES IN MAN WITH SPECIAL REFERENCE TO THE EFFECTS OF OXYGEN

Thesis presented to the University of Glasgow for the degree of Doctor of Medicine

Volume II

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September, 1970.

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APPENDIX 1

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Table 1

Age, height, weight and body surface area in 20 healthy men

| Subject no. | Age (yr.) | Height (m.) | Weight (kg.) | Body surface area ($m.^2$) |
|---|---|---|---|---|
| 1 | 20 | 1.83 | 57.2 | 1.75 |
| 2 | 21 | 1.70 | 67.2 | 1.78 |
| 3 | 22 | 1.84 | 83.0 | 2.06 |
| 4 | 21 | 1.75 | 65.0 | 1.79 |
| 5 | 24 | 1.75 | 63.5 | 1.77 |
| 6 | 21 | 1.74 | 85.0 | 2.00 |
| 7 | 24 | 1.82 | 65.1 | 1.84 |
| 8 | 22 | 1.75 | 57.6 | 1.70 |
| 9 | 24 | 1.80 | 63.8 | 1.81 |
| 10 | 26 | 1.80 | 65.4 | 1.83 |
| 11 | 22 | 1.80 | 71.1 | 1.90 |
| 12 | 22 | 1.87 | 79.2 | 2.04 |
| 13 | 26 | 1.65 | 60.3 | 1.66 |
| 14 | 23 | 1.88 | 89.1 | 2.16 |
| 15 | 22 | 1.80 | 76.0 | 1.95 |
| 16 | 28 | 1.79 | 69.4 | 1.87 |
| 17 | 37 | 1.77 | 70.0 | 1.86 |
| 18 | 24 | 1.83 | 72.6 | 1.94 |
| 19 | 24 | 1.82 | 75.2 | 1.96 |
| 20 | 23 | 1.75 | 66.7 | 1.81 |

Table 2

Heart rate, cardiac index and stroke index in 20 healthy men

| Subject no. | Heart rate (per min.) | | | Cardiac index (litres per min. per $m.^2$) | | | Stroke index (ml. per beat per $m.^2$) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 1 | 80 | 72 | 68 | 3.96 | 3.64 | 3.77 | 51 | 51 | 56 |
| 2 | 68 | 68 | 60 | 4.18 | 4.03 | 3.65 | 61 | 59 | 61 |
| 3 | 77 | 72 | 76 | 3.63 | 3.36 | 3.11 | 47 | 47 | 41 |
| 4 | 66 | 66 | 66 | 4.69 | 4.32 | 4.23 | 71 | 65 | 64 |
| 5 | 68 | 64 | 64 | 3.84 | 3.20 | 3.70 | 57 | 50 | 58 |
| 6 | 60 | 60 | 72 | 3.40 | 3.15 | 3.25 | 57 | 53 | 45 |
| 7 | 88 | 65 | 73 | 5.21 | 4.29 | 4.51 | 59 | 66 | 62 |
| 8 | 70 | 70 | 66 | 3.69 | 3.36 | 3.62 | 53 | 48 | 55 |
| 9 | 66 | 62 | 62 | 3.32 | 2.93 | 2.89 | 50 | 47 | 47 |
| 10 | 70 | 70 | 60 | 2.88 | 2.77 | 2.58 | 41 | 39 | 43 |
| 11 | 70 | 62 | 58 | 3.26 | 2.85 | 2.64 | 47 | 46 | 46 |
| 12 | 72 | 68 | 62 | 3.36 | 2.93 | 2.90 | 47 | 43 | 47 |

Table 2 (continued)

| Subject no. | Heart rate (per min.) | | | Cardiac index (litres per min. per m.$^2$) | | | Stroke index (ml. per beat per m.$^2$) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 13 | 62 | 62 | 63 | 3.14 | 2.84 | 2.80 | 51 | 46 | 45 |
| 14 | 60 | 62 | 62 | 2.99 | 2.70 | 2.95 | 50 | 44 | 47 |
| 15 | 66 | 66 | 56 | 3.65 | 3.34 | 2.98 | 55 | 51 | 53 |
| 16 | 64 | 60 | 64 | 3.74 | 3.50 | 3.64 | 58 | 58 | 57 |
| 17 | 68 | 60 | 58 | 3.36 | 3.60 | 3.30 | 49 | 60 | 57 |
| 18 | 74 | 74 | 70 | 3.54 | 3.39 | 3.28 | 48 | 46 | 47 |
| 19 | 60 | 54 | 52 | 3.28 | 3.02 | 2.44 | 55 | 56 | 47 |
| 20 | 74 | 72 | 74 | 3.89 | 3.72 | 3.57 | 52 | 52 | 48 |
| Mean values | 69.2 | 65.5$^+$ | 64.3$^+$ | 3.65 | 3.35$^{++}$ | 3.28$^{++}$ | 53 | 51 | 51 |

ATA = atmospheres absolute pressure

+ $P < 0.01$ when compared with initial values during inhalation of air at 1 ATA

++ $P < 0.001$ when compared with initial values during inhalation of air at 1 ATA

Table 3

Arterial blood pressure, systemic vascular resistance and left ventricular work in 20 healthy men

| Subject no. | Arterial blood pressure (mm.Hg) | | | Mean arterial blood pressure (mm.Hg) | | | Systemic vascular resistance (dyne.sec. $cm.^{-5}$ per $m.^2$) | | | Left-ventricula work (kg. m. per mir per $m.^2$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | | Air | Oxyger | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 AT |
| 1 | 116/76 | 110/78 | 118/74 | 89 | 89 | 89 | 1798 | 1956 | 1889 | 4.793 | 4.406 | 4.56 |
| 2 | 126/88 | 116/76 | 132/72 | 101 | 99 | 92 | 1933 | 1965 | 2016 | 5.741 | 5.426 | 4.56 |
| 3 | 140/80 | 128/78 | 128/78 | 100 | 95 | 95 | 2204 | 2262 | 2444 | 4.937 | 4.341 | 4.01 |
| 4 | 118/70 | 124/68 | 126/76 | 86 | 87 | 93 | 1467 | 1611 | 1759 | 5.485 | 5.111 | 5.35 |
| 5 | 120/84 | 110/68 | 126/66 | 96 | 82 | 86 | 1859 | 2050 | 1859 | 5.013 | 3.569 | 4.32 |
| 6 | 130/90 | 136/90 | 152/100 | 103 | 105 | 117 | 2424 | 2667 | 2880 | 4.763 | 4.498 | 5.17 |
| 7 | 125/74 | 124/60 | 120/76 | 92 | 81 | 91 | 1413 | 1510 | 1614 | 6.519 | 4.726 | 5.58 |
| 8 | 108/68 | 110/84 | 106/72 | 81 | 93 | 83 | 1756 | 2214 | 1834 | 4.065 | 4.250 | 4.08 |
| 9 | 118/68 | 114/68 | 118/68 | 84 | 83 | 83 | 2024 | 2266 | 2298 | 3.793 | 3.307 | 3.26 |
| 10 | 140/92 | 132/86 | 132/82 | 108 | 101 | 98 | 3000 | 2917 | 3039 | 4.230 | 3.805 | 3.43 |

Table 3 (continued)

| Subject no. | Arterial blood pressure (mm.Hg) | | | Mean arterial blood pressure (mm.Hg) | | | Systemic vascular resistance (dyne.sec. $cm.^{-5}$ per $m.^2$) | | | Left ventricular work (kg. m. per min per $m.^2$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 11 | 140/86 | 144/88 | 134/98 | 104 | 106 | 110 | 2552 | 2975 | 3333 | 4.611 | 4.108 | 3.94 |
| 12 | 130/88 | 134/98 | 128/92 | 102 | 110 | 104 | 2429 | 3003 | 2869 | 4.661 | 4.383 | 4.10 |
| 13 | 108/70 | 132/88 | 134/88 | 83 | 101 | 103 | 2115 | 2845 | 2943 | 3.544 | 3.901 | 3.92 |
| 14 | 130/82 | 142/84 | 142/84 | 98 | 103 | 103 | 2622 | 3052 | 2793 | 3.985 | 3.782 | 4.13 |
| 15 | 130/76 | 130/72 | 122/74 | 94 | 91 | 90 | 2060 | 2180 | 2416 | 4.666 | 4.133 | 3.64 |
| 16 | 118/68 | 126/90 | 130/88 | 85 | 102 | 102 | 1818 | 2331 | 2242 | 4.323 | 4.855 | 5.04 |
| 17 | 118/80 | 118/84 | 120/78 | 93 | 95 | 92 | 2214 | 2111 | 2230 | 4.249 | 4.650 | 4.12 |
| 18 | 132/76 | 140/86 | 150/94 | 95 | 104 | 113 | 2147 | 2454 | 2756 | 4.573 | 4.794 | 5.04 |
| 19 | 136/94 | 136/92 | 134/86 | 108 | 107 | 102 | 2634 | 2834 | 3344 | 4.817 | 4.394 | 3.38 |
| 20 | 126/80 | 134/86 | 136/90 | 95 | 102 | 105 | 1954 | 2194 | 2353 | 5.024 | 5.159 | 5.09 |
| Mean Values | 125/79 | 137/81 | 139/83 | 94.8 | 96.8 | 97.5 | | | | | | |

Table 4

Arterial blood oxygen tension in 10 healthy men

(mm.Hg)

| Subject no. | Air | Oxygen | |
|---|---|---|---|
| | 1 ATA | 1 ATA | 2 ATA |
| 1 | 85 | 571 | 1228 |
| 3 | 89 | 497 | 1123 |
| 5 | 88 | 434 | 977 |
| 6 | 100 | 668 | 1469 |
| 7 | 87 | 536 | 1186 |
| 12 | 96 | 569 | 1205 |
| 16 | 91 | 434 | 1105 |
| 17 | 88 | 588 | 1286 |
| 18 | 90 | 619 | 1283 |
| 19 | 94 | 452 | 1180 |
| Mean values | 91 | 537 | 1204 |

ATA = atmospheres absolute pressure

Table 5

Age, height, weight and body surface area in 17 healthy men.

| Subject No. | Age (yr.) | Height (m.) | Weight (kg.) | Body surface area ($m.^2$) |
|---|---|---|---|---|
| 21 | 21 | 1.78 | 70.0 | 1.87 |
| 22 | 20 | 1.79 | 63.2 | 1.80 |
| 23 | 22 | 1.80 | 78.6 | 1.98 |
| 24 | 20 | 1.75 | 67.0 | 1.81 |
| 25 | 23 | 1.88 | 78.0 | 2.04 |
| 26 | 23 | 1.75 | 64.8 | 1.79 |
| 27 | 21 | 1.83 | 67.0 | 1.87 |
| 28 | 24 | 1.80 | 69.0 | 1.86 |
| 29 | 21 | 1.72 | 66.2 | 1.78 |
| 30 | 24 | 1.77 | 66.5 | 1.82 |
| 31 | 29 | 1.72 | 62.4 | 1.74 |
| 32 | 20 | 1.75 | 66.8 | 1.81 |
| 33 | 24 | 1.74 | 65.0 | 1.78 |
| 34 | 19 | 1.79 | 65.3 | 1.82 |
| 35 | 22 | 1.82 | 74.5 | 1.95 |
| 36 | 24 | 1.74 | 70.0 | 1.84 |
| 37 | 21 | 1.85 | 74.8 | 1.98 |

Table 6

Heart rate, cardiac index and stroke index in 18 healthy men after exercise for 10 minutes at 600 K.p.m.

| Subject no. | Heart rate (per min.) | | | Cardiac index (litres per min. per $m.^2$) | | | Stroke index (ml. per beat per $m.^2$) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 1 | 120 | 112 | 104 | 7.12 | 6.53 | 6.74 | 59 | 58 | 65 |
| 2 | 100 | 87 | 92 | 7.53 | 6.85 | 5.39 | 75 | 79 | 59 |
| 3 | 104 | 112 | 112 | 5.24 | 5.78 | 4.50 | 50 | 52 | 40 |
| 4 | 120 | 118 | 126 | 7.65 | 7.21 | 8.41 | 64 | 57 | 67 |
| 5 | 108 | 104 | 104 | 6.56 | 6.06 | 6.10 | 61 | 58 | 59 |
| 6 | 96 | 92 | 96 | 4.73 | 4.46 | 4.35 | 49 | 48 | 45 |
| 7 | 91 | 87 | 87 | 7.56 | 7.03 | 7.50 | 83 | 81 | 86 |
| 8 | 84 | 82 | 86 | 5.14 | 5.24 | 4.65 | 61 | 64 | 54 |
| 9 | 98 | 95 | 91 | 5.16 | 4.40 | 5.15 | 53 | 46 | 57 |

Table 6 (continued)

| Subject no. | Heart rate (per min.) | | | Cardiac index (litres per min. per $m.^2$) | | | Stroke index (ml. per beat per $m.^2$) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 10 | 106 | 106 | 92 | 4.28 | 4.39 | 3.79 | 40 | 41 | 41 |
| 11 | 101 | 91 | 99 | 4.68 | 4.09 | 4.07 | 46 | 45 | 41 |
| 12 | 100 | 100 | 90 | 4.34 | 4.05 | 3.83 | 43 | 41 | 43 |
| 13 | 113 | 102 | 95 | 6.66 | 5.27 | 5.02 | 59 | 52 | 53 |
| 14 | 94 | 88 | 82 | 4.10 | 3.62 | 3.43 | 44 | 41 | 42 |
| 15 | 88 | 82 | 80 | 4.87 | 4.25 | 4.22 | 55 | 52 | 53 |
| 16 | 106 | 104 | 100 | 5.61 | 5.56 | 5.24 | 53 | 56 | 52 |
| 17 | 112 | 100 | 96 | 6.35 | 5.97 | 5.47 | 57 | 60 | 57 |
| 18 | 106 | 104 | 98 | 5.95 | 5.15 | 4.33 | 56 | 50 | 44 |
| Mean values | 103 | 98++ | 96++ | 5.75 | 5.33+++ | 5.12+++ | 56 | 54.5 | 53 |

ATA = atmospheres absolute pressure

++ $P < 0.01$ when compared with initial values during inhalation of air at 1 AT

+++ $P < 0.001$ when compared with initial values during inhalation of air at 1 A

Table 7

Arterial blood pressure, mean arterial blood pressure and systemic vascular resistance in 18 healthy men after exercise for 10 minutes at 600 K.p.m.

| Subject no. | Arterial blood pressure (mm.Hg) | | | Mean arterial blood pressure (mm.Hg) | | | Systemic vascular resistance (dyne.sec. $cm.^{-5}$ per $m.^2$) | | | Left ventricular work (kg. m. per min. per $m.^2$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 1 | 140/78 | 146/80 | 146/86 | 99 | 102 | 106 | 1112 | 1250 | 1258 | 9.586 | 9.058 | 9.71 |
| 2 | 148/76 | 134/72 | 120/74 | 100 | 93 | 89 | 1062 | 1086 | 1321 | 10.241 | 8.664 | 6.52 |
| 3 | 154/78 | 172/78 | 160/80 | 103 | 109 | 107 | 1572 | 1509 | 1902 | 7.340 | 8.568 | 6.54 |
| 4 | 126/60 | 128/66 | 132/80 | 82 | 87 | 97 | 857 | 965 | 923 | 8.531 | 8.531 | 11.09 |
| 5 | 156/76 | 142/68 | 152/74 | 102 | 92 | 103 | 1244 | 1214 | 1351 | 9.100 | 7.582 | 8.54 |
| 6 | 140/90 | 162/82 | 162/96 | 106 | 108 | 118 | 1793 | 1937 | 2170 | 6.819 | 6.551 | 6.98 |
| 7 | 138/60 | 142/68 | 142/70 | 86 | 93 | 94 | 910 | 1058 | 1002 | 8.842 | 8.892 | 9.58 |
| 8 | 128/72 | 126/72 | 120/80 | 91 | 90 | 93 | 1416 | 1374 | 1600 | 6.361 | 6.414 | 5.88 |

Table 7 (continued)

| Subject no. | Arterial blood pressure (mm.Hg) | | | Mean arterial blood pressure (mm.Hg) | | | Systemic vascular resistance (dyne.sec. $cm.^{-5}$ per $m.^2$) | | | Left ventricula work (kg. m. per min per $m.^2$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | | Air | Oxyg | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 AT |
| 9 | 142/78 | 142/72 | 140/78 | 99 | 95 | 99 | 1535 | 1727 | 1538 | 6.947 | 5.685 | 6.93 |
| 10 | 156/86 | 160/88 | 144/94 | 109 | 112 | 111 | 2037 | 2041 | 2343 | 6.345 | 6.687 | 5.72 |
| 11 | 138/88 | 144/84 | 128/84 | 105 | 104 | 99 | 1795 | 2034 | 1946 | 6.683 | 5.785 | 5.48 |
| 12 | 148/98 | 150/100 | 138/98 | 114 | 116 | 111 | 2101 | 2291 | 2318 | 6.729 | 6.389 | 5.78 |
| 13 | 200/102 | 164/82 | 152/88 | 135 | 99 | 109 | 1622 | 1503 | 1737 | 12.228 | 7.096 | 7.44 |
| 14 | 142/78 | 152/84 | 150/82 | 99 | 107 | 105 | 1932 | 2365 | 2449 | 5.520 | 5.268 | 4.89 |
| 15 | 138/74 | 128/74 | 126/70 | 95 | 92 | 89 | 1561 | 1732 | 1687 | 6.292 | 5.318 | 5.10 |
| 16 | 158/90 | 144/80 | 148/94 | 113 | 101 | 112 | 1611 | 1453 | 1710 | 8.621 | 7.637 | 7.98 |
| 17 | 144/80 | 146/86 | 138/82 | 101 | 106 | 101 | 1272 | 1420 | 1477 | 8.722 | 8.606 | 7.51 |
| 18 | 158/90 | 158/92 | 162/108 | 113 | 114 | 126 | 1519 | 1771 | 2328 | 9.144 | 7.985 | 7.47 |
| Mean Values | 147/81 | 147/79 | 142/84 | 103 | 101 | 104 | 1497 | $1596^{+}$ | $1725^{+++}$ | 8.003 | $7.262^{+}$ | 7.17 |

Table 7 (continued)

ATA = atmospheres absolute pressure

\+ $P < 0.05$ when compared with initial values during inhalation of air at 1 ATA

++ $P < 0.01$ when compared with initial values during inhalation of air at 1 ATA

+++ $P < 0.001$ when compared with initial values during inhalation of air at 1 ATA

Table 8

Heart rate, cardiac index and stroke index in 17 healthy men after exercise for 6 minutes at 1,500 K.p.m.

| Subject no. | Heart rate (per min.) | | | Cardiac index (litres per min. per $m.^2$) | | | Stroke index (ml. per beat per $m.^2$) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 21 | 148 | 160 | 152 | 8.58 | 7.89 | 7.04 | 58 | 49 | 46 |
| 22 | 142 | 148 | 154 | 7.80 | 7.83 | 6.67 | 55 | 53 | 43 |
| 23 | 156 | 148 | 132 | 6.16 | 5.86 | 5.16 | 39 | 40 | 39 |
| 24 | 152 | 140 | 134 | 6.86 | 6.33 | 6.13 | 45 | 45 | 46 |
| 25 | 148 | 132 | 104 | 9.61 | 7.25 | 5.91 | 65 | 55 | 57 |
| 26 | 140 | 144 | 150 | 8.38 | 8.04 | 5.61 | 60 | 56 | 37 |
| 27 | 176 | 168 | 148 | 6.76 | 7.08 | 6.82 | 38 | 42 | 46 |
| 28 | 134 | 134 | 128 | 7.22 | 8.06 | 6.76 | 54 | 60 | 53 |
| 29 | 136 | 140 | 140 | 10.68 | 10.28 | 9.16 | 78 | 73 | 65 |

Table 8 (continued)

| Subject no. | Heart rate (per min.) | | | Cardiac index (litres per min. per m.$^2$) | | | Stroke index (ml. per beat per m.$^2$) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 30 | 150 | 148 | 156 | 9.27 | 9.25 | 9.04 | 62 | 59 | 58 |
| 31 | 160 | 142 | 144 | 8.53 | 7.49 | 6.59 | 53 | 53 | 46 |
| 32 | 160 | 182 | 174 | 5.90 | 6.54 | 6.72 | 37 | 36 | 39 |
| 33 | 156 | 170 | 152 | 9.13 | 8.87 | 7.92 | 59 | 52 | 52 |
| 34 | 178 | 176 | 172 | 7.94 | 8.45 | 8.08 | 45 | 48 | 47 |
| 35 | 146 | 136 | 128 | 6.18 | 5.08 | 4.70 | 42 | 37 | 37 |
| 36 | 184 | 178 | 172 | 7.07 | 7.31 | 8.26 | 38 | 41 | 48 |
| 37 | 104 | 98 | 96 | 8.38 | 7.63 | 7.35 | 81 | 78 | 77 |
| Mean values | 151 | 150 | 143 | 7.91 | 7.60 | 6.94$^{++}$ | 53 | 52 | 49$^{+}$ |

ATA = atmospheres absolute pressure

\+ $P < 0.05$ when compared with initial values during inhalation of air at1 A

++ $P < 0.01$ when compared with initial values during inhalation of air at1 A

Table 9

Arterial blood pressure, mean arterial blood pressure and systemic vascular resistance in 17 healthy men after exercise for 6 minutes at 1,500 K.p.m.

| Subject no. | Arterial blood pressure (mm.Hg) | | | Mean arterial blood pressure (mm.Hg) | | | Systemic vascular resistance (dyne.sec. $cm.^{-5}$ per $m.^2$) | | | Left ventricular work (kg. m. per min. per $m.^2$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 AT |
| 21 | 190/92 | 198/90 | 204/92 | 125 | 126 | 129 | 1166 | 1278 | 1466 | 14.586 | 13.520 | 12.35 |
| 22 | 186/80 | 198/88 | 214/96 | 115 | 125 | 135 | 1179 | 1277 | 1619 | 12.199 | 13.311 | 12.24 |
| 23 | 170/80 | 176/84 | 156/84 | 110 | 115 | 108 | 1429 | 1570 | 1674 | 9.215 | 9.165 | 7.57 |
| 24 | 192/76 | 220/90 | 180/76 | 115 | 133 | 111 | 1341 | 1681 | 1449 | 10.729 | 11.450 | 9.25 |
| 25 | 197/76 | 184/70 | 165/75 | 116 | 108 | 105 | 966 | 1191 | 1421 | 15.161 | 10.649 | 8.43 |
| 26 | 190/90 | 186/88 | 200/90 | 123 | 121 | 127 | 1174 | 1204 | 1811 | 14.018 | 13.231 | 9.69 |
| 27 | 178/68 | 178/74 | 168/84 | 105 | 109 | 112 | 1243 | 1232 | 1314 | 9.653 | 10.495 | 10.38 |
| 28 | 186/90 | 190/84 | 196/96 | 122 | 119 | 129 | 1352 | 1181 | 1527 | 11.979 | 13.044 | 11.86 |

Table 9 (continued)

| Subject no. | Arterial blood pressure (mm.Hg) | | | Mean arterial blood pressure (mm.Hg) | | | Systemic vascular resistance (dyne.sec. $cm.^{-5}$ per $m.^2$) | | | Left ventricular work (kg. m. per $m.^2$ per min.) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 AT |
| 29 | 196/74 | 204/108 | 182/96 | 115 | 140 | 125 | 861 | 1089 | 1092 | 16.704 | 19.573 | 15.57 |
| 30 | 185/78 | 195/75 | 202/70 | 114 | 115 | 114 | 984 | 995 | 1009 | 14.372 | 14.467 | 14.01 |
| 31 | 204/94 | 200/98 | 194/94 | 131 | 132 | 127 | 1229 | 1410 | 1542 | 15.197 | 13.446 | 11.38 |
| 32 | 196/98 | 204/106 | 212/98 | 131 | 139 | 136 | 1776 | 1700 | 1619 | 10.511 | 12.363 | 12.42 |
| 33 | 194/86 | 186/82 | 198/94 | 122 | 117 | 129 | 1069 | 1055 | 1303 | 15.148 | 14.114 | 13.89 |
| 34 | 194/90 | 212/90 | 208/90 | 125 | 131 | 129 | 1259 | 1240 | 1277 | 13.498 | 15.055 | 14.17 |
| 35 | 200/72 | 188/78 | 200/82 | 118 | 115 | 121 | 1528 | 1811 | 2060 | 9.918 | 7.945 | 7.73 |
| 36 | 214/92 | 230/90 | 226/96 | 133 | 137 | 135 | 1505 | 1499 | 1308 | 12.788 | 13.620 | 15.16 |
| 37 | 206/80 | 202/88 | 204/94 | 122 | 126 | 131 | 1165 | 1321 | 1426 | 13.904 | 13.075 | 13.09 |
| Mean Values | 193/83 | 197/87 | 195/89+ | 120 | 124 | 124+ | 1249 | 1337+ | 1466+++ | 12.916 | 12.854 | 11.72 |

Table 9 (continued)

ATA = atmospheres absolute pressure

\+ $P < 0.05$ when compared with initial values during inhalation of air at 1 ATA

++ $P < 0.01$ when compared with initial values during inhalation of air at 1 ATA

+++ $P < 0.001$ when compared with initial values during inhalation of air at 1 ATA

Table 10

Venous blood lactate levels (m.moles/litre) in 14 healthy subjects before and after six minutes exercise at 1500 K.p.m.

| Subject No. | Venous blood lactate values (m.moles/litre) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Before exercise | | | After exercise | | | Difference | | |
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 21 | 1.805 | 2.122 | 2.313 | 5.491 | 7.812 | 6.247 | 3.586 | 5.690 | 3.934 |
| 22 | 2.196 | 1.334 | 0.874 | 2.914 | 2.608 | 6.447 | 0.718 | 1.274 | 5.573 |
| 23 | 1.395 | 4.240 | 3.601 | 5.166 | 6.434 | 6.668 | 3.771 | 2.194 | 3.067 |
| 24 | 2.753 | - | 3.105 | 4.695 | | 4.655 | 1.942 | - | 1.550 |
| 26 | 1.738 | 1.791 | 1.752 | 5.611 | 8.112 | - | 3.873 | 6.321 | - |
| 27 | 2.353 | 2.233 | - | 8.580 | 7.238 | - | 6.227 | 5.005 | - |
| 28 | 1.110 | 3.758 | 3.918 | 8.465 | 5.978 | 7.013 | 7.355 | 2.220 | 1.095 |
| 30 | 2.196 | 3.957 | 2.183 | 5.377 | 9.574 | 8.582 | 3.181 | 5.617 | 6.399 |
| 31 | 1.498 | 3.852 | 3.041 | 8.047 | 5.217 | 6.886 | 6.549 | 1.365 | 3.845 |
| 32 | 1.632 | 2.426 | 2.053 | 7.043 | 12.455 | 7.486 | 5.411 | 9.929 | 5.433 |
| 33 | 2.069 | 2.782 | 2.795 | 4.625 | 4.815 | 6.873 | 2.556 | 2.033 | 4.078 |
| 34 | 2.718 | 2.410 | 1.420 | 9.261 | 8.426 | 4.788 | 6.543 | 6.016 | 3.368 |

Table 10(continued)

| Subject | Before exercise | | | After exercise | | | Difference | | |
|---|---|---|---|---|---|---|---|---|---|
| No. | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 35 | 1.334 | 0.950 | 1.097 | 4.267 | 3.473 | 3.665 | 2.933 | 2.523 | 2.568 |
| 36 | 1.868 | 3.563 | 2.414 | 10.838 | 7.161 | 7.004 | 8.970 | 3.598 | 4.590 |
| Mean Values | 1.967 | 2.801 | 2.351 | 6.456 | 6.869 | 6.359 | 4.472 | 4.063 | 3.792 |

Table 11

Clinical details of 51 patients with acute myocardial infarction

| Patient no. | Age (yrs.) | Time after infarct (hrs.) | Condition on admission | E.C.G. findings | Maximum S.G.O.T. levels (Frankel units per ml.) | Complications | Chest X-ray |
|---|---|---|---|---|---|---|---|
| 1 | 38 | 5 | Good | Sinus antero-septal infarct | 280 | - | - |
| 2 | 49 | 2 | Good | Sinus + VES Posterior infarct | 100 | - | - |
| 3 | 75 | 3 | Agitated.Cold extremities | Sinus + VES Antero-septal infarct | 310 | Atrial tachycardia | - |
| 4 | 65 | 18 | Good | Sinus Posterior infarct | 97 | - | - |
| 5 | 72 | 3 | J.V.P. elevated Ankle oedema + triple rhythm | Sinus Widespread anterior infarct | 610 | ?Pulmonary infarction | Consolidat ? infarct |
| 6 | 43 | 2 | Good | Sinus + VES Posterior infarct | 43 | - | LV + |

Table 11 (continued)

| Patient no. | Age (yrs.) | Time after infarct (hrs.) | Condition on admission | E.C.G. findings | Maximum S.G.O.T. levels (Frankel units per ml.) | Complications | Chest X-ray |
|---|---|---|---|---|---|---|---|
| 7 | 67 | 2 | Good | Sinus + VES Posterior infarct | 154 | CCF 7 days after admission | Cardiac enlargeme |
| 8 | 54 | 1½ | J.V.P. = 4cm. Hypertensive Presystolic triple rhythm | Sinus Posterior infarct | 540 | - | L.V. hypertrop |
| 9 | 38 | 3 | Good | Sinus | 470 | - | - |
| 10 | 63 | 3½ | Pale, sweating Cold clammy skin Triple rhythm | Sinus Antero-septal infarction | 168 | - | Pulmonary congestic |
| 11 | 56 | 6 | Good | Sinus Antero-septal infarct | 366 | Ventricular tachycardia 48 hours after admission | - |

Table 11 (continued)

| Patient | Age (yrs.) | Time after infarct (hrs.) | Condition on admission | E.C.G. findings | Maximum S.G.O.T. levels (Frankel units per ml.) | Complications | Chest X-ray |
|---|---|---|---|---|---|---|---|
| 12 | 59 | ½ | Pallor + Sweating + Heart rate 200/min. B.P. unrecordable. Cardioversion sinus | Ventricular tachycardia sinus Antero-septal infarct | 40 | Ventricular tachycardia Cardiac arrest with ventricular fibrillation Died 8 days | - |
| 13 | 66 | 4 | Good | Sinus Antero-septal infarct | 280 | - | - |
| 14 | 77 | 8 | Crepitations at bases | Sinus Anterior infarct | 140 | C.C.F. | - |
| 15 | 60 | 6 | Crepitations at bases. Hypotension | Sinus Posterior infarct | 280 | Died 3 days | - |

Table 11 (continued)

| Patient no. | Age (yrs.) | Time after infarct (hrs.) | Condition on admission | E.C.G. findings | Maximum S.G.O.T. levels (Frankel units per ml.) | Complications | Chest X-ray |
|---|---|---|---|---|---|---|---|
| 16 | 52 | 2 | Pallor<br>Presystolic triple rhythm | Sinus<br>1st degree heart block. Posterior infarct | 290 | - | - |
| 17 | 61 | 23 | Grey, cold extremities<br>Hypotensive | Sinus. Recent posterior infarct<br>Previous antero-septal infarction | 650 | Persistent hypotension<br>Died 5 days | - |
| 18 | 64 | 1½ | Not distressed<br>Crepitations at bases | Sinus<br>Antero-septal infarct | 165 | Developed V.S.D.<br>C.C.F.<br>Died 10 weeks later | Pulmonary congestio |
| 19 | 60 | 3 | Good | Sinus<br>Posterior infarct | 173 | - | - |
| 20 | 64 | 19 | Good | Sinus<br>Antero-septal infarction | 165 | - | - |
| 21 | 41 | 2 | Good | Sinus<br>Antero-septal infarct | 114 | - | LV + |

Table 11 (continued)

| Patient no. | Age (yrs.) | Time after infarct (hrs.) | Condition on admission | E.C.G. findings | Maximum S.G.O.T. levels (Frankel units per ml.) | Complications | Chest X-ray |
|---|---|---|---|---|---|---|---|
| 22 | 61 | 2 | Restless ++ | Sinus + VES . Widespread anterior infarct | 165 | - | LV + |
| 23 | 67 | 9 | Dyspnoeic at rest. No C.C.F. Crepitations at both bases Pericardial friction + | Sinus + VES L.B.B.B. (later tracings showed lateral infarction | 40 | Atrial fibrillation Pulmonary infarction | Pulmonary infarct |
| 24 | 72 | 3 | Pale, sweating cyanosed. Hypotensive Crepitations at both bases | Sinus Antero-lateral infarct | 570 | Persistent hypotension Died 24 hours | - |
| 25 | 52 | 5 | Agitated + | Sinus + VES Postero-lateral infarct | 40 | - | - |
| 26 | 38 | 12 | Good | Sinus Antero-lateral infarct | 145 | - | - |

Table 11 (continued)

| Patient no. | Age (yrs.) | Time after infarct (hrs.) | Condition on admission | E.C.G. findings | Maximum S.G.O.T. levels (Frankel units per ml.) | Complications | Chest X-ray |
|---|---|---|---|---|---|---|---|
| 27 | 42 | 4 | Agitated ++ Sweating Thyrotoxic | Sinus Antero-septal infarct | 113 | - | - |
| 28 | 75 | 6 | Good | Sinus Posterior infarct | 85 | - | - |
| 29 | 58 | 15 | Good | Sinus + VES Postero-lateral infarct | 162 | - | Cardiac enlargemen |
| 30 | 69 | 3 | Pale, sweating 3rd heart sound present | Sinus + VES Postero-lateral infarct | 280 | Pulmonary infarction | Pulmonary infarct |
| 31 | 55 | 12 | Distressed + Still in pain | Sinus + VES Posterior infarct | 157 | - | - |
| 32 | 58 | 6 | Good | Sinus Posterior infarct | 155 | - | - |
| 33 | 58 | 3 | Pallor ++ | Sinus Antero-septal infarct | 410 | Atrial fibrillation | - |

Table 11 (continued)

| Patient | Age (yrs.) | Time after infarct (hrs.) | Condition on admission | E.C.G. findings | Maximum S.G.O.T. levels (Frankel units per ml.) | Complications | Chest X-ray |
|---|---|---|---|---|---|---|---|
| 34 | 47 | 12 | Not distressed<br>J.V.P. = 4cm. | Sinus + VES<br>Antero-septal infarct | 730 | Hypotension | Heart enlarged |
| 35 | 68 | 8 | Triple rhythm<br>Crepitations at bases | Sinus + VES<br>Widespread anterior infarct | 210 | Atrial fibrillation | |
| 36 | 56 | 8 | Good | Sinus<br>Widespread anterior infarct | 230 | Atrial tachycardia<br>Atrial fibrillation | - |
| 37 | 54 | 1½ | Pale, distressed | Sinus + AES + VES<br>Posterior infarction | 143 | - | - |
| 38 | 50 | 2 | Good | Sinus<br>Antero-septal infarct | 41 | - | - |
| 39 | 54 | 2 | Pallor + Cyanosis<br>J.V.P. = 7cm. | Sinus<br>L.B.B.B.<br>Antero-lateral infarct | 41 | Left ventricular failure | - |

Table 11 (continued)

| Patient no. | Age (yrs.) | Time after infarct (hrs.) | Condition on admission | E.C.G. findings | Maximum S.G.O.T. levels (Frankel units per ml.) | Complications | Chest X-ray |
|---|---|---|---|---|---|---|---|
| 40 | 59 | 4 | Cyanosed. J.V.P. elevated. Triple rhythm | Sinus Widespread anterior infarct | 540 | Left ventricular failure | - |
| 41 | 59 | 2 | Good | Sinus + VES Antero-septal infarct | 310 | - | LV + |
| 42 | 58 | 1 | Pale, sweating Cold clammy extremities | Atrial fibrillation initially then sinus Posterior infarction | 710 | C.C.F. Died 3 weeks | Heart enlarged Pulmonary congestion |
| 43 | 51 | 6 | Pallor ++ Cold clammy extremities Hypotensive | Sinus Widespread anterior infarction | - | Hypotension Died 6 hours after admission | - |
| 44 | 60 | 8 | Good | Sinus + VES Posterior infarct | 199 | Cerebro-vascular incident Died 17 days | Heart enlarged |

Table 11 (continued)

| Patient no. | Age (yrs.) | Time after infarct (hrs.) | Condition on admission | E.C.G. findings | Maximum S.G.O.T. levels (Frankel units per ml.) | Complications | Chest X-ray |
|---|---|---|---|---|---|---|---|
| 45 | 49 | 1 | Pale, sweating | Sinus + VES. Postero-lateral infarct | 410 | | - |
| 46 | 56 | 1½ | Good | Sinus posterior infarct | 337 | Deep venous thrombosis Left ventricular failure | Heart enlarged Pulmonary congestion |
| 47 | 33 | 4 | Distressed, sweating Xanthelasma Triple rhythm | Sinus tachycardia Antero-septal infarct | 480 | - | - |
| 48 | 40 | 9 | Good | Sinus. Antero-lateral and septal infarct | 335 | - | - |
| 49 | 64 | 2 | J.V.P. = 2cm. Crepitations at both bases | Complete heart block initially with spontaneous reversion to sinus. Posterior infarct | 342 | - | - |

Table 11 (continued)

| Patient no. | Age (yrs.) | Time after infarct (hrs.) | Condition on admission | E.C.G. findings | Maximum S.G.O.T. levels (Frankel units per ml.) | Complications | Chest X-ray |
|---|---|---|---|---|---|---|---|
| 50 | 68 | 2 | Acutely dyspnoeic Cyanosed ++ Crepitations at both bases ++ | Sinus + VES Antero-septal infarct | 250 | Left ventricular failure | Heart enlarged Pulmonary congestion |
| 51 | 60 | 5 | Good | Sinus Posterior infarct | 128 | - | - |

VES = ventricular ectopic beat

Table 12

Estimated age of infarct

on admission

| Hours | Cases |
|---|---|
| 0 - 6 | 38 |
| 7 - 12 | 9 |
| 13 - 18 | 2 |
| 19 - 24 | 2 |

Table 13

Maximum S.G.O.T. leads in

51 patients with acute

myocardial infarction

| Frankel units per ml. | Cases |
|---|---|
| 0 - 50 | 6 |
| 51 - 200 | 19 |
| 201 - 300 | 8 |
| 301 - 400 | 6 |
| 401 - | 11 |

N.B. One patient died before blood could be taken for enzyme estimation.

Table 14

Heart rate, cardiac output and stroke volume in 16 patients with acute myocardial infarction

| Patient No. | Heart Rate (per min.) | | Cardiac Output (litres per min.) | | Stroke Volume (ml.) | |
|---|---|---|---|---|---|---|
| | Air 1 ATA | Oxygen 1 ATA | Air 1 ATA | Oxygen 1 ATA | Air 1 ATA | Oxygen 1 ATA |
| 1 | 125 | 117 | 4.83 | 4.56 | 39 | 39 |
| 2 | 68 | 66 | 8.70 | 6.51 | 128 | 99 |
| 3 | 58 | 55 | 2.00 | 1.73 | 35 | 31 |
| 4 | 54 | 58 | 5.76 | 4.66 | 107 | 80 |
| 5 | 100 | 96 | 7.01 | 5.14 | 70 | 53 |
| 6 | 66 | 66 | 6.21 | 5.45 | 94 | 83 |
| 7 | 61 | 42 | 3.41 | 2.03 | 56 | 48 |
| 8 | 75 | 65 | 3.61 | 5.39 | 48 | 83 |
| 9 | 107 | 125 | 5.17 | 4.96 | 48 | 40 |
| 10 | 96 | 105 | 4.66 | 3.79 | 48 | 36 |
| 11 | 48 | 51 | 3.30 | 3.63 | 69 | 71 |

Table 14 (continued)

| Patient No. | Heart Rate (per min.) | | Cardiac Output (litres per min.) | | Stroke Volume (ml.) | |
|---|---|---|---|---|---|---|
| | Air 1 ATA | Oxygen 1 ATA | Air 1 ATA | Oxygen 1 ATA | Air 1 ATA | Oxygen 1 ATA |
| 12 | 90 | 99 | 5.79 | 5.25 | 64 | 53 |
| 13 | 71 | 74 | 5.60 | 5.86 | 79 | 79 |
| 14 | 83 | 93 | 6.11 | 5.63 | 74 | 61 |
| 15 | 94 | 108 | 5.86 | 6.27 | 62 | 58 |
| 16 | 71 | 69 | 7.43 | 6.41 | 105 | 93 |
| Mean Values | 79 | 81 | 5.34 | 4.83+ | 70 | 63+ |

ATA = atmospheres absolute pressure

+P <0.05 when compared with initial values during inhalation of air at 1 ATA

Table 15

Arterial blood pressure and systemic vascular resistance in 16 patients with acute myocardial infarction

| Patient No. | Arterial B.P. (mm.Hg.) | | Mean Arterial Blood Pressure (mm.Hg.) | | Systemic Vascular Resistance (dynes. sec. $cm.^{-5}$) | |
|---|---|---|---|---|---|---|
| | Air 1 ATA | Oxygen 2 ATA | Air 1 ATA | Oxygen 2 ATA | Air 1 ATA | Oxygen 2 ATA |
| 1. | 135/90 | 137/92 | 105 | 107 | 1739 | 1877 |
| 2. | 127/65 | 136/70 | 86 | 92 | 791 | 1131 |
| 3. | 105/45 | 125/60 | 68 | 82 | 2720 | 3791 |
| 4. | 124/60 | 154/64 | 80 | 98 | 1111 | 1682 |
| 5. | 137/65 | 155/80 | 85 | 107 | 970 | 1665 |
| 6. | 150/90 | 158/120 | 110 | 133 | 1417 | 1953 |
| 7. | 136/54 | 76/28 | 78 | 44 | 1830 | 1734 |
| 8. | 240/137 | 230/125 | 180 | 160 | 3989 | 2375 |
| 9. | 150/96 | 154/100 | 114 | 118 | 1764 | 1903 |
| 10. | 128/53 | 146/71 | 68 | 97 | 1167 | 2047 |
| 11. | 116/56 | 116/58 | 77 | 82 | 1867 | 1807 |

Table 15 (continued)

| Patient No. | Arterial B.P. (mm.Hg.) | | Mean Arterial Blood Pressure (mm.Hg.) | | Systemic Vascular Resistance (dynes. sec. $cm.^{-5}$) | |
|---|---|---|---|---|---|---|
| | Air 1 ATA | Oxygen 2 ATA | Air 1 ATA | Oxygen 2 ATA | Air 1 ATA | Oxygen 2 ATA |
| 12. | 100/48 | 102/50 | 62 | 72 | 857 | 1097 |
| 13. | 136/68 | 132/64 | 90 | 88 | 1286 | 1201 |
| 14. | 90/56 | 112/62 | 66 | 78 | 864 | 1108 |
| 15. | 90/60 | 92/64 | 70 | 73 | 956 | 931 |
| 16. | 100/64 | 136/70 | 76 | 92 | 818 | 1148 |
| Mean Values | 129/69 | 135/74+ | 88 | 95+ | 1509 | 1716+ |

ATA = atmospheres absolute pressure

+ $P < 0.05$ when compared with initial values during inhalation of air at 1 ATA

Table 16

Arterial blood gas tensions and pH values in 16 patients with acute myocardial infarction

| Patient no. | Arterial blood oxygen tension (mm.Hg) | | Arterial blood carbon dioxide tension (mm.Hg) | | pH | |
|---|---|---|---|---|---|---|
| | Air 1 ATA | Oxygen 1 ATA | Air 1 ATA | Oxygen 1 ATA | Air 1 ATA | Oxygen 1 ATA |
| 1 | 69 | 575 | 37 | 26 | 7.42 | 7.55 |
| 2 | 85 | 430 | 36 | 34 | 7.45 | 7.47 |
| 3 | 86 | 491 | 39 | 36 | 7.46 | 7.41 |
| 4 | 98 | 486 | 17 | 30 | 7.58 | 7.58 |
| 5 | 53 | 261 | 38 | 42 | 7.43 | 7.40 |
| 6 | 90 | 435 | 44 | 40 | 7.40 | 7.53 |
| 7 | 68 | 378 | - | - | - | - |
| 8 | 58 | 475 | - | - | - | - |
| 9 | 73 | 452 | 36 | 37 | 7.45 | 7.45 |

Table 16 (continued)

| Patient no. | Arterial blood oxygen tension (mm.Hg) | | Arterial blood carbon dioxide tension (mm.Hg) | | pH | |
|---|---|---|---|---|---|---|
| | Air 1 ATA | Oxygen 1 ATA | Air 1 ATA | Oxygen 1 ATA | Air 1 ATA | Oxygen 1 ATA |
| 10 | 34 | 237 | 40 | 45 | 7.39 | 7.35 |
| 11 | 59 | 542 | 47 | 39 | 7.41 | 7.50 |
| 12 | 79 | 571 | 41 | 43 | 7.42 | 7.43 |
| 13 | 73 | 311 | 34 | 30 | 7.43 | 7.48 |
| 14 | 51 | 411 | 32 | 37 | 7.50 | 7.43 |
| 15 | 28 | 395 | 35 | 36 | 7.44 | 7.44 |
| 16 | 62 | 305 | 35 | 37 | 7.51 | 7.48 |
| Mean Values | 67 | 422 | 36 | 37 | 7.45 | 7.46 |

Table 16 (continued)

ATA = atmospheres absolute pressure

\+ $P < 0.05$ when compared with initial values during inhalation of air at 1 ATA

++ $P < 0.01$ when compared with initial values during inhalation of air at 1 ATA

+++ $P < 0.001$ when compared with initial values during inhalation of air at 1 ATA

Table 17

Heart rate, cardiac output and stroke volume in 35 patients with acute myocardial infarction

| Patient no. | Heart Rate (per min.), | | | Cardiac Output (litres per min.) | | | Stroke Volume (ml.) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 17 | 72 | 71 | 79 | 3.50 | 3.48 | 3.40 | 49 | 49 | 43 |
| 18 | 68 | 70 | 70 | 6.24 | 4.97 | 4.84 | 92 | 71 | 69 |
| 19 | 56 | 58 | 62 | 3.70 | 3.85 | 3.32 | 66 | 66 | 51 |
| 20 | 72 | 76 | 72 | 7.50 | 5.70 | 5.80 | 104 | 75 | 81 |
| 21 | 80 | 76 | 74 | 6.15 | 5.96 | 5.83 | 77 | 78 | 79 |
| 22 | 66 | 70 | 68 | 3.80 | 3.62 | 3.19 | 58 | 52 | 47 |
| 23 | 124 | 112 | 108 | 4.45 | 4.16 | 3.36 | 36 | 37 | 31 |
| 24 | 100 | 108 | 100 | 5.20 | 4.66 | 4.82 | 52 | 43 | 48 |
| 25 | 70 | 68 | 68 | 4.44 | 4.14 | 3.65 | 63 | 61 | 54 |
| 26 | 120 | 100 | 100 | 7.83 | 6.66 | 5.40 | 65 | 66 | 54 |
| 27 | 120 | 110 | 116 | 9.55 | 7.78 | 6.98 | 79 | 71 | 60 |

Table 17 (continued)

| Patient no. | Heart Rate (per min.) | | | Cardiac Output (litres per min.) | | | Stroke Volume (ml.) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 28 | 80 | 64 | 62 | 4.93 | 3.44 | 3.31 | 62 | 56 | 54 |
| 29 | 84 | 84 | 80 | 5.68 | 4.92 | 5.09 | 68 | 59 | 63 |
| 30 | 72 | 74 | 70 | 7.19 | 6.65 | 6.36 | 100 | 90 | 91 |
| 31 | 60 | 56 | 56 | 5.59 | 5.42 | 5.23 | 93 | 97 | 93 |
| 32 | 68 | 58 | 60 | 3.84 | 4.15 | 4.61 | 57 | 72 | 77 |
| 33 | 64 | 66 | 72 | 3.66 | 3.56 | 3.51 | 57 | 54 | 49 |
| 34 | 74 | 82 | 82 | 4.28 | 4.40 | 4.11 | 58 | 54 | 50 |
| 35 | 64 | 76 | 72 | 5.58 | 5.88 | 5.62 | 87 | 77 | 78 |
| 36 | 100 | 100 | 100 | 6.11 | 4.53 | 4.46 | 61 | 45 | 44 |
| 37 | 57 | 55 | 59 | 3.47 | 3.77 | 4.70 | 61 | 69 | 80 |
| 38 | 56 | 54 | 54 | 4.53 | 4.10 | 4.39 | 81 | 76 | 81 |
| 39 | 83 | 83 | 100 | 4.41 | 3.41 | 3.10 | 53 | 41 | 31 |

Table 17 (continued)

| Patient no. | Heart Rate (per min.) | | | Cardiac Output (litres per min.) | | | Stroke Volume (ml.) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 40 | 83 | 83 | 83 | 5.40 | 5.16 | 4.48 | 65 | 62 | 54 |
| 41 | 83 | 85 | 82 | 5.80 | 5.01 | 5.48 | 70 | 59 | 67 |
| 42 | 115 | 116 | 104 | 2.82 | 3.11 | 2.86 | 25 | 27 | 27 |
| 43 | 102 | 114 | 100 | 1.32 | 2.56 | 2.48 | 13 | 23 | 25 |
| 44 | 82 | 70 | 64 | 3.46 | 3.67 | 3.61 | 42 | 52 | 57 |
| 45 | 88 | 88 | 84 | 6.16 | 5.57 | 5.13 | 70 | 63 | 61 |
| 46 | 98 | 89 | 91 | 5.71 | 4.72 | 5.54 | 58 | 53 | 61 |
| 47 | 81 | 96 | 102 | 5.08 | 4.64 | 4.75 | 63 | 48 | 47 |
| 48 | 81 | 92 | 99 | 5.63 | 5.72 | 5.05 | 69 | 62 | 51 |
| 49 | 73 | 73 | 66 | 4.58 | 4.28 | 4.18 | 63 | 59 | 63 |
| 50 | 100 | 99 | 112 | 7.53 | 6.41 | 6.14 | 75 | 65 | 55 |
| 51 | 68 | 68 | 60 | 6.48 | 6.36 | 6.17 | 95 | 94 | 103 |
| Mean Values | 82 | 81 | 81 | 5.19 | 4.75$^{+++}$ | 4.60$^{+++}$ | 65 | 61$^{++}$ | 59$^{+}$ |

Table 17 (continued)

ATA = atmospheres absolute pressure

\+ $P < 0.05$ when compared with initial values during inhalation of air at 1 ATA

++ $P < 0.01$ when compared with initial values during inhalation of air at 1 ATA

+++ $P < 0.001$ when compared with initial values during inhalation of air at 1 ATA

Table 18

Arterial blood pressure, systemic vascular resistance and left ventricular work in 35 patients with acute myocardial infarction

| Patient No. | Arterial blood pressure (mm.Hg.) | | | Mean arterial blood pressure (mm.Hg.) | | | Systemic vascular resistance (dynes.sec.cm.$^{-5}$) | | | Left ventricular work (Kg. m. per min.) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 17 | 80/52 | 77/55 | 75/55 | 61 | 62 | 61 | 1394 | 1425 | 1435 | 2.904 | 2.934 | 2.821 |
| 18 | 112/90 | 120/77 | 140/82 | 97 | 90 | 100 | 1244 | 1449 | 1653 | 8.232 | 6.083 | 6.582 |
| 19 | 75/40 | 77/40 | 85/42 | 52 | 60 | 55 | 1124 | 1247 | 1325 | 2.617 | 3.142 | 2.483 |
| 20 | 157/98 | 180/110 | 182/117 | 115 | 142 | 148 | 1227 | 1993 | 2041 | 11.730 | 11.008 | 11.674 |
| 21 | 140/92 | 140/82 | 137/82 | 100 | 100 | 100 | 1301 | 1342 | 1372 | 8.364 | 8.106 | 7.929 |
| 22 | 137/83 | 138/90 | 140/92 | 94 | 105 | 103 | 1979 | 2320 | 2583 | 4.858 | 5.169 | 4.469 |
| 23 | 152/85 | 150/90 | 142/90 | 95 | 100 | 110 | 1708 | 1923 | 2619 | 5.749 | 5.658 | 5.026 |
| 24 | 75/47 | 107/65 | 107/67 | 57 | 77 | 85 | 877 | 1322 | 1411 | 4.031 | 4.880 | 5.572 |
| 25 | 114/55 | 145/70 | 155/75 | 80 | 88 | 107 | 1441 | 1700 | 2345 | 4.831 | 4.955 | 5.311 |
| 26 | 125/75 | 110/67 | 115/70 | 80 | 82 | 82 | 817 | 985 | 1215 | 8.519 | 7.427 | 6.022 |
| 27 | 112/55 | 117/60 | 130/70 | 70 | 77 | 90 | 586 | 792 | 1032 | 9.092 | 8.147 | 8.544 |

Table 18 (continued)

| Patient No. | Arterial blood pressure (mm.Hg.) | | | Mean arterial blood pressure (mm.Hg.) | | | Systemic vascular resistance (dynes.sec.cm.$^{-5}$) | | | Left ventricular work (Kg. m. per min.) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 28 | 65/30 | 87/42 | 115/57 | 50 | 54 | 75 | 811 | 1256 | 1813 | 3.352 | 2.526 | 3.376 |
| 29 | 117/70 | 125/70 | 135/75 | 87 | 90 | 90 | 1225 | 1463 | 1415 | 6.721 | 6.022 | 6.230 |
| 30 | 110/45 | 120/60 | 105/40 | 62 | 75 | 70 | 690 | 902 | 880 | 6.062 | 6.783 | 6.055 |
| 31 | 102/55 | 102/52 | 105/50 | 70 | 70 | 70 | 1002 | 1033 | 1071 | 5.322 | 5.160 | 4.979 |
| 32 | 87/45 | 97/55 | 105/52 | 60 | 70 | 72 | 1250 | 1349 | 1249 | 3.133 | 3.951 | 4.514 |
| 33 | 140/82 | 125/75 | 152/98 | 102 | 95 | 123 | 2229 | 2135 | 2803 | 5.077 | 4.600 | 5.872 |
| 34 | 87/57 | 113/75 | 125/75 | 67 | 88 | 91 | 1252 | 1600 | 1771 | 3.900 | 5.266 | 5.087 |
| 35 | 180/80 | 180/90 | 180/95 | 115 | 125 | 125 | 1649 | 1701 | 1779 | 8.727 | 9.996 | 9.554 |
| 36 | 130/100 | 140/110 | 134/106 | 110 | 124 | 114 | 1440 | 2190 | 2045 | 9.141 | 7.639 | 6.915 |
| 37 | 100/52 | 132/66 | 140/66 | 68 | 88 | 91 | 1568 | 1867 | 1549 | 3.209 | 4.512 | 5.817 |
| 38 | 108/74 | 122/72 | 142/82 | 88 | 94 | 102 | 1554 | 1834 | 1859 | 5.421 | 5.241 | 6.090 |
| 39 | 96/58 | 94/60 | 102/70 | 68 | 72 | 80 | 1234 | 1689 | 2065 | 4.078 | 3.339 | 3.373 |
| 40 | 152/74 | 152/68 | 156/82 | 100 | 96 | 107 | 1481 | 1488 | 1911 | 7.344 | 6.737 | 6.519 |

Table 18 (continued)

| Patient No. | Arterial blood pressure (mm.Hg.) | | | Mean arterial blood pressure (mm.Hg.) | | | Systemic vascular resistance (dynes.sec.cm.$^{-5}$) | | | Left ventricular work (Kg. m. per min.) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 41 | 100/64 | 132/72 | 146/92 | 80 | 90 | 114 | 1103 | 1437 | 1664 | 6.310 | 6.132 | 8.496 |
| 42 | 106/74 | 102/66 | 110/72 | 88 | 80 | 92 | 2496 | 2058 | 2573 | 3.375 | 3.384 | 3.578 |
| 43 | 60/40 | 52/40 | 56/46 | 44 | 40 | 48 | 2667 | 1250 | 1548 | 0.790 | 1.393 | 1.619 |
| 44 | 118/84 | 134/74 | 138/74 | 96 | 94 | 102 | 2220 | 2049 | 2260 | 4.517 | 4.692 | 5.008 |
| 45 | 160/104 | 162/112 | 160/94 | 116 | 126 | 114 | 1506 | 1810 | 1778 | 9.718 | 9.545 | 7.954 |
| 46 | 142/76 | 144/74 | 162/87 | 88 | 100 | 110 | 1233 | 1695 | 1588 | 6.834 | 6.419 | 8.288 |
| 47 | 116/70 | 126/70 | 120/70 | 85 | 88 | 92 | 1338 | 1517 | 1549 | 5.872 | 5.553 | 5.943 |
| 48 | 140/91 | 145/95 | 151/99 | 110 | 110 | 121 | 1563 | 1538 | 1917 | 8.422 | 8.557 | 8.310 |
| 49 | 94/56 | 106/62 | 100/56 | 70 | 72 | 68 | 1223 | 1346 | 1301 | 4.360 | 4.191 | 3.866 |
| 50 | 138/44 | 150/70 | 200/90 | 66 | 100 | 112 | 701 | 1248 | 1459 | 6.759 | 8.718 | 9.352 |
| 51 | 105/55 | 117/65 | 112/55 | 75 | 80 | 75 | 926 | 1006 | 972 | 6.610 | 6.920 | 6.293 |
| Mean Values | 115/67 | 123/71 | 130/75 | 82 | 89 | 94 | 1373 | 1542 | 1710 | 5.885 | 5.851 | 5.959 |
| | | +++ | +++ | | +++ | +++ | | + | +++ | | | |

Table 18 (continued)

ATA = atmospheres absolute pressure

\+ $P < 0.05$ when compared with initial values during inhalation of air at 1 ATA

++ $P < 0.01$ when compared with initial values during inhalation of air at 1 ATA

+++ $P < 0.001$ when compared with initial values during inhalation of air at 1 ATA

Table 19

Arterial blood gas tensions and pH values in 35 patients with acute myocardial infarction

| Patient no. | Arterial blood oxygen tension (mm.Hg.) | | | Arterial blood carbon dioxide tension (mm.Hg) | | | pH | | |
|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 17 | 97 | 295 | 997 | 38 | 32 | 26 | 7.33 | 7.42 | 7.47 |
| 18 | 97 | 538 | 1120 | - | - | - | - | - | - |
| 19 | 88 | 522 | 1130 | 40 | 44 | 36 | 7.30 | 7.30 | 7.36 |
| 20 | 74 | 312 | 855 | 49 | 39 | 44 | 7.39 | 7.35 | 7.30 |
| 21 | 50 | 260 | 840 | 34 | 35 | 39 | 7.44 | 7.44 | 7.49 |
| 22 | 100 | 342 | 908 | 39 | 39 | 47 | 7.40 | 7.38 | 7.41 |
| 23 | 43 | 390 | 914 | 29 | 34 | 37 | 7.47 | 7.47 | 7.43 |
| 24 | 24 | 141 | 508 | 37 | 36 | 36 | 7.25 | 7.37 | 7.36 |
| 25 | 61 | 367 | 582 | 37 | 33 | 33 | 7.45 | 7.44 | 7.42 |

Table 19 (continued)

| Patient no. | Arterial blood oxygen tension (mm.Hg) | | | Arterial blood carbon dioxide tension (mm.Hg) | | | pH | | |
|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 26 | 63 | 470 | 916 | 41 | 38 | 36 | 7.45 | 7.46 | 7.41 |
| 27 | 82 | 423 | 798 | 32 | 41 | 48 | 7.44 | 7.47 | 7.47 |
| 28 | 70 | 406 | 639 | 37 | 38 | 40 | 7.40 | 7.44 | 7.40 |
| 29 | 59 | 406 | 1048 | 35 | 39 | 37 | 7.52 | 7.51 | 7.52 |
| 30 | 61 | 496 | 1150 | 34 | 36 | 33 | 7.48 | 7.45 | 7.50 |
| 31 | 52 | 481 | 1043 | 34 | 31 | 34 | 7.50 | 7.55 | 7.50 |
| 32 | 60 | 565 | 1160 | 37 | 37 | 40 | 7.50 | 7.49 | 7.47 |
| 33 | 81 | 542 | 857 | 31 | 31 | 40 | 7.53 | 7.49 | 7.49 |
| 34 | 82 | 603 | 1028 | 33 | 36 | 36 | 7.46 | 7.45 | 7.45 |
| 35 | 54 | 366 | 1312 | 39 | 42 | 42 | 7.45 | 7.43 | 7.46 |
| 36 | 51 | 486 | 1196 | 44 | 41 | 41 | 7.43 | 7.38 | 7.38 |
| 37 | 65 | 625 | 1570 | 46 | 46 | 38 | 7.40 | 7.48 | 7.33 |

Table 19 (continued)

| Patient no. | Arterial blood oxygen tension (mm.Hg) | | | Arterial blood carbon dioxide tension (mm.Hg) | | | pH | | |
|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 38 | 70 | 610 | 1300 | 42 | 50 | 40 | 7.47 | 7.47 | 7.45 |
| 39 | 51 | 459 | 993 | 37 | 39 | 42 | 7.44 | 7.44 | 7.35 |
| 40 | 56 | 496 | 821 | 45 | 48 | 52 | 7.38 | 7.32 | 7.36 |
| 41 | 56 | 423 | 1018 | 37 | 43 | 42 | 7.45 | 7.42 | 7.39 |
| 42 | 73 | 649 | 1150 | 35 | 34 | 40 | 7.32 | 7.33 | 7.29 |
| 43 | 54 | 181 | 480 | 32 | 35 | 33 | 7.35 | 7.32 | 7.20 |
| 44 | 59 | 440 | 985 | 39 | 44 | 31 | 7.48 | 7.42 | 7.50 |
| 45 | 61 | 474 | 1109 | 41 | 50 | - | 7.43 | 7.37 | 7.37 |
| 46 | 63 | 396 | 845 | 35 | 38 | 48 | 7.42 | 7.44 | 7.46 |
| 47 | 51 | 510 | 1210 | 35 | 36 | 37 | 7.55 | 7.57 | 7.52 |
| 48 | 72 | 555 | 1199 | 39 | 27 | 30 | 7.48 | 7.52 | 7.55 |
| 49 | 56 | 435 | 980 | 40 | 41 | 46 | 7.45 | 7.46 | 7.46 |

Table 19 (continued)

| Patient no. | Arterial blood oxygen tension (mm.Hg) | | | Arterial blood carbon dioxide tension (mm.Hg) | | | pH | | |
|---|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 50 | 73 | 237 | 1095 | 39 | 42 | 37 | 7.37 | 7.38 | 7.37 |
| 51 | 73 | 542 | 1106 | 45 | 46 | 41 | 7.45 | 7.41 | 7.40 |
| Mean Values | 65 | 441$^{+++}$ | 996$^{+++}$ | 38 | 39 | 39 | 7.43 | 7.43 | 7.42 |

ATA = atmospheres absolute pressure

\+ $P < 0.05$ when compared with initial values during inhalation of air at 1 ATA

++ $P < 0.01$ when compared with initial values during inhalation of air at 1 ATA

+++ $P < 0.001$ when compared with initial values during inhalation of air at 1 ATA

Table 20

Arterial blood lactate and pyruvate values in 35 patients with myocardial infarction

| Patient no. | Arterial Blood Lactate m-moles/lit. | | | Arterial Blood Pyruvate m-moles/lit. | | |
|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 17 | 2.247 | - | 2.287 | - | - | - |
| 18 | 1.538 | - | 1.685 | 0.035 | - | 0.037 |
| 19 | 1.322 | - | 1.578 | 0.067 | - | 0.075 |
| 20 | - | - | - | - | - | - |
| 21 | 1.356 | - | 1.057 | 0.075 | - | 0.077 |
| 22 | 2.755 | - | 0.587 | - | - | - |
| 23 | 1.658 | 1.968 | 2.875 | 0.048 | 0.042 | 0.039 |
| 24 | 5.700 | 4.539 | 3.772 | 0.172 | 0.157 | 0.103 |
| 25 | 1.967 | 1.658 | 1.328 | 0.047 | 0.076 | 0.102 |
| 26 | 2.529 | 1.177 | 1.498 | 0.036 | 0.042 | 0.029 |

Table 20 (continued)

| Patient no. | Arterial Blood Lactate m-moles/lit. | | | Arterial Blood Pyruvate m-moles/lit. | | |
|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 27 | 3.357 | 2.582 | 2.822 | 0.286 | 0.035 | 0.047 |
| 28 | 2.011 | 2.069 | 2.768 | 0.043 | 0.027 | 0.032 |
| 29 | 0.910 | 1.334 | 2.208 | 0.083 | 0.045 | 0.037 |
| 30 | 1.322 | - | 1.880 | 0.022 | 0.033 | 0.050 |
| 31 | 2.502 | 1.565 | 1.346 | 0.049 | 0.039 | 0.039 |
| 32 | 0.874 | 1.177 | 1.383 | 0.046 | 0.051 | 0.048 |
| 33 | 2.582 | 1.946 | 3.469 | 0.059 | 0.057 | 0.030 |
| 34 | 1.322 | 1.334 | 1.407 | 0.042 | 0.031 | 0.024 |
| 35 | 1.283 | 1.334 | 2.662 | 0.037 | 0.047 | 0.043 |
| 36 | 1.632 | 1.346 | 1.618 | 0.044 | 0.040 | 0.041 |
| 37 | 1.929 | 0.924 | 0.682 | 0.028 | 0.025 | 0.032 |
| 38 | 1.512 | 0.788 | 0.775 | 0.021 | 0.020 | 0.024 |

Table 20 (continued)

| Patient no. | Arterial Blood Lactate m-moles/lit. | | | Arterial Blood Pyruvate m-moles/lit. | | |
|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 39 | 1.217 | 0.990 | 1.070 | 0.059 | 0.054 | 0.032 |
| 40 | 4.722 | 3.397 | 4.267 | 0.025 | 0.032 | 0.024 |
| 41 | 2.742 | 1.432 | 1.395 | 0.025 | 0.027 | 0.024 |
| 42 | 6.654 | 2.327 | 1.070 | 0.033 | 0.037 | 0.024 |
| 43 | 7.056 | 6.434 | 16.890 | 0.027 | - | 0.016 |
| 44 | 1.485 | 1.070 | 1.632 | 0.062 | 0.019 | 0.056 |
| 45 | 1.163 | 0.626 | 1.893 | 0.043 | 0.020 | 0.015 |
| 46 | 2.477 | 1.203 | 3.905 | 0.043 | 0.025 | - |
| 47 | 2.011 | 1.043 | 2.662 | 0.023 | 0.024 | 0.023 |
| 48 | 4.058 | 0.963 | 1.905 | 0.016 | 0.010 | 0.013 |
| 49 | 0.735 | 0.546 | 0.574 | 0.042 | 0.033 | 0.040 |

Table 20 (continued)

| Patient no. | Arterial Blood Lactate m-moles/lit. | | | Arterial Blood Pyruvate m-moles/lit. | | |
|---|---|---|---|---|---|---|
| | Air | Oxygen | | Air | Oxygen | |
| | 1 ATA | 1 ATA | 2 ATA | 1 ATA | 1 ATA | 2 ATA |
| 50 | 3.130 | 2.287 | 0.788 | 0.025 | 0.031 | 0.026 |
| 51 | 1.898 | 1.868 | 2.977 | 0.061 | 0.062 | 0.058 |
| Mean Values | 2.402 | 1.783$^{+++}$ | 2.375 | 0.054 | 0.041 | 0.041 |

ATA = atmospheres absolute pressure

+++ $P < 0.001$ when compared with initial values during inhalation of air at 1 ATA

Table 21

Heart rate (per min.) in 9 patients with acute myocardial infarction breathing air and oxygen at one and two atmospheres absolute pressure

| Patient No. | Air 1 ATA | Oxygen 1 ATA | Oxygen 2 ATA | Air 2 ATA | Oxygen 2 ATA | Oxygen 1 ATA |
|---|---|---|---|---|---|---|
| 18 | 68 | 70 | 70 | 68 | 71 | 70 |
| 19 | 56 | 58 | 62 | 58 | 65 | 58 |
| 20 | 72 | 76 | 72 | 72 | 78 | 80 |
| 21 | 80 | 76 | 74 | 74 | 76 | 74 |
| 22 | 66 | 70 | 68 | 64 | 64 | 68 |
| 23 | 124 | 112 | 108 | 108 | 106 | 104 |
| 24 | 100 | 100 | 108 | 120 | 122 | 130 |
| 25 | 70 | 68 | 68 | 70 | 68 | 72 |
| 25 | 116 | 100 | 110 | 110 | 100 | 100 |
| Mean Values | 84 | 81 | 82 | 83 | 83 | 84 |

ATA = atmospheres absolute pressure

Table 22

Cardiac output (litres per min.) in 9 patients with acute myocardial infarction breathing air and oxygen at one and two atmospheres absolute pressure

| Patient No. | Air 1 ATA | Oxygen 1 ATA | Oxygen 2 ATA | Air 2 ATA | Oxygen 2 ATA | Oxygen 1 ATA |
|---|---|---|---|---|---|---|
| 18 | 6.24 | 4.97 | 4.84 | 5.23 | 4.63 | 5.21 |
| 19 | 3.70 | 3.85 | 3.32 | 4.32 | - | - |
| 20 | 7.50 | 5.70 | 5.80 | 6.30 | 5.70 | 6.90 |
| 21 | 6.15 | 5.96 | 5.83 | 7.00 | 6.12 | 5.97 |
| 22 | 3.80 | 3.62 | 3.19 | 3.49 | 3.51 | 4.03 |
| 23 | 4.45 | 4.16 | 3.36 | 3.41 | 4.04 | 3.42 |
| 24 | 5.20 | 4.66 | 4.82 | 5.70 | 4.67 | 5.57 |
| 25 | 4.44 | 4.14 | 3.65 | 3.88 | 3.82 | 3.86 |
| 26 | 7.83 | 6.66 | 5.40 | 6.86 | 6.38 | 7.18 |
| Mean Values | 5.48 | 4.86 | 4.47 | 5.13$^{++}$ | 4.86 | 5.27 |

ATA = atmospheres absolute pressure

++$P < 0.01$ when compared with value during initial inhalation of oxygen at 2 ATA

Table 23

Stroke volume (ml.) in 9 patients with acute myocardial infarction breathing air and oxygen at one and two atmospheres absolute pressure

| Patient no. | Air 1 ATA | Oxygen 1 ATA | Oxygen 2 ATA | Air 2 ATA | Oxygen 2 ATA | Oxygen 1 ATA |
|---|---|---|---|---|---|---|
| 18 | 92 | 71 | 69 | 77 | 65 | 74 |
| 19 | 66 | 66 | 51 | 74 | - | - |
| 20 | 104 | 75 | 81 | 88 | 73 | 86 |
| 21 | 77 | 78 | 79 | 95 | 81 | 81 |
| 22 | 58 | 52 | 47 | 55 | 55 | 59 |
| 23 | 36 | 37 | 31 | 32 | 38 | 33 |
| 24 | 52 | 47 | 45 | 47 | 38 | 43 |
| 25 | 63 | 61 | 54 | 56 | 56 | 54 |
| 26 | 68 | 67 | 49 | 62 | 64 | 72 |
| Mean Values | 68 | 62 | 56 | 65++ | 59 | 63 |

ATA = atmospheres absolute pressure

++ $P < 0.01$ when compared with value during initial inhalation of oxygen at

Table 24

Arterial blood pressure (mm.Hg.) in 9 patients with acute myocardial infarction breathing air and oxygen at one and two atmospheres absolute pressure

| Patient No. | Air 1 ATA | Oxygen 1 ATA | Oxygen 2 ATA | Air 2 ATA | Oxygen 2 ATA | Oxygen 1 ATA |
|---|---|---|---|---|---|---|
| 18 | 112/90 | 120/77 | 140/82 | 125/75 | 140/80 | 135/80 |
| 19 | 75/40 | 77/40 | 85/42 | 87/45 | 93/48 | 92/50 |
| 20 | 157/98 | 180/112 | 182/117 | 170/102 | 185/117 | 175/110 |
| 21 | 140/92 | 140/82 | 137/82 | 147/90 | 145/82 | 145/92 |
| 22 | 137/83 | 138/90 | 140/92 | 136/88 | 140/88 | 140/90 |
| 23 | 152/85 | 150/90 | 142/90 | 115/75 | 122/85 | 120/82 |
| 24 | 75/47 | 107/65 | 107/67 | 105/70 | 125/80 | 125/80 |
| 25 | 114/55 | 145/70 | 155/75 | 153/75 | 162/80 | 162/85 |
| 26 | 125/75 | 110/67 | 115/70 | 112/72 | 110/67 | 110/67 |
| Mean Values | 121/74 | 130/77 | 134/80 | 128/77 | 136/81 | 134/82 |

ATA = atmospheres absolute pressure

Table 25

Mean arterial blood pressure (mm.Hg.) in 9 patients with acute myocardial infarction breathing air and oxygen at one and two atmospheres absolute pressure

| Patient No. | Air 1 ATA | Oxygen 1 ATA | Oxygen 2 ATA | Air 2 ATA | Oxygen 2 ATA | Oxygen 2 ATA |
|---|---|---|---|---|---|---|
| 18 | 97 | 90 | 100 | 95 | 100 | 100 |
| 19 | 52 | 47 | 60 | 55 | 55 | 60 |
| | 115 | 142 | 148 | 135 | 150 | 137 |
| 21 | 100 | 100 | 100 | 110 | 110 | 105 |
| 22 | 94 | 105 | 103 | 105 | 103 | 100 |
| 23 | 95 | 100 | 110 | 90 | 97 | 87 |
| 24 | 57 | 77 | 85 | 77 | 95 | 97 |
| 25 | 80 | 88 | 107 | 107 | 110 | 120 |
| 26 | 80 | 82 | 82 | 82 | 77 | 85 |
| Mean Values | 85.55 | 92.33 | 99.44 | 95.11 | 99.67 | 99.00 |

ATA = atmospheres absolute pressure

Table 26

Systemic vascular resistance (dyne. sec. $cm.^{-5}$) in 9 patients with acute myocardial infarction breathing air and oxygen at 1 and 2 atmospheres absolute pressure

| Patient No. | Air 1 ATA | Oxygen 1 ATA | Oxygen 2 ATA | Air 2 ATA | Oxygen 2 ATA | Oxygen 1 ATA |
|---|---|---|---|---|---|---|
| 18. | 1243 | 1449 | 1653 | 1453 | 1728 | 1536 |
| 19. | 1124 | 1247 | 1446 | 1018 | - | - |
| 20. | 1227 | 1993 | 2041 | 1714 | 2105 | 1588 |
| 21. | 1301 | 1342 | 1372 | 1257 | 1438 | 1407 |
| 22. | 1978 | 2320 | 2583 | 2407 | 2347 | 1985 |
| 23. | 1708 | 1923 | 2619 | 2111 | 1921 | 2035 |
| 24. | 877 | 1322 | 1411 | 1081 | 1627 | 1393 |
| 25. | 1441 | 1700 | 2345 | 2206 | 2304 | 2487 |
| 26. | 817 | 985 | 1215 | 956 | 966 | 947 |
| Mean Values | 1302 | 1557 | 1854 | 1578++ | 1804 | 1672 |

ATA = atmospheres absolute pressure

++P $<$ 0.01 when compared with value for initial inhalation of oxygen at 2 ATA

Table 27

Arterial oxygen tension (mm.Hg.) in 9 patients with acute myocardial infarction breathing air and oxygen at one and two atmospheres absolute pressure

| Patient No. | Air 1 ATA | Oxygen 1 ATA | Oxygen 2 ATA | Air 2 ATA | Oxygen 2 ATA | Oxygen 1 ATA |
|---|---|---|---|---|---|---|
| 18 | 97 | 538 | 1120 | 151 | 1010 | 438 |
| 19 | 88 | 522 | 1130 | 176 | 1070 | 491 |
| 20 | 74 | 312 | 855 | 106 | 985 | 111 |
| 21 | 50 | 260 | 840 | 126 | 500 | 168 |
| 22 | 100 | 342 | 908 | 140 | 908 | 326 |
| 23 | 43 | 390 | 914 | 79 | 835 | 255 |
| 24 | 24 | 141 | 508 | 62 | 228 | 57 |
| 25 | 61 | 367 | 582 | 122 | 504 | 377 |
| 26 | 63 | 470 | 916 | 89 | 633 | 178 |
| Mean Values | 67 | 371 | 864 | 117 | 741 | 267 |

Table 28

Right ventricular or pulmonary arterial systolic pressure (mm.Hg.) in 12 patients with acute myocardial infarction breathing air at one atmosphere and oxygen at one and two atmospheres absolute pressure

| Patient No. | Air 1 ATA | Oxygen 1 ATA | Oxygen 2 ATA |
|---|---|---|---|
| 27 | 26* | 20* | 40* |
| 28 | 35 | 18 | 26 |
| 29 | 18 | 12 | 20 |
| 31 | 24 | 20 | 20 |
| 32 | 27 | 21 | 20 |
| 42 | 20 | 20 | 32 |
| 44 | 18* | 25* | 28* |
| 45 | 25 | 26 | 28 |
| 47 | 30* | 30* | 32* |
| 48 | 26* | 33* | 30 |
| 50 | 40 | 35 | 40 |
| 51 | 27* | 28* | 24* |

Table 28 (continued)

| Patient No. | Air 1 ATA | Oxygen 1 ATA | Oxygen 2 ATA |
|---|---|---|---|
| Mean Values | 26 | 24 | 28 |

* indicates right ventricular pressure

ATA = atmospheres absolute pressure

Table 29

PR interval (sec) in 10 patients with acute myocardial infarction breathing air at one atmosphere and oxygen at one and two atmospheres absolute pressure

| Patient No. | Air 1 ATA | Oxygen 1 ATA | Oxygen 2 ATA |
|---|---|---|---|
| 24 | 0.14 | 0.16 | 0.16 |
| 25 | 0.16 | 0.16 | 0.16 |
| 26 | 0.16 | 0.16 | 0.16 |
| 27 | 0.20 | 0.20 | 0.20 |
| 29 | 0.18 | 0.16 | 0.16 |
| 30 | 0.16 | 0.16 | 0.16 |
| 32 | 0.16 | 0.16 | 0.16 |
| 33 | 0.20 | 0.16 | 0.16 |
| 34 | 0.12 | 0.12 | 0.12 |
| 36 | 0.22 | 0.22 | 0.20 |

Table 30

Clinical details of 3 patients with chronic ischaemic heart disease

| Patient No. | Age (yrs.) | History | E.C.G. findings | Chest X-ray |
|---|---|---|---|---|
| 1. | 56 | Myocardial infarction 4 years previously. Severe angina since, preventing work. | Old antero-septal myocardial infarction. | Left ventricular enlargement. |
| 2. | 58 | Persistent severe anginal symptoms of 8 years duration forcing patient to stop work. | Lateral myocardial ischaemia at rest. Transient R.B.B.B. with widespread ischaemic changes during pain. | Slight pulmonary congestion. |
| 3. | 62 | 1 year history of severe angina. | Posterolateral ischaemia at rest with further antero-lateral ischaemic changes after exercise. | - |

Table 31

Cardiac output, stroke volume and arterial oxygen tension in 3 patients during atrial pacing

| Patient No. | Rhythm | Heart rate (per min.) | | Cardiac output (litres per min.) | | Stroke volume (ml.) | | Arterial blood oxygen tension (mm.Hg.) | |
|---|---|---|---|---|---|---|---|---|---|
| | | Air 1 ATA | Oxygen 2 ATA | Air 1 ATA | Oxygen 2 ATA | Air 1 ATA | Oxygen 2 ATA | Air 1 ATA | Oxygen 2 ATA |
| 1. | Sinus | 84 | | 4.32 | 4.83 | 51 | | 88 | 1243 |
| | Pacing | 90 | 90 | 4.25 | 5.13 | 47 | 57 | | |
| | Pacing | 120 | 120 | 4.12 | 4.84 | 34 | 40 | | |
| | Pacing | 135 | 135 | 3.86 | 5.35 | 29 | 40 | | |
| 2. | Sinus | 62 | 72 | 3.69 | 2.98 | 59 | 41 | 88 | 1017 |
| | Pacing | 90 | 90 | 4.00 | 3.47 | 44 | 38 | | |
| | Pacing | 120 | 120 | 3.39 | 3.90 | 28 | 32 | | |
| | Pacing | 135 | 135 | 4.23 | 3.23 | 31 | 24 | | |
| 3. | Sinus | 57 | 66 | 4.35 | 4.39 | 79 | 67 | 80 | 1010 |
| | Pacing | 90 | 90 | 5.57 | - | 62 | - | | |

Table 31 (continued)

| Patient No. | Rhythm | Heart rate (per min.) | | Cardiac output (litres per min.) | | Stroke volume (ml.) | | Arterial blood oxygen tension (mm.Hg.) | |
|---|---|---|---|---|---|---|---|---|---|
| | | Air 1 ATA | Oxygen 2 ATA | Air 1 ATA | Oxygen 2 ATA | Air 1 ATA | Oxygen 2 ATA | Air 1 ATA | Oxygen 2 ATA |
| 3 | Pacing | 120 | 120 | 4.96 | - | 41 | - | | |
| | Pacing | 135 | 135 | - | - | - | - | | |

Table 31A

Arterial blood pressure and systemic vascular resistance in 3 patients during atrial pacing

| Patient No. | Rhythm | Heart rate (per min.) | | Arterial blood pressure (mm.Hg.) | | Mean arterial blood pressure (mm.Hg.) | | Systemic vascular resistance (dyne. sec. cm.$^{-5}$) | |
|---|---|---|---|---|---|---|---|---|---|
| | | Air 1 ATA | Oxygen 2 ATA | Air 1 ATA | Oxygen 2 ATA | Air 1 ATA | Oxygen 2 ATA | Air 1 ATA | Oxygen 2 ATA |
| 1. | Sinus | 84 | | 141/73 | 152/82 | 95 | 105 | 1759 | 1740 |
| | Pacing | 90 | 90 | 136/72 | 155/82 | 93 | 106 | 1751 | 1653 |
| | Pacing | 120 | 120 | 130/70 | 148/80 | 90 | 103 | 1748 | 1702 |
| | Pacing | 135 | 135 | 122/80 | 146/84 | 94 | 105 | 1948 | 1976 |
| 2. | Sinus | 62 | 72 | 122/62 | 130/80 | 82 | 97 | 1778 | 2604 |
| | Pacing | 90 | 90 | 144/76 | 138/86 | 99 | 103 | 1980 | 2374 |
| | Pacing | 120 | 120 | 134/82 | 134/86 | 99 | 102 | 2336 | 2092 |
| | Pacing | 135 | 135 | 124/80 | 146/94 | 95 | 111 | 1797 | 2749 |
| 3. | Sinus | 57 | 66 | 210/115 | 225/125 | 147 | 158 | 2704 | 2879 |
| | Pacing | 90 | 90 | 205/125 | 230/135 | 152 | 167 | 2183 | - |
| | Pacing | 120 | 120 | 200/125 | - | 150 | - | 2419 | - |
| | Pacing | 135 | 135 | 190/120 | - | 150 | - | - | - |

Table 32

Age, height, weight and body surface area in 10 healthy men

| Subject No. | Age (yr.) | Height (m.) | Weight (kg.) | Body surface area ($m^2$) |
|---|---|---|---|---|
| A1 | 22 | 1.80 | 69.5 | 1.88 |
| A2 | 22 | 1.83 | 78.3 | 2.00 |
| A3 | 22 | 1.82 | 84.5 | 2.06 |
| A4 | 23 | 1.68 | 61.8 | 1.70 |
| A5 | 19 | 1.71 | 63.3 | 1.74 |
| A6 | 22 | 1.83 | 86.0 | 2.08 |
| A7 | 22 | 1.82 | 66.5 | 1.86 |
| A8 | 21 | 1.79 | 73.1 | 1.91 |
| A9 | 22 | 1.80 | 75.2 | 1.94 |
| A10 | 22 | 1.78 | 75.5 | 1.93 |

Table 33

Heart rate, cardiac index and stroke index in three healthy subjects breathing air at one atmosphere and oxygen at two atmospheres absolute pressure followed by administration of atropine

| Subject No. | Heart rate (per min.) | | | Cardiac Index (litres per min. per $m^2$.) | | | Stroke index (ml. per beat per $m^2$.) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Air 1 ATA | Oxygen 2 ATA | Oxygen 2 ATA after atropine | Air 1 ATA | Oxygen 2 ATA | Oxygen 2 ATA after atropine | Air 1 ATA | Oxygen 2 ATA | Oxygen 2 ATA after atropine |
| A1 | 64 | 64 | 72 | 3.97 | 3.41 | 4.45 | 62 | 53 | 62 |
| A2 | 64 | 54 | 72 | 2.68 | 2.59 | 3.36 | 42 | 48 | 47 |
| A3 | 62 | 54 | 64 | 2.80 | 2.16 | 2.65 | 45 | 40 | 41 |
| Mean Values | 63 | 57 | 69 | 3.15 | 2.72 | 3.49 | 50 | 47 | 50 |

ATA = atmospheres absolute pressure

Table 34

Arterial blood pressure and systemic vascular resistance in three healthy subjects breathing air at one atmosphere and oxygen at two atmospheres absolute pressure followed by administration of atropine

| Subject No. | Arterial blood pressure (mm.Hg.) | | | Mean arterial blood pressure (mm.Hg.) | | | Systemic vascular resistance (dyne. sec. $cm^{-5}$ per $m^2$.) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Air 1 ATA | Oxygen 2 ATA | Oxygen 2 ATA after atropine | Air 1 ATA | Oxygen 2 ATA | Oxygen 2 ATA after atropine | Air 1 ATA | Oxygen 2 ATA | Oxygen 2 ATA after atropine |
| A1 | 120/82 | 116/86 | 118/86 | 95 | 96 | 97 | 1914 | 2252 | 1744 |
| A2 | 148/90 | 152/94 | 150/92 | 109 | 113 | 111 | 3254 | 3490 | 2643 |
| A3 | 134/82 | 132/92 | 128/90 | 99 | 105 | 103 | 2828 | 3889 | 3110 |
| Mean Values | 134/85 | 133/91 | 132/89 | 101 | 105 | 104 | 2665 | 3210 | 2499 |

ATA = atmospheres absolute pressure

Table 35

Heart rate, cardiac index and stroke index in 7 healthy men breathing air, before and after intramuscular injection of atropine and breathing oxygen at one and two atmospheres absolute pressure after atropine

| Subject no. | Heart Rate (per min.) | | | | Cardiac Index (litres per min. per $m^2$) | | | | Stroke Index (ml. per beat per $m^2$) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | C | D | A | B | C | D | A | B | C | D |
| A4 | 76 | 108 | 100 | 89 | 5.10 | 6.42 | 4.75 | 5.03 | 67 | 59 | 47 | 96 |
| A5 | 62 | 72 | 73 | 68 | 3.35 | 3.52 | 3.46 | 3.10 | 54 | 49 | 47 | 46 |
| A6 | 56 | 76 | 80 | 64 | 3.08 | 4.90 | 4.53 | 3.44 | 55 | 64 | 57 | 54 |
| A7 | 58 | 86 | 90 | 86 | 3.42 | 4.01 | 4.11 | 3.90 | 59 | 47 | 46 | 45 |
| A8 | 66 | 100 | 104 | 102 | 3.50 | 4.86 | 4.21 | 3.67 | 53 | 49 | 41 | 36 |
| A9 | 64 | 66 | 72 | 70 | 3.98 | 4.38 | 3.95 | 3.18 | 62 | 66 | 55 | 45 |
| A10 | 66 | 80 | 80 | 72 | 2.91 | 3.63 | 2.93 | 2.79 | 44 | 45 | 37 | 39 |
| Mean Values | 64 | 84 | 86 | 79 | 3.62 | 4.53 | $3.99^{+}$ | 3.59 | 56 | 54 | $47^{+}$ | 52 |

A = Air 1 ATA

B = Air 1 ATA 45 mins. after atropine 1.2 mg. I.M.

C = O2 2 ATA 60 mins. after atropine

D = O2 2 ATA 90 mins. after atropine

ATA = atmospheres absolute pressure

Table 36

Arterial blood pressure, mean arterial blood pressure and systemic vascular resistance in 7 healthy men breathing air, before and after intramuscular injection of atropine and breathing oxygen at one and two atmospheres absolute pressure after atropine

| Subject No. | Arterial Blood Pressure (mm.Hg.) | | | | Mean Arterial Blood Pressure (mm.Hg.) | | | | Systemic Vascular Resistance (dynes sec. $cm^{-5}$ per $m^2$) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | C | D | A | B | C | D | A | B | C | D |
| A4 | 126/76 | 120/80 | 124/94 | 126/90 | 92 | 93 | 104 | 102 | 1443 | 1159 | 1752 | 1622 |
| A5 | 126/68 | 124/86 | 140/86 | 134/86 | 87 | 99 | 104 | 102 | 2078 | 2250 | 2405 | 2632 |
| A6 | 150/100 | 135/92 | 146/96 | 138/92 | 116 | 106 | 112 | 107 | 3013 | 1731 | 1978 | 2488 |
| A7 | 116/78 | 124/84 | 136/94 | 130/88 | 94 | 97 | 108 | 102 | 2199 | 1935 | 2102 | 2092 |
| A8 | 122/76 | 120/82 | 120/90 | 124/90 | 91 | 95 | 100 | 101 | 2080 | 1564 | 1900 | 2201 |
| A9 | 118/62 | 114/56 | 136/84 | 144/88 | 80 | 75 | 101 | 106 | 1608 | 1370 | 2046 | 2667 |
| A10 | 130/74 | 126/74 | 126/82 | 134/90 | 93 | 91 | 97 | 105 | 2557 | 2005 | 2648 | 3011 |
| Mean Values | 127/76 | 123/79 | 133/89+ | 133/89 | 93 | 94 | 104+ | 104 | 2140 | 1716 | 2119+ | 2388 |

Table 36 (continued)

A = Air 1 ATA

B = Air 1 ATA 45 mins. after atropine 1.2 mg. I.M.

C = O2 2 ATA 60 mins. after atropine

D = O2 2 ATA 90 mins. after atropine

ATA = atmospheres absolute pressure

+P $<$ 0.05 when compared with value for B

Table 37

Cardiac output and stroke volume in 5 patients with fixed heart rate breathing air at one atmosphere and oxygen at two atmospheres absolute pressure

| Patient No. | Heart rate (per min.) | Arterial oxygen tension (mm.Hg.) | | Cardiac output (litres per min.) | | Stroke volume (ml.) | |
|---|---|---|---|---|---|---|---|
| | | Air 1 ATA | Oxygen 2 ATA | Air 1 ATA | Oxygen 2 ATA | Air 1 ATA | Oxygen 2 ATA |
| P1 | 72 | 86 | 904 | 5.45 | 4.90 | 76 | 68 |
| P2 | 66 | - | 938 | 5.77 | 5.46 | 87 | 83 |
| P3 | 69 | 85 | 1356 | 6.42 | 5.24 | 93 | 76 |
| P4 | 72 | - | - | 2.50 | 2.38 | 35 | 33 |
| P5 | 65 | 88 | 1243 | 4.83 | 3.97 | 74 | 61 |
| | 70 | 88 | 1243 | 4.85 | 4.46 | 69 | 64 |
| | 75 | 88 | 1243 | 5.21 | 4.06 | 69 | 54 |
| | 80 | 88 | 1243 | 5.20 | 4.21 | 65 | 53 |
| | 85 | 88 | 1243 | 4.72 | 4.21 | 56 | 53 |
| | 90 | 88 | 1243 | 4.93 | 4.04 | 55 | 45 |
| Mean | | | | | $4.20^{+++}$ | | $53^{+++}$ |

Table 37 (continued)

ATA = atmospheres absolute pressure

+++$P < 0.001$ when compared with initial values during inhalation of air at 1 ATA

Table 38

Arterial blood pressure and systemic vascular resistance in 5 patients with fixed heart rate, breathing air at one atmosphere and oxygen at two atmospheres absolute pressure

| Patient No. | Arterial blood pressure (mm.Hg.) | | Mean arterial blood pressure (mm.Hg.) | | Systemic vascular resistance (dyne. sec. $cm.^{-5}$) | |
|---|---|---|---|---|---|---|
| | Air 1 ATA | Oxygen 2 ATA | Air 1 ATA | Oxygen 2 ATA | Air 1 ATA | Oxygen 2 ATA |
| P1 | 104/36 | 122/44 | 58 | 66 | 851 | 1078 |
| P2 | 110/58 | 116/74 | 75 | 88 | 1039 | 1289 |
| P3 | 114/58 | 128/70 | 76 | 88 | 947 | 1344 |
| P4 | 142/50 | 170/66 | 76 | 92 | 2432 | 3092 |
| P5 | 114/46 | 152/52 | 68 | 85 | 1126 | 1713 |
| | 140/68 | 148/74 | 92 | 99 | 1517 | 1775 |
| | 130/62 | 140/78 | 85 | 98 | 1305 | 1930 |
| | 132/68 | 150/80 | 89 | 103 | 1369 | 1957 |
| | 120/66 | 140/80 | 84 | 100 | 1423 | 1900 |
| | 120/70 | 150/84 | 87 | 106 | 1411 | 1720 |

Table 38 (continued)

| Patient no. | Arterial blood pressure (mm.Hg.) | | Mean arterial blood pressure (mm.Hg.) | | Systemic vascular resistance (dyne. sec. cm.$^{-5}$) | |
|---|---|---|---|---|---|---|
| | Air | Oxygen | Air | Oxygen | Air | Oxygen |
| | 1 ATA | 2 ATA | 1 ATA | 2 ATA | 1 ATA | 2 ATA |
| Mean Values | 123/58 | 142/70$^{+++}$ | 79 | 92$^{+++}$ | 1342 | 1780$^{+++}$ |

ATA = atmospheres absolute pressure

+++ $P < 0.001$ when compared with initial value during inhalation of air at 1 ATA

Table 39

Clinical details of Patients (Chapter V)

| | Age | Sex | Diagnosis | Rhythm | Electrocardiogram | X-ray |
|---|---|---|---|---|---|---|
| 1. | 56 | M | A.S., M.S. | A.F. | - | L.A.+, P.A.+, L.V.+ |
| 2. | 40 | M | A.S. (congenital) | S.R. | Posterior Myocardial Ischaemia | - |
| 3. | 44 | M | M.I. | S.R. | - | L.A.+, L.V.+ |
| 4. | 40 | F | M.I. | A.F. | - | L.A.+, L.V.+ |
| 5. | 38 | M | M.S. | A.F. | - | L.A.+, R.V.+ |
| 6. | 48 | M | A.S., M.S., M.I., A.I. | A.F. | Left Ventricular Hypertrophy: Myocardial Ischaemia | L.V.++ |
| 7. | 46 | M | M.S. | S.R. | - | - |
| 8. | 42 | M | M.S. (Post-valvotomy) | S.R. | - | - |
| 9. | 33 | F | A.S., A.I. | S.R. | - | - |
| 10. | 39 | F | M.S., M.I., A.I. | A.F. | - | L.A.+, L.V.+ |

A.S. = Aortic stenosis
M.S. = Mitral stenosis
A.I. = Aortic incompetence
M.I. = Mitral incompetence
A.F. = Atrial fibrillation
S.R. = Sinus rhythm

[illegible] enlargement of left atrium, left ventricle,

Table 40

Cardiac output, heart rate and stroke volume in 10 patients breathing air and oxygenate one atmosphere absolute pressure

| Patient No. | Cardiac Output (litres per min.) | | Heart rate (per min.) | | Sttoke volume (ml.) | |
|---|---|---|---|---|---|---|
| | Air | Oxygen | Air | Oxygen | Air | Oxygen |
| 1. | 3.15 | 3.43 | 84 | 62 | 37 | 55 |
| 2. | 3.85 | 4.16 | 72 | 65 | 53 | 64 |
| 3. | 4.13 | 3.81 | 56 | 62 | 74 | 61 |
| 4. | 2.42 | 2.32 | 104 | 88 | 23 | 26 |
| 5. | 3.80 | 3.43 | 68 | 57 | 56 | 60 |
| 6. | 3.68 | 2.89 | 90 | 84 | 41 | 34 |
| 7. | 2.68 | 3.03 | 60 | 63 | 44 | 48 |
| 8. | 4.69 | 4.78 | 78 | 72 | 60 | 66 |
| 9. | 3.74 | 3.76 | 51 | 48 | 73 | 78 |
| 10. | 2.28 | 2.13 | 108 | 98 | 21 | 21 |
| Mean Values | 3.44 | 3.37 | 77 | 70+ | 48 | 51 |

Table 41

Arterial blood pressure, systemic vascular resistance and myocardial blood flow in 10 patients breathing air and oxygen at one atmosphere absolute pressure.

| Patient No. | Arterial blood pressure (mm.Hg) | | Mean arterial blood pressure (mm.Hg.) | | Systemic vascular resistance (dynes. sec. cm.$^{-5}$) | | Myocardial blood flow (ml./100g/min.) | |
|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | Air | Oxygen | Air | Oxygen | Air | Oxygen |
| 1. | 160/80 | 167/80 | 105 | 100 | 2667 | 2332 | 57.0 | 57.7 |
| 2. | 95/70 | 125/80 | 80 | 95 | 1662 | 1827 | 71.6 | 70.6 |
| 3. | 104/60 | 116/72 | 74 | 84 | 1433 | 1764 | 61.0 | 52.6 |
| 4. | 146/80 | 146/86 | 100 | 98 | 3306 | 3379 | 78.6 | 60.5 |
| 5. | 110/68 | 128/74 | 78 | 86 | 1643 | 2005 | 47.2 | 47.2 |
| 6. | 100/54 | 96/50 | 68 | 64 | 1479 | 1772 | 78.9 | 52.6 |
| 7. | 104/62 | 120/70 | 78 | 88 | 2329 | 2324 | 52.4 | 39.3 |
| 8. | 98/60 | 110/68 | 78 | 84 | 1330 | 1406 | 55.5 | 42.9 |
| 9. | 88/48 | 108/54 | 62 | 70 | 1326 | 1479 | 68.0 | 64.5 |
| 10. | 156/83 | 153/78 | 110 | 110 | 3860 | 4131 | 72.6 | 72.6 |
| Mean Values | 116/66 | 127/71$^{+}$ | 83 | 88 | 2103 | 2242$^{+}$ | 64.3 | 56.1$^{++}$ |

+ $P < 0.05$ when compared with initial value during inhalation of air

Table 42

Arterial and coronary venous blood oxygen values in 10 patients breathing air and oxygen at one atmosphere absolute pressure

| Patient No. | Arterial Oxygen Saturation (%) | | Coronary Venous Oxygen Saturation (%) | | Arterial Oxygen Content (Vols.%) | | Coronary Venous Oxygen Content (Vols.%) | |
|---|---|---|---|---|---|---|---|---|
| | Air | Oxygen | Air | Oxygen | Air | Oxygen* | Air | Oxygen |
| 1. | 95 | 100 | 28 | 38 | 21.37 | 24.36 | 6.30 | 8.55 |
| 2. | 98 | 100 | 46 | 46 | 20.89 | 22.18 | 9.81 | 9.81 |
| 3. | 96 | 99 | 53 | 63 | 20.47 | 22.97 | 11.31 | 13.44 |
| 4. | 95 | 100 | 36 | 44 | 19.14 | 22.01 | 7.25 | 8.87 |
| 5. | 95 | 100 | 30 | 44 | 18.95 | 21.81 | 5.99 | 8.78 |
| 6. | 95 | 99 | 28 | 38 | 13.94 | 16.39 | 4.11 | 5.58 |
| 7. | 93 | 99 | 34 | 40 | 18.94 | 22.03 | 6.93 | 8.15 |
| 8. | 93 | 99 | 37 | 42 | 19.32 | 22.42 | 7.68 | 8.72 |
| 9. | 96 | 99 | 41 | 36 | 14.65 | 16.98 | 6.26 | 5.49 |
| 10. | 94 | 100 | 18 | 28 | 20.59 | 22.77 | 3.94 | 6.13 |
| Mean Values | 95 | 99.5++ | 35 | 42++ | 18.83 | 21.39++ | 6.96 | 8.35++ |

* Corrected to oxygen tension of 600 mm.Hg.

Table 43

Coronary arterio-venous oxygen content difference, myocardial oxygen uptake and myocardial oxygen availability in 10 patients breathing air and oxygen at one atmosphere absolute pressure

| Patient No. | Arterio-Venous Oxygen Content Difference (Vols.%) | | Myocardial Oxygen Uptake (ml./100g/min.) | | Myocardial Oxygen Availability (ml./100g/min.) | |
|---|---|---|---|---|---|---|
| | Air | Oxygen | Air | Oxygen | Air | Oxygen |
| 1. | 15.07 | 15.81 | 8.59 | 9.12 | 12.19 | 14.06 |
| 2. | 11.08 | 12.37 | 7.93 | 8.73 | 14.96 | 15.66 |
| 3. | 9.16 | 9.53 | 5.59 | 5.01 | 12.49 | 12.08 |
| 4. | 11.89 | 13.14 | 9.35 | 7.95 | 15.04 | 13.32 |
| 5. | 12.96 | 13.03 | 6.12 | 6.15 | 8.94 | 10.29 |
| 6. | 9.83 | 10.81 | 7.76 | 5.69 | 11.00 | 8.62 |
| 7. | 12.01 | 13.88 | 6.29 | 5.45 | 9.92 | 8.66 |
| 8. | 11.64 | 13.70 | 6.46 | 5.88 | 10.72 | 9.62 |
| 9. | 8.39 | 11.49 | 5.71 | 7.41 | 9.96 | 10.95 |
| 10. | 16.65 | 16.64 | 12.09 | 12.81 | 14.95 | 16.53 |

Table 43 ( continued)

| Patient No. | Arterio-Venous Oxygen Content Difference (Vols.%) | | Myocardial Oxygen Uptake (ml./100g/min.) | | Myocardial Oxygen Availability (ml./100g/min.) | |
|---|---|---|---|---|---|---|
| | Air | Oxygen | Air | Oxygen | Air | Oxygen |
| Mean Values | 11.87 | 13.04++ | 7.59 | 7.42 | 12.01 | 11.98 |

++ $P < 0.01$ when compared with initial value during inhalation of air.

Table 44

Arterial and coronary venous blood lactate values in 10 patients breathing air and oxygen at one atmosphere absolute pressure

| Patient No. | Arterial Blood Lactate (m-moles/litre) | | Coronary Venous Lactate (m-moles/litre) | | Myocardial Lactate Extraction Ratio | |
|---|---|---|---|---|---|---|
| | Air | Oxygen | Air | Oxygen | Air | Oxygen |
| 1. | 0.854 | 0.721 | 0.277 | 0.410 | 67.6 | 43.1 |
| 2. | 0.599 | 0.555 | 0.543 | 0.299 | 9.1 | 46.1 |
| 3. | 1.043 | 0.865 | 0.677 | 0.743 | 35.1 | 14.1 |
| 4. | 0.876 | 0.843 | 0.355 | 0.666 | 59.5 | 21.0 |
| 5. | 0.455 | 0.566 | 0.477 | 0.455 | -4.8 | 19.6 |
| 6. | 0.788 | 0.732 | 0.666 | 0.555 | 15.5 | 24.2 |
| 7. | 0.699 | 0.666 | 0.421 | 0.577 | 39.8 | 13.4 |
| 8. | 0.788 | 0.643 | 0.721 | 0.577 | 8.5 | 10.3 |
| 9. | 0.721 | 0.677 | 0.388 | 0.266 | 46.2 | 60.7 |
| 10. | 0.710 | 0.488 | 0.433 | 0.322 | 39.0 | 34.0 |
| Mean Values | 0.753 | 0.676+ | 0.496 | 0.487 | 31.55 | 28.65 |

+ $P < 0.05$ when compared with initial value during inhalation of air

Table 45

Arterial and coronary venous pyruvate values in 10 patients breathing air and oxygen at one atmosphere absolute pressure

| Patient No. | Arterial Blood Pyruvate (m-moles/litre) | | Coronary Venous Pyruvate (m-moles/litre) | | Coronary Venous Lactate/Pyruvate Ratio | |
|---|---|---|---|---|---|---|
| | Air | Oxygen | Air | oxygen | Air | Oxygen |
| 1. | 0.044 | 0.041 | 0.027 | 0.034 | 10.18 | 12.0 |
| 2. | 0.046 | 0.056 | 0.042 | 0.026 | 12.93 | 11.4 |
| 3. | 0.050 | 0.044 | 0.045 | 0.044 | 14.91 | 16.7 |
| 4. | 0.035 | 0.035 | 0.034 | 0.035 | 10.44 | 18.9 |
| 5. | 0.043 | 0.043 | 0.032 | 0.041 | 15.00 | 11.1 |
| 6. | 0.046 | 0.043 | 0.040 | 0.037 | 16.82 | 14.8 |
| 7. | 0.025 | 0.025 | 0.017 | 0.024 | 24.91 | 24.2 |
| 8. | 0.026 | 0.028 | 0.015 | 0.023 | 49.05 | 25.4 |
| 9. | 0.025 | 0.018 | 0.017 | 0.011 | 22.82 | 23.5 |
| 10. | 0.023 | 0.020 | 0.014 | 0.017 | 31.84 | 19.0 |
| Mean Values | 0.036 | 0.035 | 0.028 | 0.029 | 20.89 | 17.7 |

# APPENDIX 2

## Critique of the methods used in the investigations

There are many technical difficulties involved in the investigation of the cardiovascular system in man and such studies are therefore particularly prone to fallacies. It is necessary therefore to be especially careful in clinical measurement in order to minimise the errors inherent in many of the techniques which are used. Some of the precautions which were taken to maintain the accuracy of the results of the investigations in this thesis will now be discussed.

Heart rate

The heart rate was measured throughout from electrocardiographic recordings. Care was taken to calculate the rate from a long tracing to avoid errors due to sinus arrhythmia. Inaccuracies due to variation of speed of the recording equipment were avoided by the use of a time marker on all tracings.

Cardiac output

Satisfactory measurement of the cardiac output in man remains a difficult exercise. Indicator dilution techniques are currently recognised to be among the most reliable methods as long as strict attention to detail is maintained. In this study, precautions were taken to ensure that the amount of

dye injected was accurate in every case. The photoelectric earpiece technique which was used to record the dye dilution curves in many of the subjects is open to criticism. It has however been shown that it is a reasonably accurate and reliable method if a meticulous technique is used (Thomas, Malmcrona and Shillingford, 1965). Great care was taken to ensure that the earpiece was correctly applied without undue pressure on the ear and that it did not alter its position throughout the procedure. In most patients little difficult was experienced in obtaining a reasonably flat baseline. The method was found to give satisfactorily reproducible dilution curves and the following are examples of the results obtained in duplicate measurements in 5 consecutive subjects:

Cardiac Output (litres per min.)

| 1st observation | 2nd observation | Difference |
|---|---|---|
| 6.18 | 6.13 | - 0.05 |
| 3.96 | 3.65 | - 0.31 |
| 4.43 | 4.47 | + 0.04 |
| 7.70 | 7.97 | + 0.27 |
| 3.50 | 3.82 | + 0.32 |

The repeatability of this method has previously been shown to be acceptable by Thomas et al. 1965. One of the main disadvantages of the earpiece technique in

the measurement of cardiac output is that only a single dye concentration (the concentration of dye in a mixed venous or arterial blood sample 3 minutes after injection of dye)is used for calibration of the curve. This undoubtedly leaves scope for error in the calculation of the absolute value for the cardiac output. It will not, however, affect the reliability of relative changes in cardiac output as the same calibration factor is used throughout a series of measurements. (Gabe, Tuckman and Shillingford 1962). An improved accuracy of calibration is obtained by the use of an arterial cuvette as several different dye concentrations can be used for calibration purposes. In this investigation the calibration graphs obtained with the Beckman densitometer were linear in most cases. Use of indocyanine green dye in place of Coomassie blue reduces errors due to variation of oxygen saturation in the blood in cyanosed patients. Further errors may occur in severely "shocked" patients due to undetected recirculation of dye occurring throughout most of the inscription of the apparently exponential downslope. (Oriol et al. 1967).

It is hoped, however, that statistical analysis has overcome some of the problems involved

in the measurement of cardiac output in these investigations as the inherent overall variability of the method should be random whereas the effect of inhalation of oxygen is not.

Arterial pressure

Arterial blood pressure was measured in the healthy subjects by sphygmomanometry. It is recognised that this is not an ideal method if accurate results are required but it was used in order to avoid arterial catheterisation. In this study the blood pressure was recorded by the same observer throughout to prevent variation due to observer bias. Errors in blood pressure measurement are systematic and comparative readings by the same observer should be reasonably accurate. In most of the other investigations intravascular pressure recording was used which should give more accurate results. The strain gauge transducers were calibrated directly with a mercury manometer and frequent calibration checks were made at each stage in the procedure. The zero levels of the transducers were also carefully adjusted to mid-chest level at the commencement of each study.

Measurement of myocardial blood flow

The measurement of myocardial perfusion was

carried out using a modification of the method of Cohen et al. (1964). This method has the advantage that it avoids the necessity for direct injection of isotope into a coronary artery, but on the other hand, it requires blood collection from the coronary sinus. This did not present a great problem, and did not cause any added disturbance to the patient. When sampling from the coronary sinus there is a danger of contamination with blood from the right atrium if the tip of the catheter is incorrectly situated. The correct position was confirmed in these investigations by radiography prior to aspiration of samples. Xenon-13 was used in place of Krypton-85 partly because it was easier to obtain, but it does have some advantages; in particular, it has a shorter half-life and there is a lower radiation danger. Cohen et al. (1964) showed that this method correlated well with flows estimated by nitrous oxide and antipyrine methods. The consistency of the results obtained by this method is good as can be seen from the following duplicate measurements which were made in 4 patients.

Myocardial blood flow (ml./100g/min.)

| 1st observation | 2nd observation | Difference |
|---|---|---|
| 52.6 | 48.0 | - 4.6 |
| 73.9 | 78.3 | + 4.4 |
| 73.2 | 73.2 | 0.0 |
| 85.0 | 89.3 | + 4.3 |

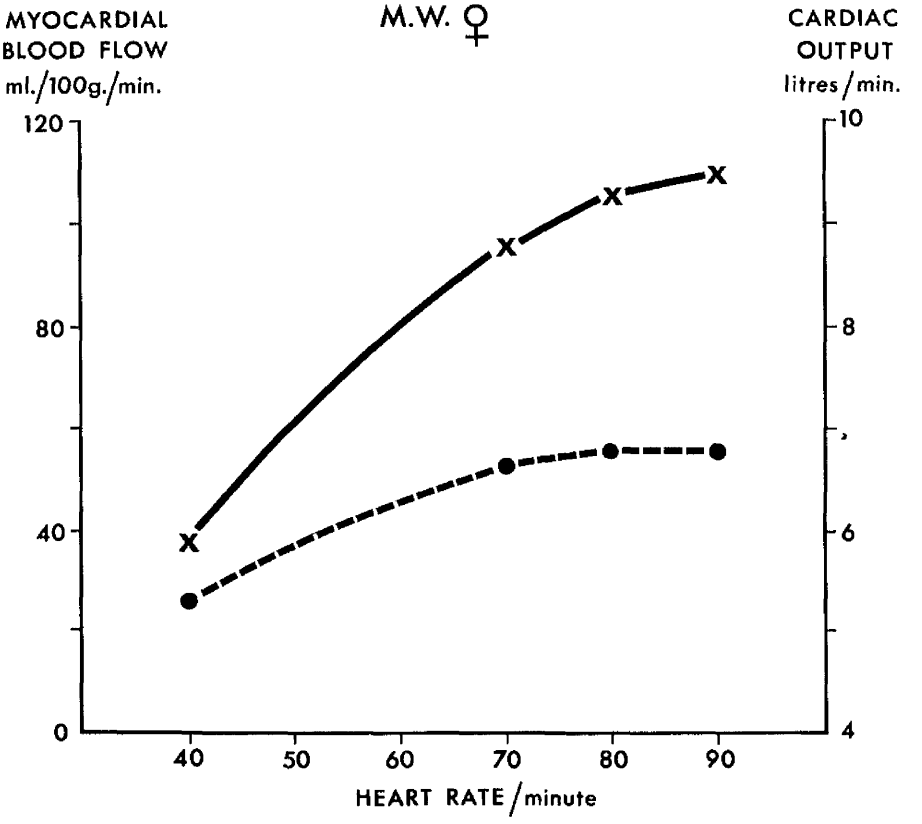


Fig. 1. Measurements of myocardial blood flow (continuous line) and cardiac output (broken line) at different heart rates during artificial pacing in a patient with complete heart block.

Further support for the accuracy of the method was obtained from studies of the change in blood flow which occurred with change in heart rate during pacing in patients with complete heart block (fig. 1). It appears that this is an accurate method of assessment of myocardial blood flow, but it must be remembered that it gives information only about the blood flow to the left ventricle. Moreover, the difference in flow between left and right coronary arteries cannot be assessed.

Blood gas analysis

Before commencing these studies it was observed that there was a considerable error in the value obtained for oxygen tension in blood samples if the blood gas analysis apparatus was calibrated with known gases as instructed by the manufacturers. For this reason a simple tonometer was constructed from two glass syringes rotating in a constant temperature water-bath. Samples of blood were equilibrated with known gas mixtures at both one and two atmospheres pressure. From these studies a calibration factor (1.11) was obtained which was checked at frequent intervals by further tonometry. The calibration factor was found to be fairly constant throughout the range of oxygen tensions which were measured. A very similar regression equation for the I.L blood gas

system has been obtained by Moran, Kettel and Cugell (1966). (X = 1.10 Y for the range 0 - 700 mm.Hg. oxygen tension). In routine use the blood gas analysis equipment was then calibrated with known gas samples and the results obtained on blood samples were adjusted according to the current calibration factor. Polypropylene membrane was used for the oxygen electrode throughout the study. Measurement of carbon dioxide tension showed no significant blood-gas error, but frequent tonometry was carried out to ensure accuracy. Calibration of the pH meter was performed using both high and low known values of pH as controls.

Estimation of lactate and pyruvate levels

Attention was paid to the method of withdrawal of the blood samples in order to reduce error. In every case blood was removed rapidly through a wide-bore cannula or needle and transferred immediately to ice-cold 10 per cent perchloric acid. Estimations were carried out in duplicate and reproducibility was good. In these few cases where there was divergence in the results of duplicate samples both estimations were repeated and the results were accepted only if agreement was then satisfactory.

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# APPENDIX 3

Examples of original recordings made during the investigation

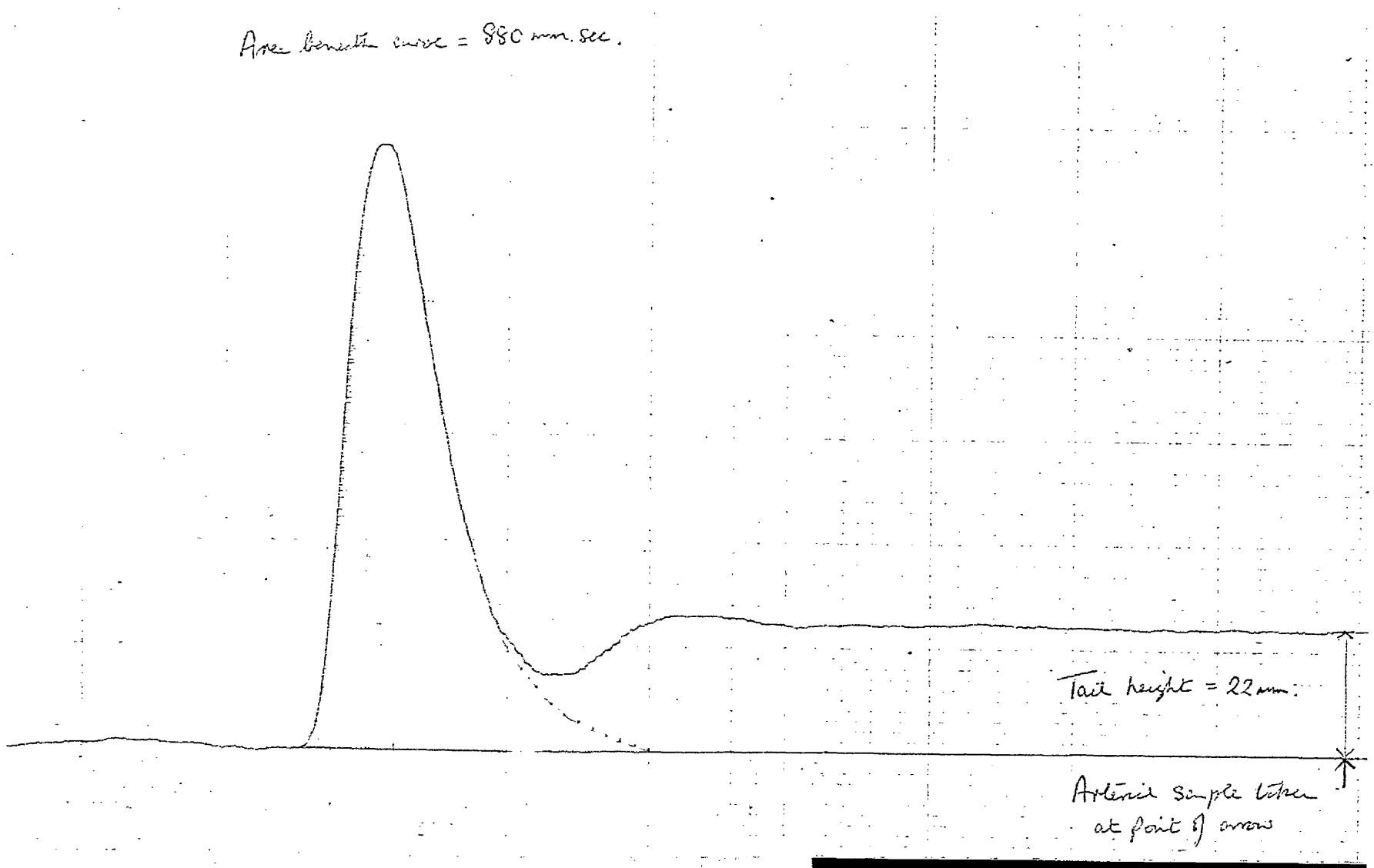



Fig. 1. Specimen of dye dilution curve obtained in a patient with acute myocardial infarction using the photo-electric earpiece and the Cambridge recorder. 40 mg. Coomassie blue dye injected into superior vena cava.

Sample calculation from Fig. 1.

Area of curve = 880 mm.sec.

Tail height = 22 mm.

Dye concentration = 14.4 mg./litre

Packed cell volume = 40%

Dye injected = 40 mg.

Cardiac output (litres per min.)

$$= \frac{\text{Dye injected (mg.)} \times 60}{\frac{\text{Area of curve (mm.sec.)}}{\text{Tail height (mm.)}} \times \text{Plasma dye concentration (mg./litre)}} \times \frac{100}{100 - \text{P.C.V.}}$$

$$= \frac{40 \times 60}{\frac{880}{22} \times 14.4} \times \frac{100}{60}$$

$$= 6.94$$

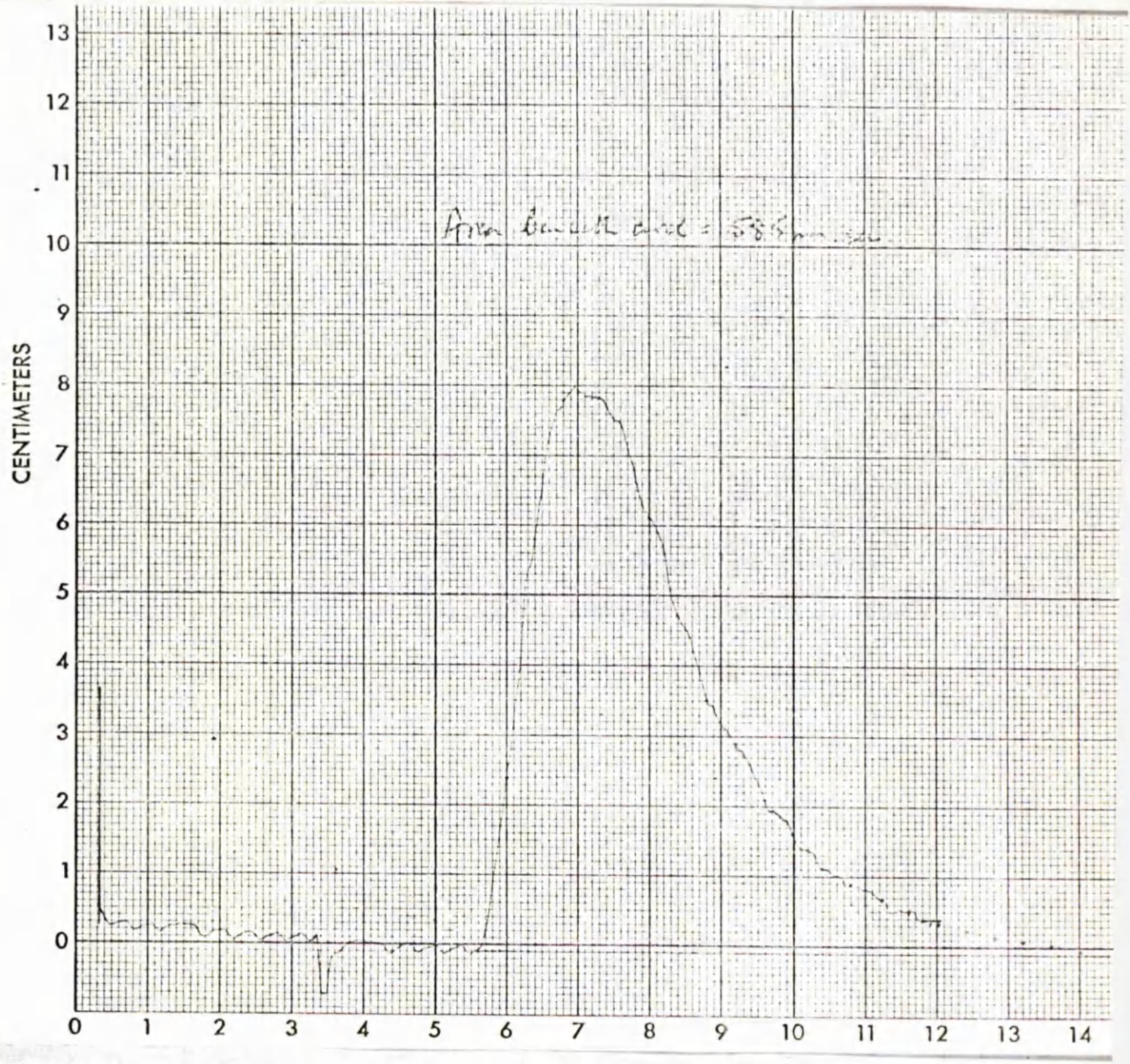



Fig. 2. Specimen of dye dilution curve obtained in a patient using the Beckman cardio-densitometer. 5 mg. Indocyanine green injected into left ventricle. Arterial blood withdrawn from femoral artery.

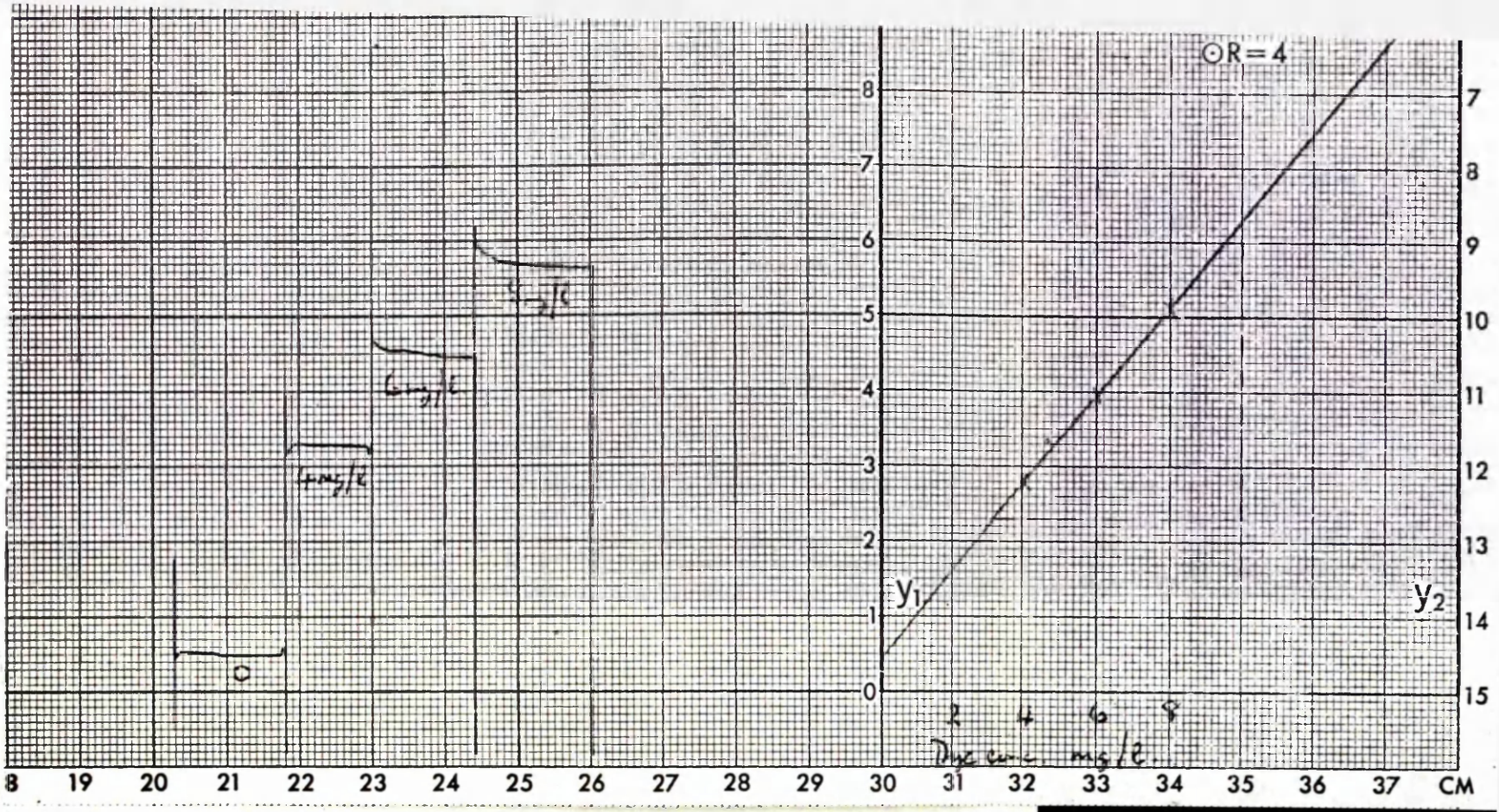



Fig. 3. Estimation of calibration factor for dilution curve shown in fig. 2. Four samples of the patients blood have been passed through the Beckman cardio-densitometer containing 0, 4, 6, 8 mg./litre indocyanine green respectively.

Sample calculation from Figs. 2 and 3

Area of curve = 585 mm. sec.

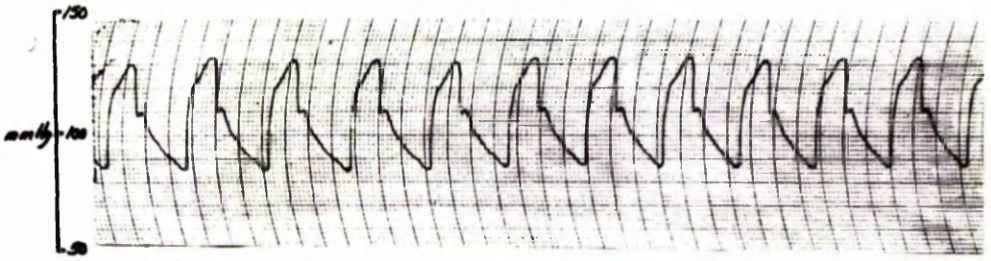
Dye injected = 5 mg.

Calibration factor = $\frac{1.7 \text{ mg./litre}}{\text{cm.}}$

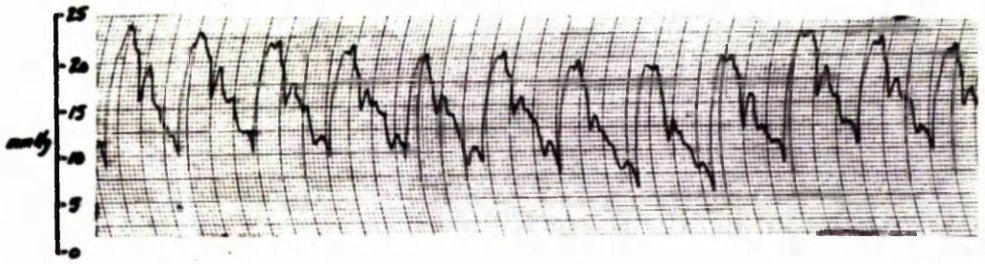
Cardiac output (litres per min.) = $\frac{\text{Dye injected (mg.)} \times 60}{\frac{\text{Area of curve (mm. sec.)}}{10} \times \text{Calibration factor } \left(\frac{\text{mg./litre}}{\text{cm.}}\right)}$

$= \frac{5 \times 60}{\frac{585}{10} \times 1.7}$

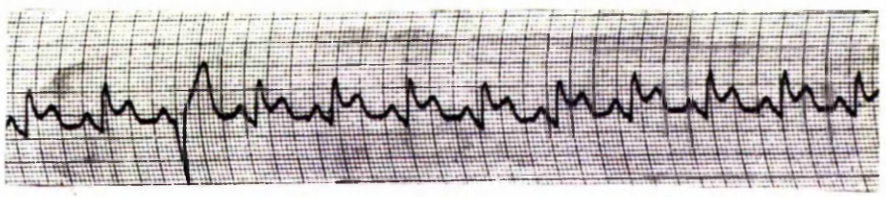
$= 3.02$



Arterial Pressure.



Pulmonary Artery Pressure.



Electrocardiogram.

Fig. 4. Pressure recordings from brachial artery and pulmonary artery in a patient with acute myocardial infarction. The pulmonary artery pressure was measured by allowing a fine catheter to float onwards from an antecubital vein until the pulmonary artery was reached.