HYPOXIA, HYPERBARIC OXYGEN AND HYPOTHERMIA

SOME EXPERIMENTAL AND CLINICAL STUDIES

by

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DEDICATION

To my parents with affection
and gratitude

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ACKNOWLEDGEMENTS

This series of studies was performed whilst a member of the staff of the University Department of Surgery at the Western Infirmary, Glasgow. I am deeply indebted to Sir Charles Illingworth for inspiring my initial interest in surgical research and to both Sir Charles and to Sir Andrew Watt Kay for their constant support and encouragement throughout the years.

Some of the early experiments were completed when Mr G. Smith was my supervisor and I am grateful to him for introducing me to the discipline of laboratory research. During the same period both Dr J.N. Norman and Dr D.G. McDowall were members of the hyperbaric group and their support is acknowledged with pleasure. The later experimental studies were performed with the collaboration of Professor J.R. Parratt, University of Strathclyde. Few are privileged to work closely with a scientist of such intellectual stature.

Almost since the beginning of these studies Mr Ian Douglas has provided expert technical assistance, initially as a junior and in recent years as a much respected colleague. His loyal support, and that of his colleagues over the years, is greatly

appreciated.

The clinical studies have necessarily involved several medical colleagues but I would particularly acknowledge the help of Dr J.G. Mone who has shared my interest in accidental hypothermia.

The technical excellence of the figures in this thesis is due entirely to the high professional standards of Mr Gabriel Donald and his staff of the Department of Medical Illustration at the Western Infirmary. Their tolerance of my repeated visits during past months is gratefully acknowledged.

Finally I wish to record my thanks to my mother for converting an illegible, unco-ordinated scrawl into recognisable text and to my wife for much clerical help in the formative stages. The preparation of the final manuscript was the responsibility of my secretary, Mrs Cathy Cope, to whom I am more than grateful for her skill and untiring dedication.

DECLARATION

The circulatory arrest model was suggested to me by Mr G. Smith. The conduct of the experiments and any modifications from the original were my sole responsibility. Dr J.N. Norman collaborated in the studies on acid-base balance and Dr D.G. McDowall advised on anaesthetic techniques.

The myocardial blood flow technique was adapted by me from the original method of Herd et al (1962) with the assistance of Dr T.I. McBride and the staff of the Regional Physics and Bioengineering Department, Glasgow. Prof. J.R. Parratt collaborated in the studies detailed in Chapters 7, 8 and 9. Some of the data reported in Chapter 7 appears in the M.D. Thesis of Dr J.P. Vance who was at that time a research fellow in my laboratory. The accuracy and reproducibility of several of the laboratory techniques utilized in these studies have been the subject of separate publications.

I initiated and actively conducted all the clinical studies. Dr J.G. Mone collaborated in the prospective clinical investigation of accidental hypothermia.

A selection of the publications relating to the content of this thesis has been included as an integral part of the text.

SUMMARY

This thesis contains details of a series of studies in which the interrelationship of hyperbaric oxygen, hypothermia and tissue hypoxia has been examined. The data derive from both experimental and clinical observations.

The early experimental studies were designed to examine the pathophysiological changes occurring in animals subjected to various generalised hypoxic insults with a view to subsequent investigation of the effects of hyperbaric oxygen and hypothermia. The limitations of both techniques were revealed in later experimental and clinical studies. These investigations, however, were by no means entirely negative and yielded much information which proved to be of value in the management of a number of clinical conditions with an hypoxic basis, e.g., cardiac arrest, shock, severe anaemia, fat embolism and accidental hypothermia.

The introductory chapter includes a summary of the mechanisms of oxygen transport from the lungs to the tissues followed by a brief description of the principal physiological and

biochemical disturbances associated with hypoxia. A review of the subjects of hyperbaric oxygen and hypothermia serves as an introduction to more detailed discussion in later chapters.

The ability of hyperbaric oxygen to increase oxygen storage capacity in the body was demonstrated by means of respiratory arrest in the anaesthetised dog. In the presence of a normally functioning circulation asphyxia was tolerated for periods of over 20 minutes after breathing oxygen at two atmospheres absolute (2 ATA). In the presence of an arrested circulation the equivalent period was eight minutes - representing only a modest increase on the duration of safe circulatory arrest attainable at normal atmospheric pressure. The combination of hyperbaric oxygen (2 ATA) and moderate hypothermia (28 deg C), induced by surface cooling techniques, extended the period of safe circulatory arrest to 30 minutes, approximately 10 minutes more than with normobaric oxygen at the same temperature.

The possibility of increasing the protective role of hypothermia and hyperbaric oxygen by further reduction in body temperature and increase in oxygen pressure was next considered. Cooling dogs to 20 deg C without the aid of cardiopulmonary bypass

presented some initial difficulties which were eventually overcome. The combination of hyperbaric oxygen (2 ATA) and deep hypothermia (20 deg C) was compatible with a maximum period of safe circulatory arrest of about 35 minutes. Increase in oxygen pressure to 3 ATA did not significantly improve this figure. The obvious conclusion from these various experiments was that the predominant factor determining the duration of safe arrest was the reduction in oxygen consumption consequent upon hypothermia. The contribution of hyperbaric oxygen was relatively minor presumably because the extra oxygen did not gain access to the tissues.

The last three chapters of the Experimental Section are devoted to studies of myocardial blood flow and metabolism in the intact dog. Hypoxia was shown to induce a substantial increase in myocardial blood flow. There was a critical arterial PO_2 (35 mm Hg) above which increases in flow did not occur and there was no evidence that hypoxic vasodilatation was mediated through vascular β-adrenoreceptors. The myocardial vascular and metabolic responses to hypoxia and hypercapnia were examined at mederate hypothermia (26 deg C) and although certain differences in these responses as compared with normothermia were detected, it was concluded that coronary vasuular reactivity in the normal heart remained unaltered in character at reduced

temperature. In studies on dogs subjected to moderate and severe haemorrhage, hyperbaric oxygen (2 ATA) did not improve myocardial oxygen availability and failed to modify the changes in cardiac output, work, efficiency and oxygen consumption of the heart that resulted from blood loss.

In the Clinical Section there are four chapters dealing in turn with miscellaneous hypoxic conditions, severe anaemia, fat embolism and accidental hypothermia. The miscellaneous conditions included coal gas poisoning, pulmonary gas exchange disturbances, cardiac arrest and cyanotic congenital heart disease. It was shown that in severe hypoxic hypoxia hyperbaric oxygen could increase arterial PO_2 and if the underlying condition was capable of resolution, long-term benefit might result. In ischaemic conditions, however, the advantages of hyperbaric oxygen were not so obvious.

The possibility that hyperbaric oxygen (2 ATA) might be of value in reducing the hazards associated with blood transfusion in the patient suffering from severe chronic anaemia was explored. Four patients with haemoglobin values ranging from 1.5 to 3.8 g/100 ml were exposed to hyperbaric oxygen during the acute phase of their illness. The resulting increase in tissue oxygen

availability appeared to reduce the related cardiovascular and metabolic disturbances.

Death from fat embolism has been attributed to a number of factors but recently it has been stated that the cause of death in this syndrome is almost invariably the hypoxia secondary to the effects of pulmonary fat emboli. The aim of a study in 11 patients with severe fat embolism was to maintain arterial PO_2 as near as possible within the normal range and, otherwise, to apply only routine supportive measures, e.g., fluids and drugs to restore normal tissue perfusion. Survival of all 11 patients seemed to confirm the overriding importance of eliminating hypoxia in the treatment of the fat embolism syndrome.

The final chapter in the Clinical Section contains details of a prospective study of 44 patients suffering from accidental hypothermia. The aim of the study was to determine the effect on outcome of an aggressive approach to treatment, including the use of active external rewarming techniques. The frequency and severity of hypoxaemia in accidental hypothermia was confirmed together with a number of other biochemical and haematological disturbances. The main components of treatment appeared to be restoration and maintenance of adequate arterial oxygenation and tissue

perfusion; intermittent positive pressure ventilation was indicated in half the patients and fluid repletion was almost always required; vasoactive agents were rarely considered necessary. Active external rewarming was found to be an entirely safe procedure. During the past 10 years no patient in the series died during the phase of rewarming. The overall mortality was 27%, the lowest in any previously published series.

Chapter 1

Introduction and Background

This thesis contains details of a series of studies in which the interrelationship of hyperbaric oxygen, hypothermia and tissue hypoxia has been examined. The data, which have been collected over a period of eighteen years, derive from both experimental and clinical observations. Throughout this period the author has published extensively on all three topics but much of the present material has not previously been submitted for publication.

The early experimental studies were designed to examine the pathophysiological changes occurring in animals subjected to various generalised hypoxic insults with a view to subsequent investigation of the effects of hyperbaric oxygen and hypothermia. The limitations of both techniques were revealed in later experimental and clinical studies. These investigations, however, were by no means entirely negative and yielded much information which proved to be of value in the management of a number of clinical conditions with an hypoxic basis, e.g., cardiac arrest, shock, severe anaemia, fat embolism and accidental hypothermia.

This introductory chapter includes a summary of the mechanisms of oxygen transport from the lungs to the tissues followed by a brief description of the principal physiological and biochemical disturbances associated with hypoxia. A concise

review of hyperbaric oxygen and hypothermia serves as an introduction to more detailed discussion of these topics in later chapters.

OXYGEN TRANSPORT

An adequate oxygen tension (PO_2) is essential for normal metabolism within the cell. In the mammalian mitochondrion the PO_2 lies between 0.13 and 1.33 kPa (1 and 10 mm Hg) (Chance, 1965) although elsewhere in the cell values up to 3 kPa (22.5 mm Hg) are reported (Nunn, 1977a). As long as intracellular PO_2 remains above a critical level substrate utilisation and oxidative phosphorylation, the aerobic process by which energy is produced in the form of adenosine triphosphate (ATP), may proceed normally.

The oxygen transport mechanism (Flenley, 1967) has been likened to a cascade with the partial pressure of oxygen remaining high as it passes from the inspired air through the alveoli to the arterial blood but falling substantially on reaching the capillary blood (Fig. 1.1). The inspired oxygen pressure is determined by the inspired oxygen concentration and the barometric pressure. At normal atmospheric pressure with water vaporised at 37 deg C the

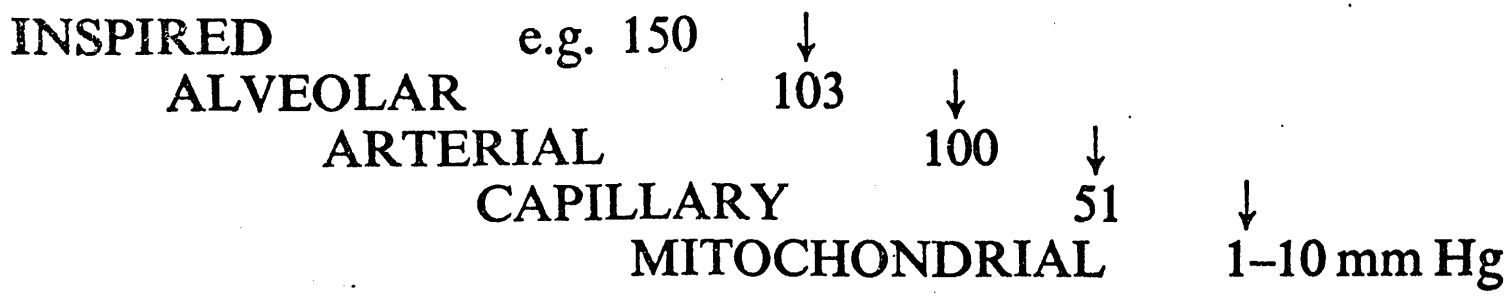


Figure 1.1. Oxygen cascade.

inspired oxygen pressure is 19.9 kPa (149 mm Hg). Alveolar PO_2 is calculated using the alveolar air equation :

$$\text{Alveolar } PO_2 = \text{dry barometric pressure} \left(\text{inspired oxygen concentration} - \frac{\text{oxygen uptake}}{\text{alveolar ventilation}} \right)$$

making allowance, when required for increased accuracy, for the small difference in volume between the inspired and expired gas. The alveolar PO_2 obtained from this equation is an 'ideal' value (Riley et al, 1946), equivalent to the PO_2 of pulmonary end-capillary blood from normally perfused alveoli (about 14 kPa (105 mm Hg)). The alveolar/arterial PO_2 difference results from pulmonary venous admixture which is a combination of (i) frank shunt of deoxygenated blood either bypassing the alveoli or passing through unventilated alveoli and (ii) the scatter of ventilation/perfusion ratios from different parts of the lung. Normally frank or 'true' shunt constitutes less than 1% of cardiac output (Lenfant, 1964). The alveolar/arterial PO_2 difference does not exceed 2 kPa (15 mm Hg) in young healthy adults which, with respect to the alveolar PO_2 indicated above, gives a minimum arterial PO_2 of 12 kPa (90 mm Hg), a value which decreases with age to a mean of about 10.8 kPa (81 mm Hg) in the absence of obvious cardiorespiratory pathology.

Oxygen availability

Oxygen transport from the heart to the tissues (otherwise known as oxygen flux, delivery or availability) is determined by arterial blood flow and the oxygen content of arterial blood, which consists predominantly of oxygen in combination with haemoglobin together with a small amount in physical solution in plasma.

Arterial oxygen content = haemoglobin x arterial oxygen saturation x 1.39 + arterial PO_2 x α

1.39 is the theoretical value of oxygen (ml) which can combine with 1g of haemoglobin. α is the Bunsen solubility coefficient of oxygen in blood (0.0214 + 0.000108 x vol% O_2 capacity ml/ml/atmosphere) or the Ostwald coefficient (0.003 vol%/mm Hg), at 37 deg C.

The normal value for arterial oxygen content is 19.30 ml/100ml blood (of which 0.25 ml/100ml is in physical solution) which when multiplied by a cardiac output of 5000 ml/min gives a figure of 1000 ml/min for oxygen availability. Oxygen consumption is approximately 250 ml/min which means that 75% of the oxygen delivered to the tissues is not utilised under resting conditions. To a certain extent this reserve can be drawn upon under conditions

of hypoxic stress (see section on hypoxia).

Oxygen dissociation

The importance of oxygen dissociation from haemoglobin in determining the adequacy of tissue oxygenation has been appreciated for many years. Changes in the shape and position of the oxygen dissociation curve (Fig. 1.2) may result from alterations in pH, PCO_2, temperature, ionic strength and haemoglobin concentration (Finch and Lenfant, 1972). Oxygen affinity for haemoglobin is also influenced by the level of 2.3 diphosphoglycerate (2.3 DPG), one of a group of organic phosphates contained in the red blood cell (Benesch and Benesch, 1967; Chanutin and Curnish, 1967).

Shifts in the oxyhaemoglobin dissociation curve are conveniently described as changes in P50 (the oxygen partial pressure at which haemoglobin is 50% saturated under standard conditions of pH and temperature), a fall in P50 indicating a shift to the left and a rise a shift to the right. Increase in hydrogen ion concentration causes a shift to the right of the oxygen dissociation curve (the Bohr effect) which is generally considered to hinder oxygen uptake in the lungs and accelerate oxygen exchange in the tissues. Such a shift in the dissociation curve has a negligible effect on arterial

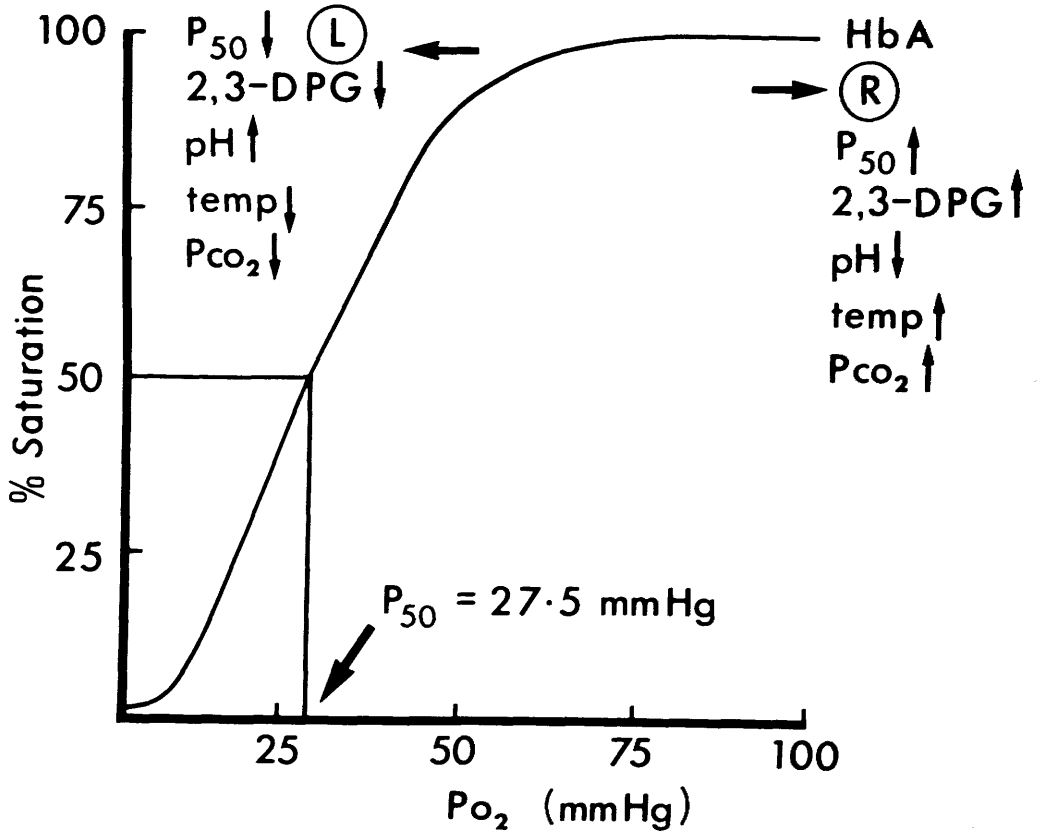


Figure 1.2. Factors influencing haemoglobin oxygen dissociation.

PO_2 unless the shift is extreme but venous PO_2 is markedly affected, rising from a normal of 5.3 kPa (40 mm Hg) to 6.9 kPa (52 mm Hg) for a fall in pH from 7.4 to 7.0 units. Since tissue PO_2 is related to venous PO_2 this effect may be viewed as compensating for some of the adverse features of acidosis. Alkalosis produces a shift to the left of the dissociation curve with the result that blood will not release substantial quantities of oxygen until the PO_2 falls to below normal levels.

2.3 DPG is a haemoglobin ligand, and when its level in the red blood cell falls, oxygen binding increases resulting in a shift to the left of the oxygen dissociation curve and consequent impairment of oxygen release to the tissues. Acidosis reduces the formation of DPG in the red cell, and in states of established acidosis the opposing action of these two mechanisms on oxygen dissociation is balanced. This balance is adversely disturbed if acidosis is corrected acutely, the increase in pH adding to the low DPG level and producing a marked reduction in P50. The reduction in P50 will be corrected only slowly as new DPG is formed. The oxygen dissociation curve of stored blood is shifted to the left (Valtis and Kennedy, 1954) because of its low organic phosphate content and infused red cells may take as long as 24 to 48 hours to acquire a normal complement

of 2.3 DPG (Fig. 1.3). The maximum effect on P50 is of the order of 0.5 kPa (3.8 mm Hg) although blood stored in citrate-phosphate-dextrose is less affected than blood stored in acid-citrate-dextrose preservative (Jesch et al, 1975).

Although an acute reduction in P50 lowers venous PO_2 and may impair oxygen discharge to the tissues, in due course compensatory haemodynamic mechanisms come into play in the form of an increase in blood flow. The magnitude of the increases is often not fully appreciated. For example, depending on the absolute value of oxygen tension in blood reaching the right side of the heart (mixed venous PO_2) a fall of 0.3 kPa (2 mm Hg) may result in a rise in cardiac output of over one litre, and if the fall exceeds 0.5 kPa (4 mm Hg), cardiac output may double to maintain a stable oxygen supply.

Tissue oxygenation

A number of factors influence oxygen delivery to a region including capillary density, local flow rates, blood viscosity, oxyhaemoglobin dissociation, the presence of local oxygen buffers such as myoglobin, vessel wall permeability and the variability of capillary perfusion pattern (Silver, 1977). Ultimately the rate of oxygen discharge from the blood to the

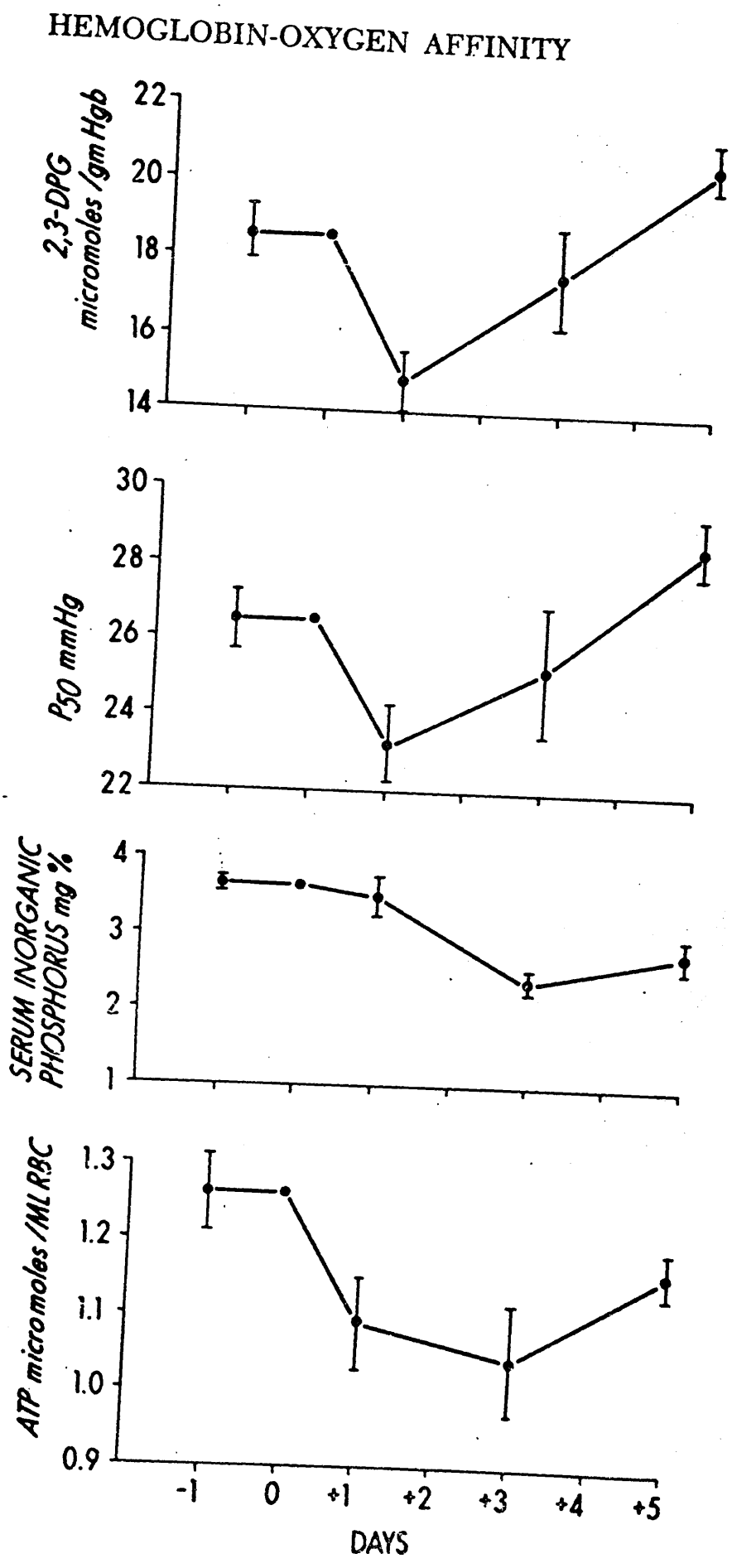


Figure 1.3. 2:3 DPG, P50, inorganic phosphorus and ATP in a group of patients subjected to open heart surgery. 2:3 DPG fell immediately after surgery and took more than two days to recover (After Young, Lichtman and Cohen, 1

tissues depends on the oxygen tension gradient between plasma and the tissue cells.

Early anatomical accounts of the microcirculation envisaged an essentially symmetrical parallel arrangement of the capillaries (Krogh, 1919 a,b) which, together with the assumption of unidirectional blood flow, made it relatively simple to calculate the presumed distribution of oxygen within the tissues (Thews, 1960). This relatively simple system did not appeal to Diemer (1963, 1965) who advanced evidence in support of a countercurrent system of blood flow. More recent studies (Fabel, 1968; Grunewald, 1969) suggest that an asymmetrical parallel array is most probable; blood may flow at varying rates in one direction in some capillaries and in the opposite direction in others and, under certain circumstances, flow may even reverse. The main advantage of this arrangement would be more uniform tissue oxygenation and greater resistance to fluctuations in oxygen delivery. Prediction of actual tissue PO_2 is, however, more difficult and venous PO_2 may at best be only a rough guide to the adequacy of tissue oxygenation (see section on hypoxia). A further complication is that only a proportion of the blood flowing through a region may traverse 'nutrient' or

'exchange' vessels (i.e., those involved in active metabolic processes) the remainder of the blood negotiating 'bypass' or 'preferred route' low impedance vessels. Accurate and reliable measurement of tissue PO_2 is the obvious solution to these difficulties and much valuable information has been obtained from experimental studies using tissue oxygen electrodes and enzyme fluorescence techniques (Kessler et al, 1969; Messmer et al, 1973). Unfortunately tissue PO_2 measurements are open to a number of criticisms and so far have not been widely applied in the clinical situation (Scacci, McMahon and Miller, 1976).

Control of tissue oxygen delivery is exercised both at systemic and local levels. Systemic control is effected via central chemoreceptors and baroreceptors and the brain stem reflexes. Local control mechanisms are less well understood. Silver (1977) describes an autoregulation feedback system (Fig. 1.4) involving a sensor, a comparator, and an effector. The precise nature of the sensor has not been established and a wide range of possibilities exist including some of the respiratory enzymes, local chemoreceptors, molecular oxygen binding processes and the relative concentration of the adenine nucleotides. The comparator is responsible for maintaining PO_2 within a narrow range around the oxygen set point which varies for different tissues, and

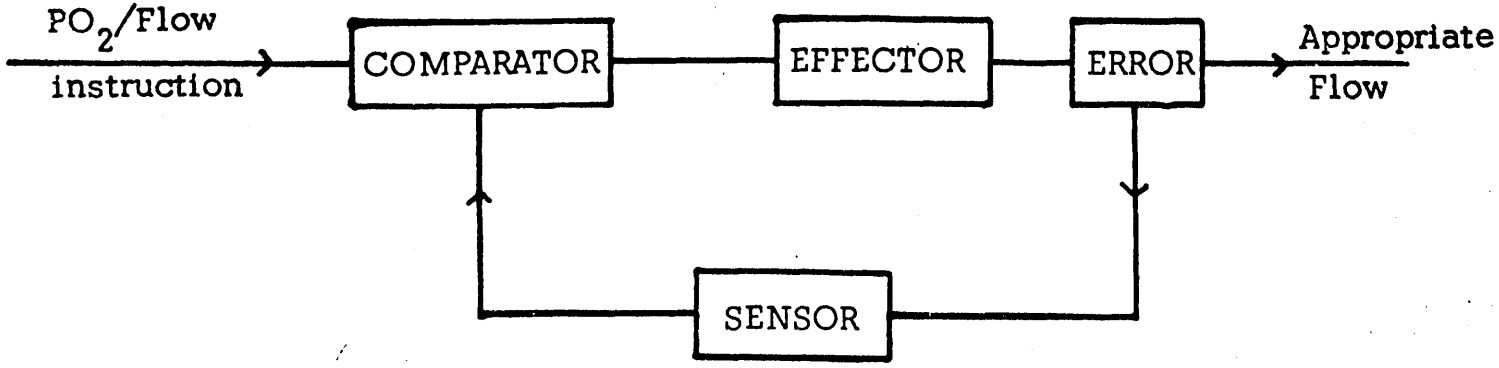


Figure 1.4. *Diagram of an autoregulation feedback system* (after Silver, 1977)

feedback may be fast or slow according to individual tissue requirement. The effector may take the form of pre-capillary sphincters but the capillaries themselves may exercise some control over their blood flow by proximal endothelial engorgement. The connection between these three mechanisms may be nervous, humoral or by membrane transfer.

HYPOXIA

Hypoxia not only stops the machine but wrecks the machinery. According to the Barcroft classification the causes of hypoxia fall readily into four categories - hypoxic, anaemic, stagnant and histotoxic. An alternative classification (Lambertsen, 1966) also has four subdivisions but arranged in a format more consistent with recent knowledge:

1) diminished blood oxygen carriage may be due to a low arterial PO_2 or to a low arterial oxygen content with a normal PO_2. In the former (corresponding to hypoxic hypoxia in the older classification) the low arterial PO_2 is a consequence of breathing gas with a reduced PO_2 or of defective pulmonary gas exchange; chemoreceptor activity is increased. In the latter (corresponding to anaemic hypoxia) the low arterial oxygen content occurs as a result

of reduced haemoglobin concentration or of defective haemoglobin oxygen carriage as in carbon monoxide poisoning or in any condition leading to the formation of methaemoglobin; stimulation of chemoreceptor activity is minimal.

2) diminished blood flow (corresponding to stagnant hypoxia) may be ischaemic or congestive in origin and generalised or localised in extent. In ischaemia an inadequate arterial blood supply causes tissue damage commensurate with the degree of reduction in blood flow and leads to the sequelae normally associated with shock (in the generalised form) or gangrene (in the localised form). Congestion and oedema usually result from venous obstruction which may be severe enough to produce thrombosis in the localised form; the consequent hypoxia is of a less dramatic character than that which follows arterial obstruction.

3) Hypoxia resulting from oxygen requirement being in excess of supply has no equivalent in the older terminology. A discrepancy between oxygen supply and demand may arise in exercise, convulsions and sepsis.

4) histotoxic hypoxia occurs when there is acute depression or inactivation of cellular oxidative systems such that the cells are unable to utilise the oxygen presented to them. Examples of this type of hypoxia are

poisoning by cyanide, sulphide and by exposure to excess amounts of oxygen.

Severity of hypoxia

The severity of hypoxic damage is influenced by a number of factors. Clearly the nature and extent of the initiating insult have an important bearing on outcome and relate to the body's ability to mobilise compensating mechanisms (Fig. 1.5).

Acute circulatory arrest and chronic hypoxaemia are at opposite ends of the spectrum, the one followed by death in minutes and dependent largely on the state of the 'oxygen stores', the other compatible with life by virtue of compensatory increases in cardiac output and haemoglobin oxygen carriage. The oxygen stores of the body are small and average 2 litres in a 70 kg man (Cherniack and Longobardo, 1970); the major proportion is in the blood and the bulk of the remainder is in the lungs (functional residual capacity). Pulmonary oxygen storage can be increased substantially by breathing oxygen with the result that asphyxia may be tolerated for as long as eight minutes;

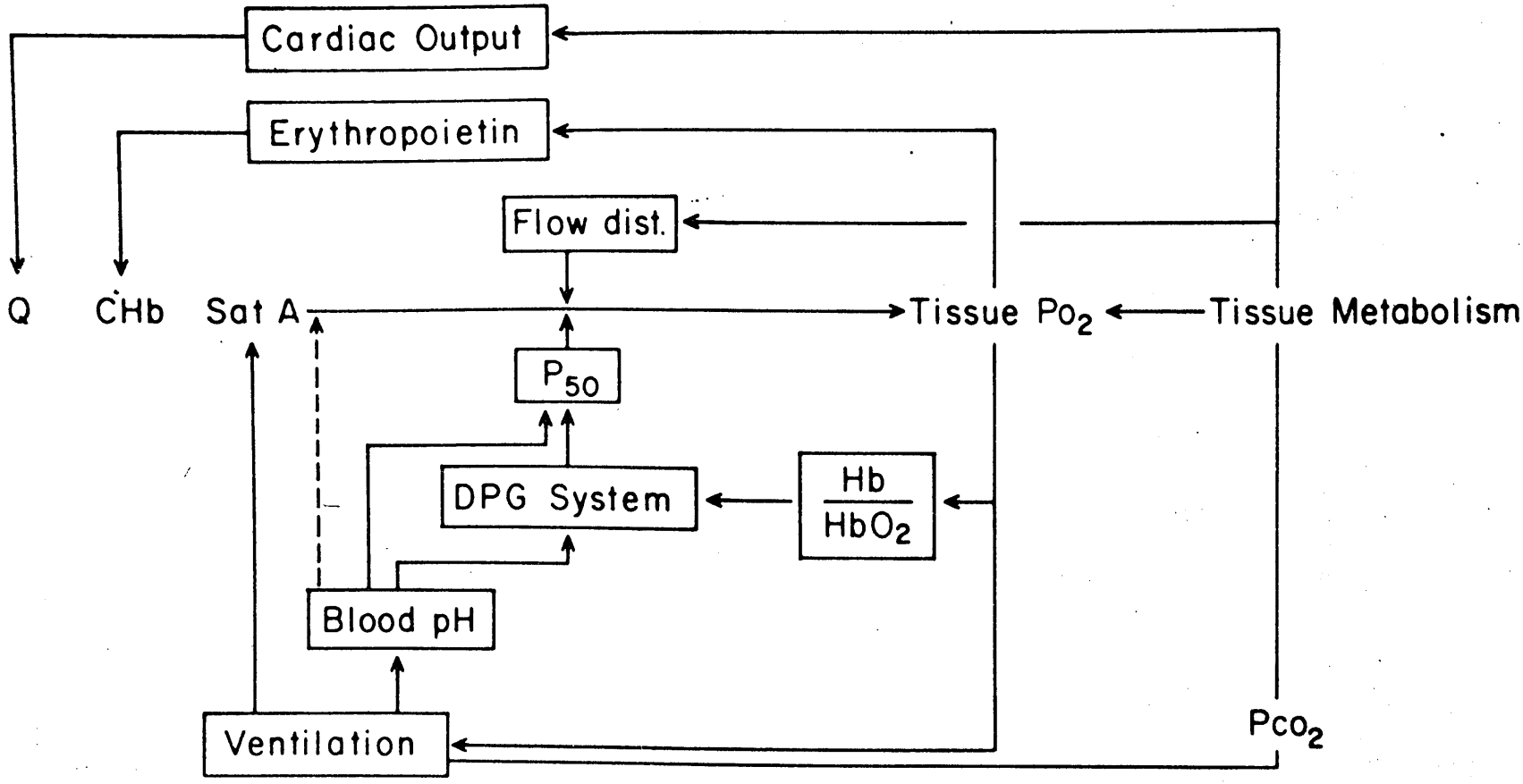


Figure 1.5. Tissue oxygen supply and its regulation; Q - cardiac output, CHb - haemoglobin concentration, Sat A - arterial oxygen saturation (after Finch and Lenfant, 1972).

the comparable value after air breathing is about one minute (Nunn, 1977b). Acute hypoxia appears to be more injurious to previously normally oxygenated tissues than to chronically hypoxic tissues possibly because glucose depletion in the latter reduces lactic acid formation (Geddes, 1967). Finally, by affecting oxygen consumption, metabolic rate modifies the impact of hypoxia on intracellular mechanisms. Pyrexia accelerates the onset of hypoxia and the opposite, i.e., protective, effect of hypothermia has been exploited in clinical practice for many years. Differences in metabolic rate between organs account, in part, for the variation in susceptibility to hypoxia from one tissue to another although the principal factor in this regard is glycogen content. Brain, with a high metabolic rate for oxygen and glucose and virtually no glycogen reserve, can withstand hypoxia for only a few seconds while resting skeletal muscle with large glycogen stores can last for two to three hours. Heart, liver and kidney occupy intermediate positions and resistance to hypoxia can be enhanced by, for example, inducing asystolic arrest of the heart or increasing glycogen stores in the liver.

In the presence of an adequate oxygen supply ATP is formed

continuously from the reaction of adenosine diphosphate (ADP) with inorganic phosphate. The energy released from hydrolysis of ATP sustains several essential processes within the body including muscle contraction, nerve excitation, active transport and synthesis of various compounds (exergonic reactions). All three foodstuffs contribute to a final common pathway which consists of the tricarboxylic acid cycle and the electron transport chain (Fig. 1.6). The common point of entry into the cycle is acetyl-coenzyme A (acetyl-CoA) and the combined processes thereafter yield 30 molecules of ATP per molecule of glucose and 17 molecules of ATP per 'molecule' of fatty acid in addition to contributions from transamination of certain amino acids which enter the cycle beyond acetyl-CoA. With the onset of hypoxia the tricarboxylic cycle becomes inactive and the only mechanism for the production of ATP is the much less effective Embden-Meyerhof pathway (Fig. 1.7). Only two molecules of ATP are produced by this cytoplasmic process and an unlimited supply of glucose substrate is essential. The pyruvate so formed is converted to lactate preventing an otherwise lethal accumulation of reduced nicotinamide adenine dinucleotide (NADH). Although the profound reduction

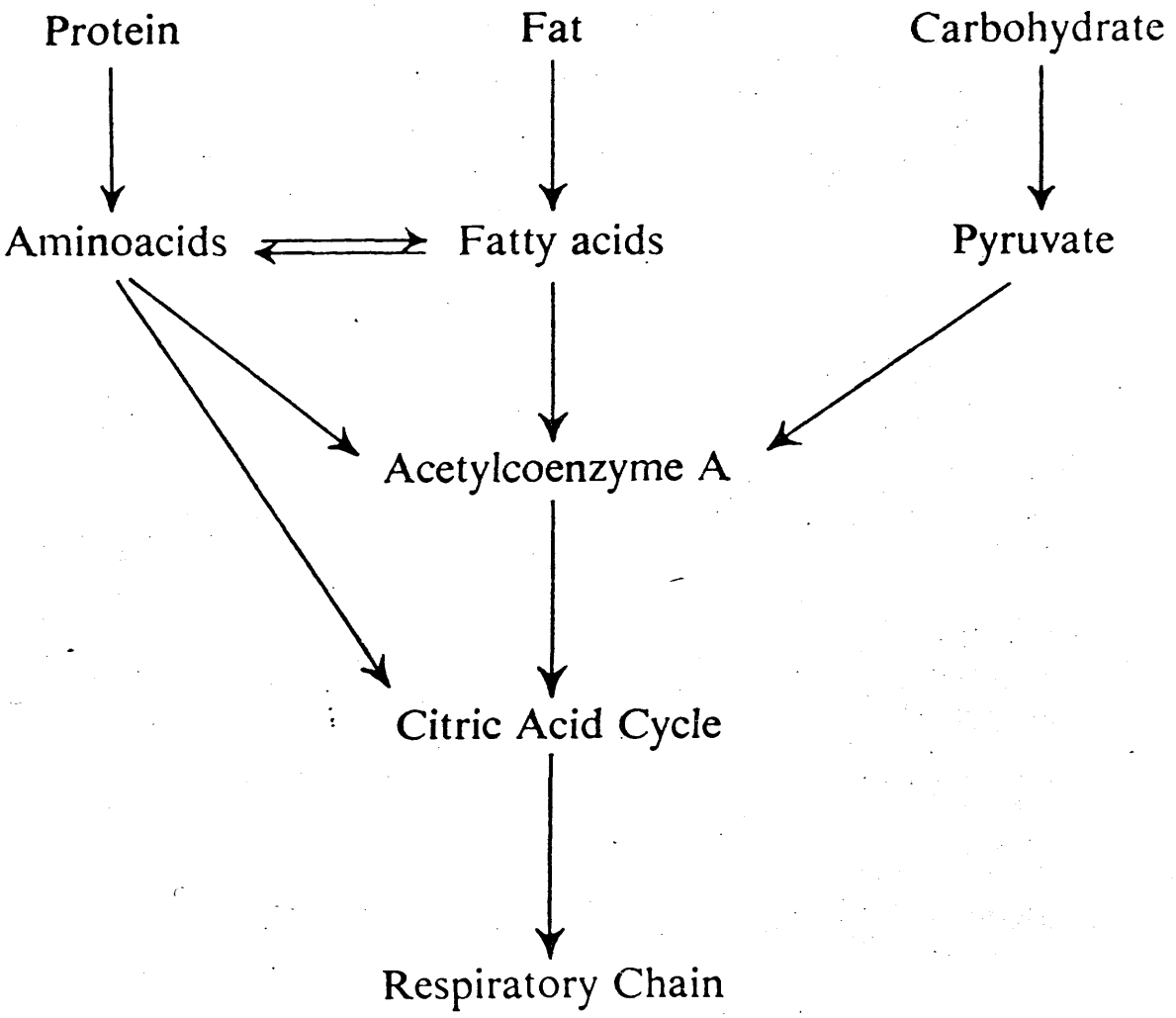


Figure 1.6. Schema of relationship between fat, protein and carbohydrate metabolism and tissue respiration (Chamberlain, 1974).

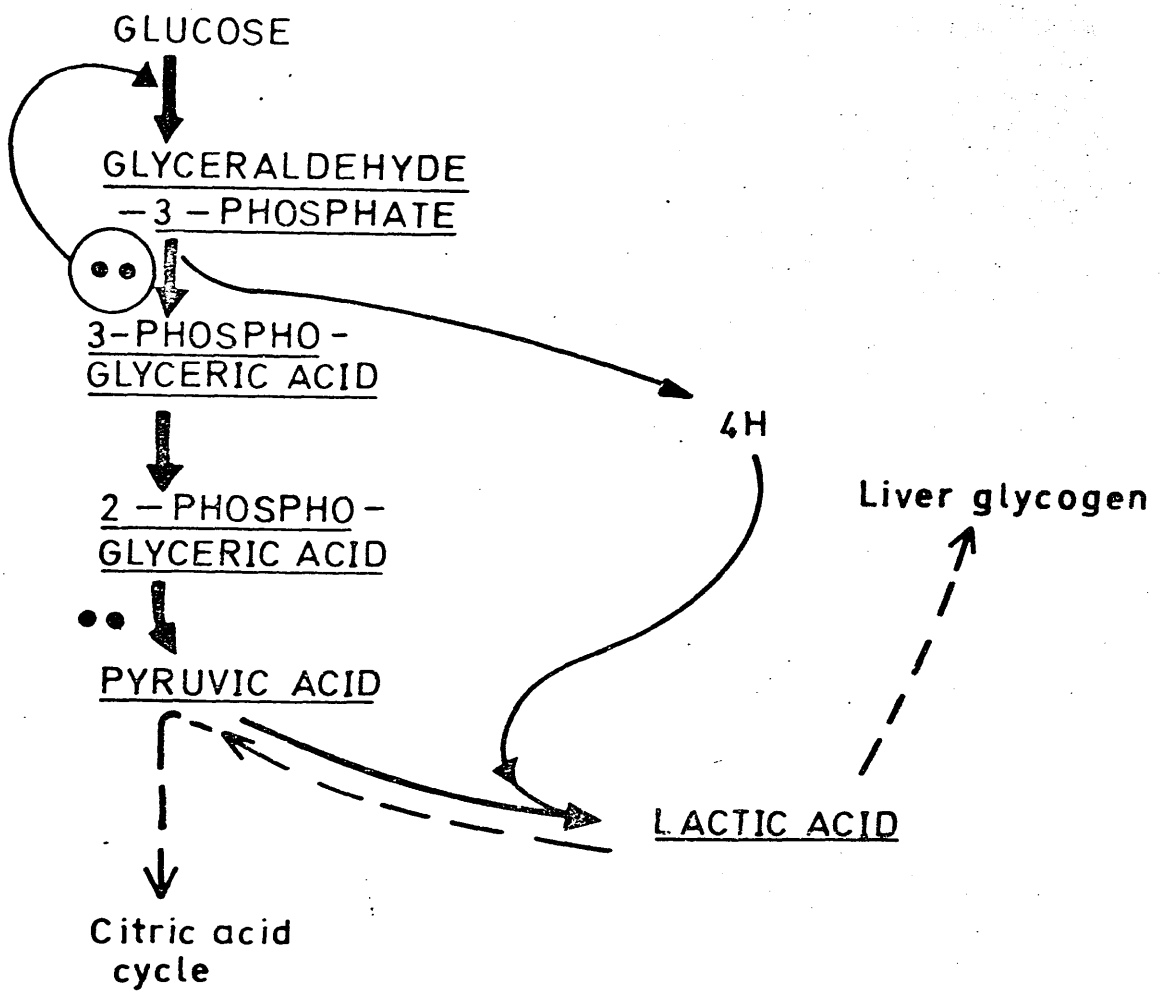


Figure 1.7. The Embden-Meyerhof pathway for anaerobic metabolism of glucose. Underlining indicates that two molecules are formed from one molecule of glucose. ATP production is shown by black dots, those produced in the second reaction being set against the two which are required to energise the first reaction. There is thus a net production of only two molecules of ATP per molecule of glucose.

in ATP formation leads to depression of exergonic reactions the Embden-Meyerhof pathway is nevertheless an important defence mechanism against the damaging effects of hypoxia (Alberti, 1977).

Detection and Assessment of Hypoxia

Detection of tissue hypoxia presents difficulties. Tissue PO_2 measurements seem the obvious solution and have proved to be of value under carefully controlled experimental conditions when the problems of electrode calibration and siting e.g., in relation to blood vessels, are not insurmountable (Lubbers and Kessler, 1972). In clinical practice such measurements have been largely restricted to the use of non-invasive transcutaneous electrodes; a linear relationship between the PO_2 of skin warmed to 44 deg C and arterial oxygen tension has been demonstrated (Al-Diaidy et al, 1977). Because of the relative difficulty of tissue PO_2 measurement, alternative sites have been sought and the results of such measurements in cerebrospinal fluid (Schoemaker, 1965), in lymph (Jacobson, 1965), in interstitial fluid (Hunt, Ledingham and Hutchison, 1966) and in urine (Bird and Bloor, 1968), amongst others, have been evaluated. The commonest indirect site for PO_2 determination, however, is venous blood. Venous PO_2 is a reflection

of overall tissue PO_2 but may be used to gauge hypoxia only under certain circumstances. The blood sampled must be draining tissue which is more or less uniformly hypoxic - patchy ischaemia will result in a disproportionate volume of blood from normally perfused tissue reaching the veins; in addition, the cells must be metabolically active, otherwise the venous blood will not become deoxygenated. In spite of these limitations venous PO_2 is measured routinely in the experimental laboratory and may be of some value in clinical practice, where the commonest measurements are of mixed venous and jugular bulb PO_2.

Mixed venous oxygen tension (or saturation) is a good indicator of the overall adequacy of tissue perfusion and oxygenation (Kasnitz et al, 1976). Ideally a true mixed venous sample should be obtained through a pulmonary artery catheter but samples withdrawn from a catheter in the right atrium may be an acceptable alternative (Schienman, Brown and Rapaport, 1969). Recently, apparatus has been developed which, by means of a dual wavelength infrared fiberoptic system, allows continuous measurement and display of mixed venous oxygen saturation (Polanyi, 1974). If arterial oxygen is

stable, mixed venous oxygen saturation (normal value 70 per cent) varies directly with cardiac output and inversely with oxygen consumption. In certain clinical situations, e.g., after cardiac surgery, oxygen consumption remains largely unaltered (Raison et al, 1970) and under these circumstances mixed venous oxygen saturation is an excellent guide to changes in cardiac output; a value below 50 per cent is associated with a low cardiac output and a poor prognosis (Kasnitz et al, 1976). In other clinical situations e.g., sepsis, interpretation of changes in mixed venous oxygen saturation may be more difficult since a number of factors may be changing simultaneously e.g., arterial oxygen content and oxygen consumption. Jugular bulb PO_2 is a useful practicable measurement of the state of oxygenation of the brain and consciousness is lost when the PO_2 falls below about 2.7 kPa (20 mm Hg), which would correspond roughly to an arterial oxygen tension of 4.8 kPa (36 mm Hg) (Nunn, 1977c).

Both tissue and venous PO_2 measurements suffer from the disadvantage that, even if valid and accurate, their real significance may be satisfactorily interpreted only when related to some other index of hypoxia. Furthermore, cell

function does not respond uniformly to a fall in PO_2 and structural damage is the last event in the sequence. This accounts, for example, for the observation that reduction in the formation of neurotransmitter substances in the brain may lead to unconsciousness at a level of hypoxia not associated with a breakdown in membrane transport systems (Miller, 1977).

A number of different techniques are used to assess tissue hypoxia. Spectrophometric analysis of excised tissue reveals the consequences of hypoxia on the respiratory chain enzymes in the form of reduced ATP/ADP and creatine phosphate/creatine ratios and an increased NADH/NAD ratio. The latter may also be studied in vivo using fluorometric techniques (Kessler et al, 1969) Direct monitoring of tissue pH such as from an electrode placed on the surface of a muscle through a small skin incision (Kung, Le Blanc and Moss, 1976) is a useful measure of hypoxia which may anticipate subsequent changes in the blood. In clinical practice, the effects of reduced oxygen tension are most commonly measured by changes in the blood levels of lactate, hydrogen ion, potassium and certain cellular enzymes (e.g., lactate dehydrogenase, aspartate transaminase and alanine transaminase).

Lactate and pyruvate are related to one another as in the following equations:

$$\text{Lactate} + NAD^+ \rightleftharpoons \text{pyruvate} + NADH + H^+$$

$$\frac{[\text{Lactate}]}{[\text{Pyruvate}]} = \frac{[NADH]}{[NAD]} \cdot \frac{1}{K} \cdot [H^+]$$

The ratio of lactate to pyruvate (L/P) is proportional to the ratio of NADH to NAD. A rise in L/P ratio in the blood will reflect intracellular changes in the NADH/NAD ratio on the assumption that lactate and pyruvate are freely and equally diffusible from inside the cell, and that a state of equilibrium has been reached. One further point must be borne in mind. An increase in hydrogen ion concentration will theoretically increase L/P ratio without necessarily any change in redox state (Alberti, 1977; Cohen and Woods, 1976). The term 'excess lactate' (Huckabee, 1958) has little obvious advantage over L/P ratio and is less popular than formerly. Arterial pH may also be used as an indicator of hypoxia but it is, of course, influenced by an even greater number of factors than lactate. The increase in serum potassium during hypoxia is a result of the build up of hydrogen ion concentration displacing potassium ions from within the cell.

Release of cell enzymes into the circulation is a harbinger of cell death.

HYPERBARIC OXYGEN

Effects on oxygen transport

The term hyperbaric oxygen (OHP) signifies the administration of oxygen at pressures exceeding normal barometric pressure. The distinction from conventional oxygen administration is a matter of descriptive convenience rather than of physiological importance. There is certainly no clearcut change in the effects of oxygen at a pressure of 101 kPa (760 mm Hg).

As inspired oxygen pressure increases, nitrogen is rapidly washed out of the tissues and ultimately the difference between ambient oxygen pressure and alveolar oxygen pressure consists solely of the sum of the partial pressures of water vapour and carbon dioxide. At three atmospheres absolute (ATA), for example, the ambient pressure is 101 x 3 = 303 kPa (2280 mm Hg), and with 100% oxygen, normal body temperature and normal ventilation, the alveolar PO_2 can be 303 - (6.25 + 6.38) = 290.4 kPa (2193 mm Hg). This represents a 22-fold increase over the PO_2 of air breathing at normal pressure. (For reasons principally relating to oxygen toxicity, pressures in excess of three ATA are not used in clinical practice).

Early studies of the alveolar/arterial PO_2 difference in man during 100% oxygen breathing at increased pressure suggested values of several hundred mm Hg (Lambertsen et al, 1953 a and b; Whalen et al, 1964 a and b; Rosenberg, Shibata and MacLean, 1966). Such differences, had they been confirmed, would have indicated major derangement of pulmonary function. Later investigations from this laboratory (McDowall, Ledingham and Tindall, 1968) indicated the source of possible previous technical errors and revealed that, in the short term at least, there were no statistically significant differences in the mean values for alveolar/arterial PO_2 difference at one, two and three ATA(Table 1.1). The absence of a large alveolar/arterial difference at hyperbaric pressures was subsequently confirmed (Clark and Lambertsen, 1971a).

From the standpoint of the clinical and experimental application of hyperbaric oxygen the Glasgow data (Table 1.2) demonstrated that the arterial PO_2 values attainable with normal respiratory function were very close to the values predictable on theoretical grounds. It should be emphasised that this statement is true for limited exposure to oxygen - at least three to five hours (Rosenberg, et al, 1966; Dewar et al, 1972); longer exposure to oxygen produces pathological changes in the lungs (Clarke et al, 1973; Shields, Smith and Ledingham, 1975) which are associated with a rapidly progressive

Table 1.1 Mean results for (A-a)DO_2 during 100% O_2 breathing at 1, 2, and 3 ATA after correction for heparin dilution.

At 1 ATA (A-a)DO_2 = 17 mm Hg (SD ± 7 mm Hg)

At 2 ATA (A-a)DO_2 = 10 mm Hg (SD ± 28 mm Hg)

At 3 ATA (A-a)DO_2 = 36 mm Hg (SD ± 33 mm Hg)

Table 1.2 Blood gas results during oxygen breathing at 1, 2, and 3 ATA pressure after correction for heparin dilution

Chamber pressure	Volunteer's No.	$PaCO_2$	PAO_2	PaO_2	(A-a)DO_2
1 ATA	12	31.2 (D)	686	666	20
	13	34.1 (D)	683	665	18
	14	36.2 (D)	681	659	22
	15	44.1 (D)	662	657	5
	16	24.0 (D)	682	662	20
2 ATA	1	36.0 (D)	1,428	1,431	-3
	2	38.5 (D)	1,426	1,445	-19
	33	32.5 (D)	1,428	1,383	45
	4	35.0 (D)	1,448	1,457	-9
	5	24.0 (I)	1,446	1,411	35
3 ATA	6	30.0 (I)	2,128	2,112	16
	7	36.0 (I)	2,206	2,226	-20
	8	32.5 (I)	2,224	2,155	69
	9	33.5 (D)	2,200	2,165	35
	10	36.5 (D)	2,219	2,162	57
	11	33.2 (D)	2,215	2,159	56

All results expressed in mm Hg. (D) = measured by direct CO_2 electrode, (I) = measured by interpolation technique.

increase in alveolar/arterial PO_2 difference.

In spite of the substantial increase in arterial PO_2 the increase in oxygen content is only of the order of 6 ml/100 ml blood (Table 1.3) at three ATA. Nevertheless, this extra amount of oxygen, largely in physical solution (Fig. 1.8), is equivalent to the normal blood oxygen extraction of the body as a whole (Dittmer and Grebe, 1958) leaving the haemoglobin supply of oxygen largely untapped. This fact received convincing experimental support many years ago when Haldane (1895) was able to protect mice from a normally lethal environment of carbon monoxide by the simultaneous administration of oxygen at two ATA. The same principle was demonstrated in the "life without blood" experiments of Boerema et al (1960) in which dogs tolerated profound degrees of anaemia with the aid of hyperbaric oxygen. It should be remembered, however, that because of oxygen extraction requirements in excess of 6 ml/100 ml blood, certain organs e.g., the heart and brain, would not survive such extreme hypoxic insults without access to some of the oxygen carried by haemoglobin, or a proportionate increase in blood flow. The effect of a large increase in arterial oxygen tension upon

Table 1.3

EFFECTS OF INCREASING INSPIRED OXYGEN PRESSURE ON ARTERIAL AND VENOUS PO_2 VALUES

	At normal barometric pressure		At 2 atm. absolute	At 3 atm. absolute
Inspired gas	Air	Oxygen	Oxygen	Oxygen
Arterial PO_2				
(kPa)	13	80	175	270
(mm Hg)	100	600	1313	2026
Arterial oxygen content				
(ml/100ml)	19.3	21.3	23.4	25.5
Venous oxygen content				
(ml/100ml)	14.3	16.3	18.4	20.5
Venous PO_2				
(kPa)	5.2	6.4	9.1	48.0
(mm Hg)	39	48	68	360

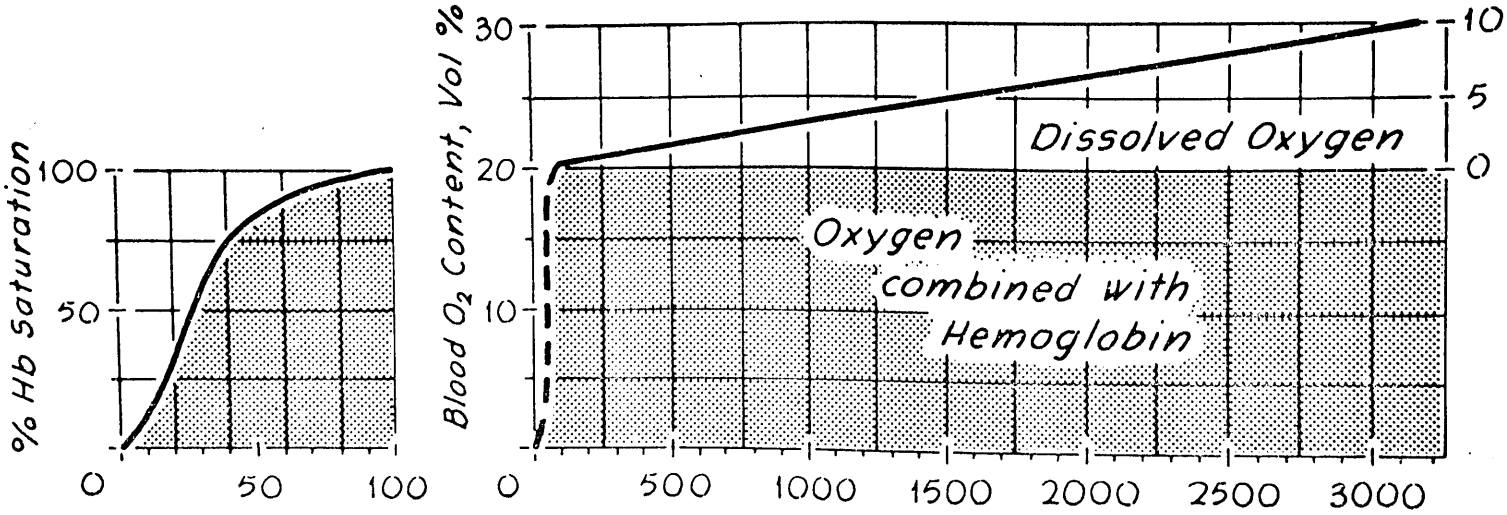


Figure 1.8. Effect of inspired oxygen pressure on blood oxygen content (After Lanphier and Brown, 1966).

venous oxygen tension can be readily understood if reference is made to figures 1.9 and 1.10. In a tissue which extracts, say, eight volumes of oxygen when the arterial PO_2 is about 13 kPa (100 mm Hg) the venous PO_2 will be about 4 kPa (30 mm Hg). If the arterial PO_2 is raised to 266 kPa (2000 mm Hg), about three ATA, the venous oxygen tension will be 8.0 kPa (60 mm Hg). When the mean oxygen extraction is lower, correspondingly increased venous PO_2 values can be expected. In conscious man, mixed venous (right atrial) PO_2 has been shown to rise from 5.5kPa (41 mm Hg) during air breathing at normal pressure to 56.4 kPa (424 mm Hg) during oxygen breathing at three ATA (Whalen et al, 1964a). It is clear that the increase in venous PO_2 in no way reflects the magnitude of increase in arterial PO_2 and only at the upper limit of the clinical hyperbaric range does mixed venous haemoglobin become fully saturated with oxygen. This pattern can be influenced by a number of factors which affect blood flow and oxygen consumption e.g., increased carbon dioxide tension and anaesthesia.

From what has been written already in this chapter it will be obvious that changes in mean tissue PO_2 resulting from hyperbaric oxygenation are considerably less dramatic than

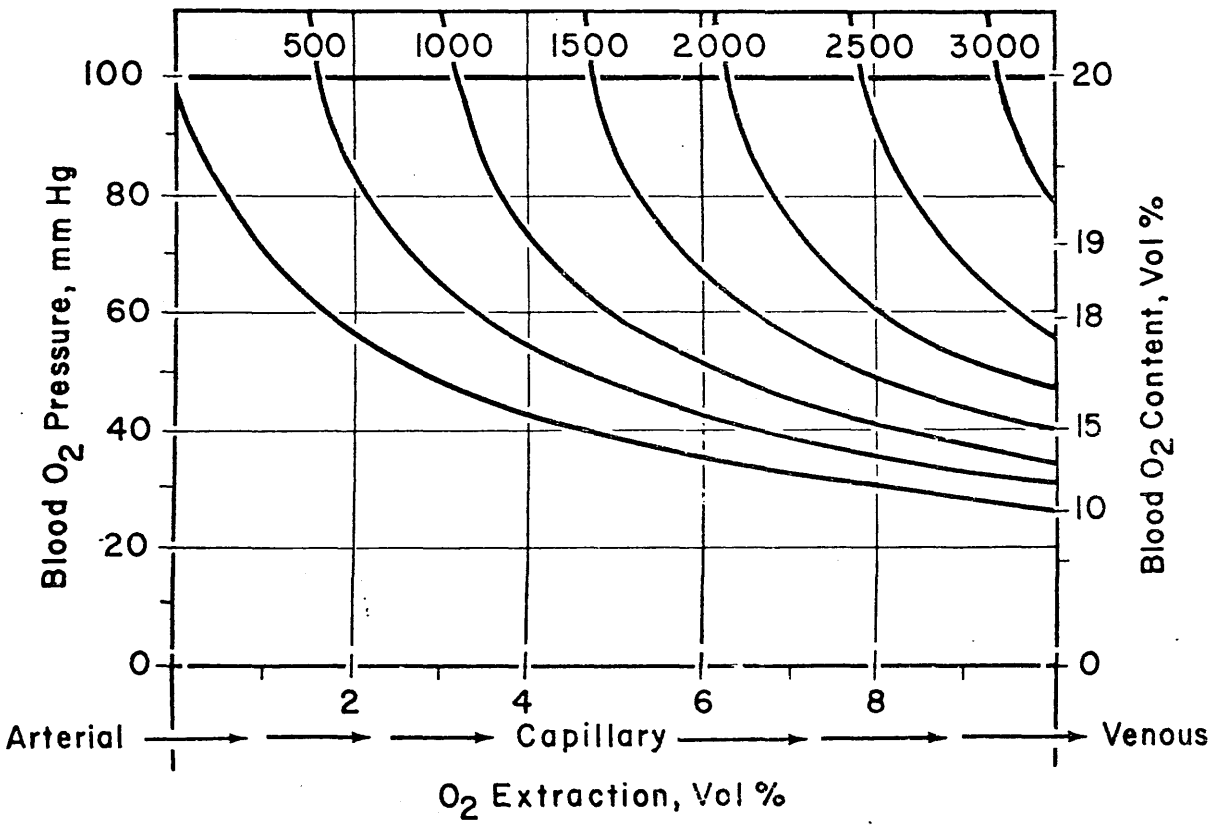


Figure 1.9. Blood oxygen pressure and content with oxygen extraction along a capillary (After Lanphier and Brown, 1966).

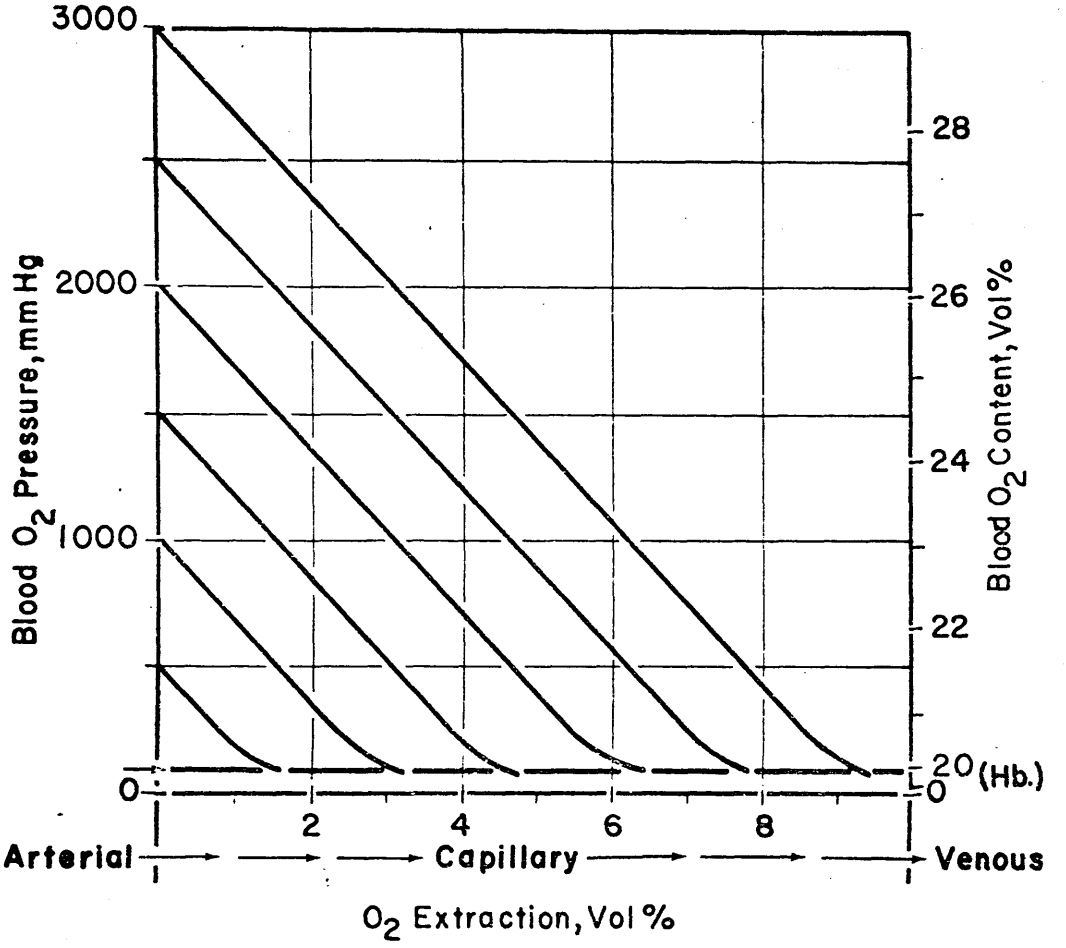


Figure 1.10. Blood oxygen pressure and content with oxygen extraction along a capillary; this graph presents the above - 100 mm Hg region (After Lanphier and Brown, 1966).

might at first sight have been supposed. Mathematical models indicate that PO_2 falls exponentially as blood passes from the arterial end of a capillary to the venous end and that mean tissue PO_2 relates largely to venous PO_2. The precise change in tissue PO_2 for a given increase in inspired PO_2 can only be determined by individual measurement since so many interreacting factors are involved. Nevertheless it can be calculated from available information that, for example, in brain exposed to 100% oxygen at three ATA, mean tissue PO_2 should increase by a factor of three to four (Fig. 1.11) with a considerable scatter of values throughout the tissue. A small number of cells sited near the arterial end of the capillary will be exposed to very high PO_2 values while the cells sited furthest from the capillary will have much lower values. One of the problems is to know which PO_2 value relates most closely to the functional requirements of the tissues. Venous PO_2 may be less satisfactory in this respect than, for example, mid-capillary PO_2 (Lanphier and Brown, 1966).

No account so far has been taken of the fact that OHP produces a fall in blood flow apparently affecting most tissues in the body (Ledingham, 1968). Although the degree of vasoconstriction varies from one region to another the overall effect is to reduce

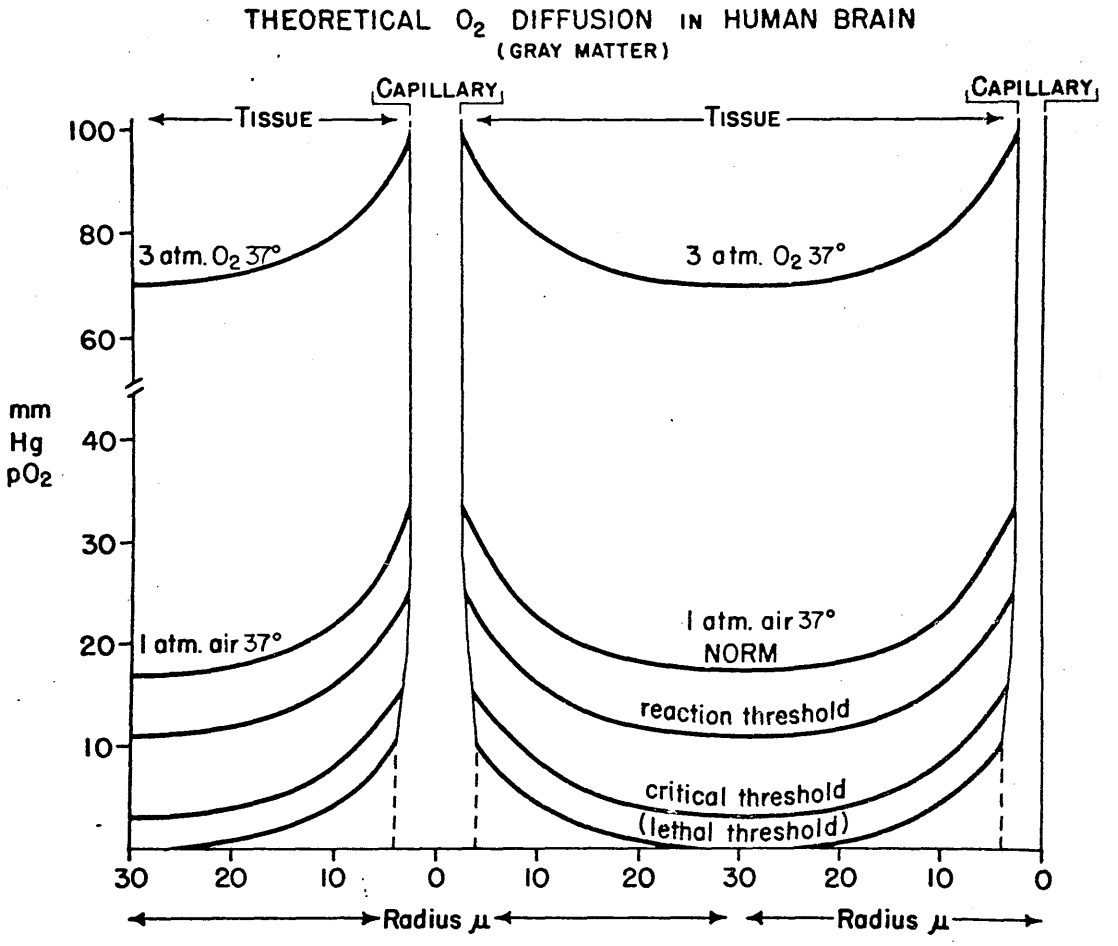


Figure 1.11. Theoretical tissue PO2 in human matter at 37°C (After Brown et al, 1965)

flow by an amount which will tend to maintain oxygen transport to the tissues at around normal (Winter et al, 1970). At the microcirculatory level the effect of reduced blood flow produced by OHP is less certain although it is probable that mean tissue PO_2 will remain substantially below what might otherwise have been attained. Nevertheless, it is a general observation that in spite of the vasoconstrictive effect of OHP there is usually a net gain of oxygen to the tissues and the gain is greatest at three ATA. A dual effect of oxygen has been demonstrated on the coronary capillaries (Bourdeau-Martini et al, 1974); it was shown that as arterial PO_2 was increased from 100 to 250 mm Hg there was a decrease in coronary capillary density but between 250 and 700 mm Hg capillary density increased.

Effects on Hypoxia

Hyperbaric oxygen was introduced into clinical medicine as a method of treating various hypoxic conditions, partly as an extension of conventional oxygen therapy and partly because of the possibility of more specific benefits.

Hypoxic hypoxia may be due to hypoventilation or to pulmonary venous admixture or to a mixture of both. If restoration of normal ventilation proves impossible hypoxaemia caused by hypoventilation is correctable by low concentrations of oxygen at normal barometric pressure. Increased pulmonary venous admixture may also be corrected by conventional oxygen administration as long as the shunt equivalent does not exceed

30% of cardiac output. In the absence of anatomical defects such gross shunts are unusual but in shock states normal pressure oxygenation may fail to restore arterial PO_2 to normal (Fig. 1.12). Hyperbaric oxygen has been shown to correct severe hypoxaemia associated with shock secondary to cardiac failure (MacKenzie et al, 1964; Cameron et al, 1966; Ledingham et al, 1968; Ledingham, 1971). If anatomical right to left shunts are present OHP consistently relieves hypoxaemia and for a number of years before cardiopulmonary bypass techniques reached their present level of sophistication, patients with cyanotic heart disease were operated upon under hyperbaric conditions. Those with major shunts were less liable to develop peroperative cardiac complications (Meijne et al, 1966; Bernhard et al, 1966).

Anaemic hypoxia, as in carbon monoxide poisoning or frank anaemia, can be successfully counteracted by hyperbaric oxygen. The previously mentioned experimental work (page has been amply confirmed by extensive clinical studies, and in carbon monoxide poisoning there is the additional advantage that carboxyhaemoglobin dissociation is accelerated (Smith et al, 1962; Douglas et al, 1962). Patients with profound anaemia, both acute and chronic, have responded favourably to OHP while more definitive measures were being instituted

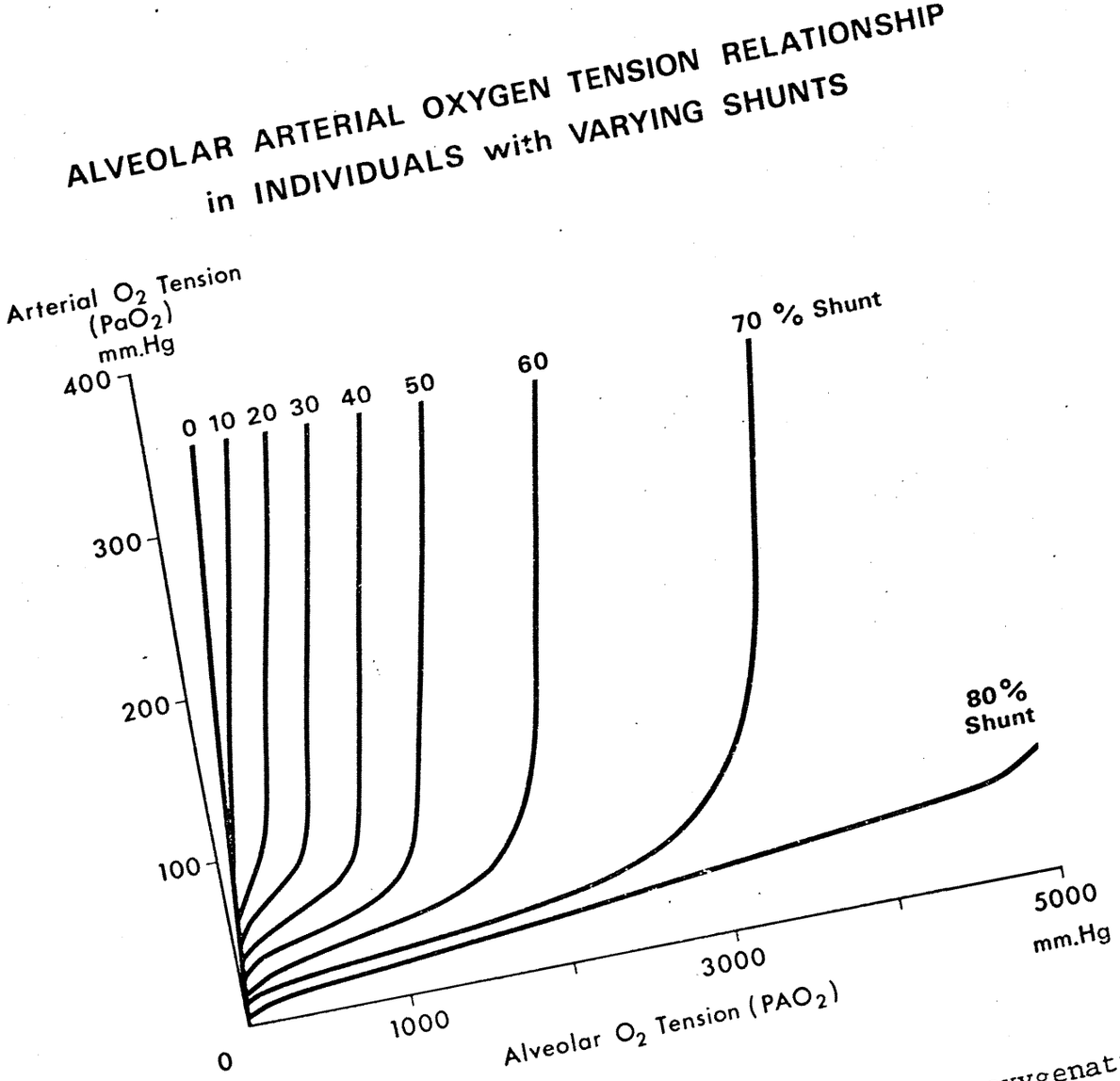


Figure 1.12. Theoretical effects of hyperbaric oxygenation upon arterial blood of patients with various right-to-left shunts.

(Amonic et al, 1969; Ledingham, 1969).

The rationale for the use of OHP in stagnant hypoxia was that the blood/tissue oxygen gradient and oxygen flow rate were both increased. Encouraging results were obtained in experimental studies of the cerebral circulation where oxygen at two ATA was shown to preserve cortical activity during ligation of the carotid and vertebral arteries (Smith et al, 1961). It soon became clear, however, that the small amount of additional oxygen in solution could not compensate for a major circulatory deficiency. The two most obvious, and indeed predictable, reasons for the disappointing effects of OHP in ischaemia were the lower than anticipated mean tissue PO_2 (to which reference has already been made) and the diffusion limitation of oxygen (penetration beyond 0.5 mm from the functional mid-capillary point is minimal). Other rather less certain factors which might also impose limitations on the duration of tissue viability during ischaemia included the reduced delivery of substrates e.g., glucose, and the reduced rate of elimination of metabolites and carbon dioxide.

The most extreme form of stagnant hypoxia is total arrest of the circulation, and OHP was viewed as a possible means of

extending the period of "safe" circulatory arrest, which might prove of value in cardiac or major vascular surgical procedures. Although when this possibility was explored at normal body temperature the results were disappointing the combination of hypothermia and OHP appeared more rewarding. Further amplification of these statements will be made in subsequent chapters.

In hypoxia resulting from a discrepancy between oxygen supply and demand, the role of OHP (as indeed the role of conventional oxygenation) is least well understood. This form of hypoxia is believed by some to occur in major sepsis although there is little convincing evidence, and others have not been impressed by the value of increasing the oxygen supply above normal in this situation (Del Guercio et al, 1966; MacLean et al, 1967).

There is no good reason to expect OHP to be of much value in relieving histotoxic hypoxia although some experimental studies seem to suggest that in cyanide poisoning the high PO_2 may bypass the blocked enzyme mechanisms and increase cellular oxygenation (Skene, Norman and Smith, 1966; Trapp, 1970).

Other effects (including oxygen toxicity)

Hyperbaric oxygen has other effects which will not be discussed to any extent in this thesis, including its action on bacterial organisms (Zobell and Hittle, 1968), its influence on the radiosensitivity of malignant cells (Davison and Kaminsky, 1974) and its ability to reduce the size of gas loculi within the body (Bennett and Elliott, 1975; Nunn, 1977d; Masterson et al, 1978). Finally oxygen toxicity, an ever present problem when oxygen is administered in high concentration or at high atmospheric pressure, justifies further mention (Donald, 1947).

An increase in the inspired PO_2 will lead eventually to a disturbance of the delicate balance which exists between pro-oxidant and anti-oxidant mechanisms within the body. Whether the tissue poison is the oxygen molecule itself or one of the several free radicals produced by excess of oxygen (Gerschmann, 1964; Menzel, 1970; Fridovich, 1975) is not known (Fig. 1.13). At the cellular level the search for a single biochemical disturbance to account for all the manifestations of oxygen toxicity has met with little success. Many enzymes and co-enzymes are inhibited in the presence of an excess of oxygen, notably the flavoproteins and those

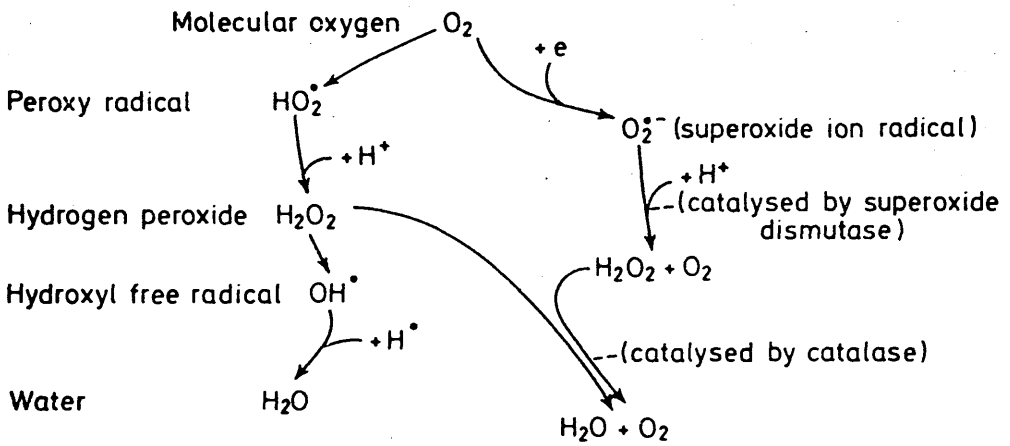


Figure 1.13. *Suggested stages in the* in vivo *reduction of oxygen. (The small black circle indicates the unpaired electron of a free radical)* (After Nunn, 1977).

containing sulphhydryl (SH) groups e.g., succinic dehydrogenase. Lipid peroxidation may also be caused by oxygen exposure, leading to disordered membrane function. Several stages of carbohydrate metabolism are susceptible to oxygen toxicity, perhaps the best documented being the oxidation of pyruvate, a number of the reactions in the tricarboxylic acid cycle and certain of the enzymes in the hydrogen- and electron-transport chain (Fig. 1.14). Formation of the adenine nucleotides also appears to be diminished in the presence of excess oxygen.

The biochemical disturbances which have been described so far might account for the long term manifestations of oxygen toxicity observed in the intact organism but are unlikely to provide a satisfactory explanation for the short-term effects e.g., convulsions. The observation that OHP causes oxidation of reduced pyridine nucleotide in the tissues of the brain, the kidney and the liver of the anaesthetised rat may be more relevant to the short-term effects (Chance, Jamieson and Coles, 1965). Furthermore, in the brain, reduction in the level of gamma aminobutyric acid (GABA) has been noted and this reduction is more obvious in animals which have exhibited severe convulsions (Wood, Watson and Stacey, 1966). Several substances

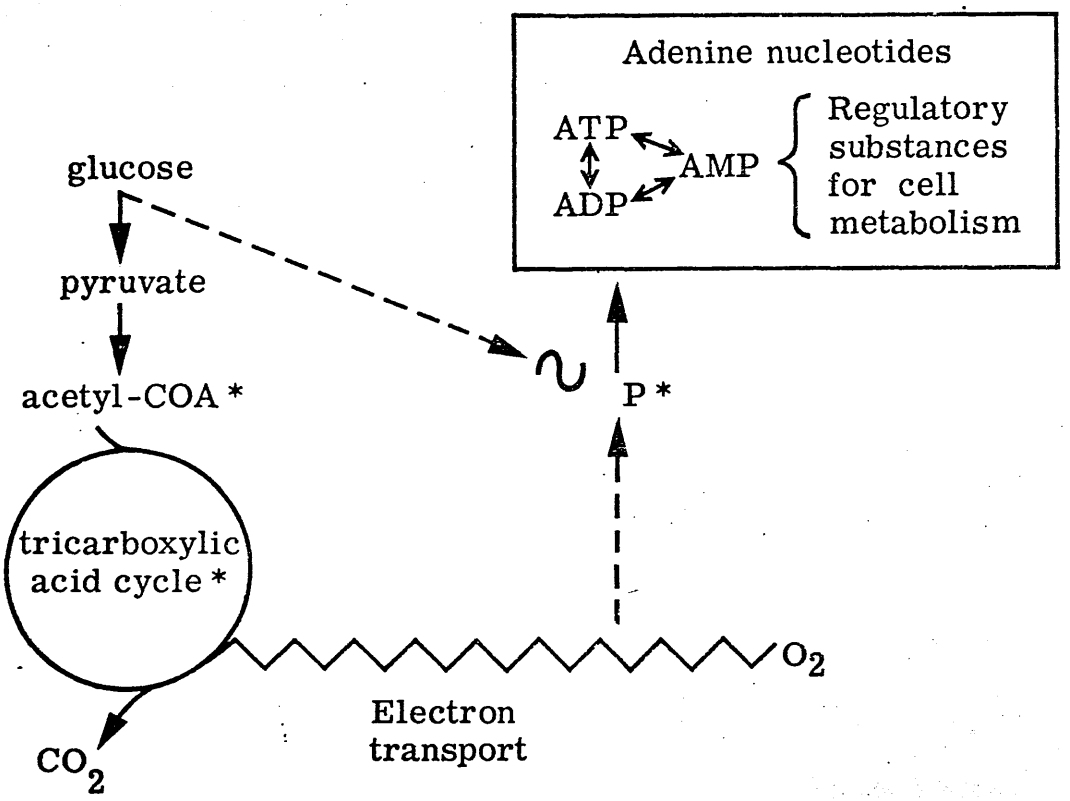


Figure 1.14. Possible sites of inactivation of metabolism by oxygen.

e.g., glutathione, ethylenediaminetetraacetic acid (EDTA), GABA and Vitamin E are known to diminish the toxic action of oxygen. Also of probable value in this respect are some of the enzymes which destroy the intermediate radicals, such as superoxide dismutase, catalase and the peroxidases (Crapo and Tierney, 1974).

In the intact organism the manifestations of oxygen toxicity vary with the absolute pressure and with the duration of exposure; a great number of factors will further modify the speed of onset of these effects (Clark and Lambertsen, 1971b; Clark, 1974). Only rarely has the tolerance of man been tried but his tolerance is almost certainly higher than that of most other species. There is only one definite report of death related directly to hyperbaric oxygen administration (Fuson et al, 1965).

A well-marked threshold for sensitivity to oxygen seems to exist and in man this value may be around 59.9 kPa (450 mm Hg) (Michel, Langevin and Gell, 1960; Mullinax and Beischer, 1958). Between 59.9 kPa (450 mm Hg) and 266 kPa (2000 mm Hg) (i.e., slightly less than 100% oxygen at three ATA) the lung is the apparent target organ. In normal subjects alterations

in pulmonary function begin to occur soon after commencement of oxygen breathing at two ATA (Fisher et al, 1967; Puy et al, 1967; Dewar et al, 1972; Hendricks et al, 1977). Vital capacity, dynamic lung compliance, diffusing capacity and capillary blood were all significantly reduced following exposures of five or more hours. At this stage the changes are reversible. A fall in arterial PO_2 occurs only late in acute pulmonary oxygen toxicity probably after the underlying changes have become irreversible. Information about the later stages of pulmonary oxygen toxicity in man is almost entirely lacking but in a prospective study (Barber, Lee and Hamilton, 1970) on patients with irreversible brain damage who were being ventilated with either air or oxygen at normal atmospheric pressure, impairment of lung function was significantly worse in the oxygen group after 40 hr, the most sensitive indicator being an increase in the alveolar/arterial PO_2 difference.

Pulmonary oxygen toxicity may be modified by anaesthesia (Bean and Zee, 1966), intermittent positive pressure ventilation (Trapp, Yoshida and Grant, 1967), the presence of an inert gas (Clarkeet al, 1973), hypoxaemia (Winter et al,

1967) and periodic respiration of air (Lambertsen, 1955; Ackerman and Brinkley, 1966; Hendricks et al, 1977). The mechanism of pulmonary oxygen toxicity falls outside the scope of this thesis but much of the available information is reviewed in two theses from this laboratory (Smith, 1971; Shields, 1976) and elsewhere (Clark and Lambertsen, 1971b; Winter and Smith, 1972).

When the PO_2 exceeds 266 kPa (2000 mm Hg) oxygen toxicity in intact animals predominantly affects the central nervous system and commonly presents in two forms - grand mal convulsions (the onset of which may occur within a few minutes of oxygen breathing) and persistent paralysis. In man hyperoxic convulsions do not appear to lead to long-term neurological sequelae (Gillen, 1966). Persistent paralysis occurs after repeated brief exposure to OHP and in the rat necrotic lesions of the globus pallidus, substantia nigra and anteromedial horn cells of the spinal cord have been described (Balentine, 1968). The distribution and histological appearances of these lesions are unlike those of ischaemia or hypoxia, and occur in the absence of convulsions (Nolte and Schnakenburg, 1974).

Certain anaesthetic agents (e.g., pentobarbitone) can effectively eliminate hyperoxic convulsions but paradoxically

increase the susceptibility to persistent paralysis. A reduction in cerebral metabolic rate seems a likely explanation for the anticonvulsant effect of the barbiturates but this hypothesis has been weakened by the observation that some other agents which are equally effective in reducing metabolic rate, do not prevent convulsions (Haugaard, 1968). Persistent paralysis has not been recorded in man.

Ever since oxygen was incriminated as the primary causative factor in retrolental fibroplasia of new-born infants the eye has been a source of interest to those concerned with oxygen toxicity. Additional pathological changes which have been described (Nichols and Lambertsen, 1969) include visual cell death, retinal detachment and microinfarct (cytoid-body formation). In man bilaterial contraction of the peripheral visual fields occurs after a minimum of four hours of oxygen breathing at three ATA and recovers quickly on resumption of air breathing (Behnke, Forbes and Motley, 1936). Individual susceptibility to optic toxicity has been described in man particularly when a history of ophthalmic disease exists (Nichols, Lambertsen and Clark, 1969). There is now reason to believe that partial and complete blindness have occurred in adult patients exposed to OHP within the therapeutic range and without other evidence of

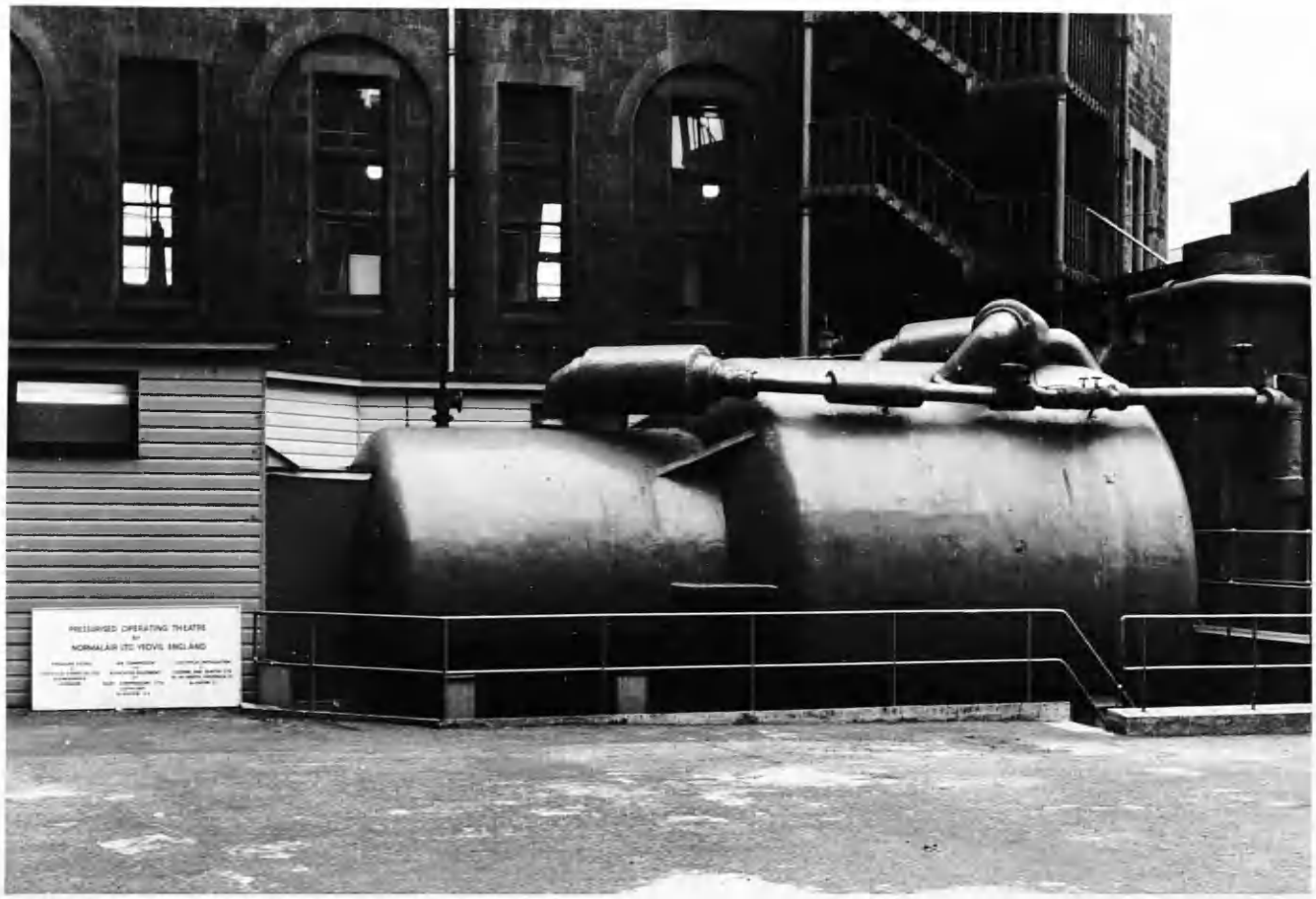
oxygen toxicity (Thurston, 1978). An interesting physiological observation is that carbon dioxide administration protects the eye from the damaging effects of OHP but increases the risk of hyperoxic convulsions (Anderson, Saltzman and Barbee, 1965).

Hyperbaric facilities

A detailed description of the whole range of hyperbaric apparatus presently available for clinical and experimental purposes would not be appropriate but a brief outline of the techniques used in the studies to be reported will be given.

Two main methods are available for the administration of high pressure oxygen. Figure 1.15 illustrates an example of a large air-compressed pressure vessel capable of containing both patient and a number of medical attendants. Only the patient breathes oxygen which he receives via an endotracheal tube if anaesthetised or through a mask system, if conscious. Attention to the efficiency of the mask system avoids the needless exposure of patients and staff to higher ambient pressures, but the necessity for regular measurement of arterial oxygen tension with any such method is obvious.

In a study designed to evaluate two different types of mask



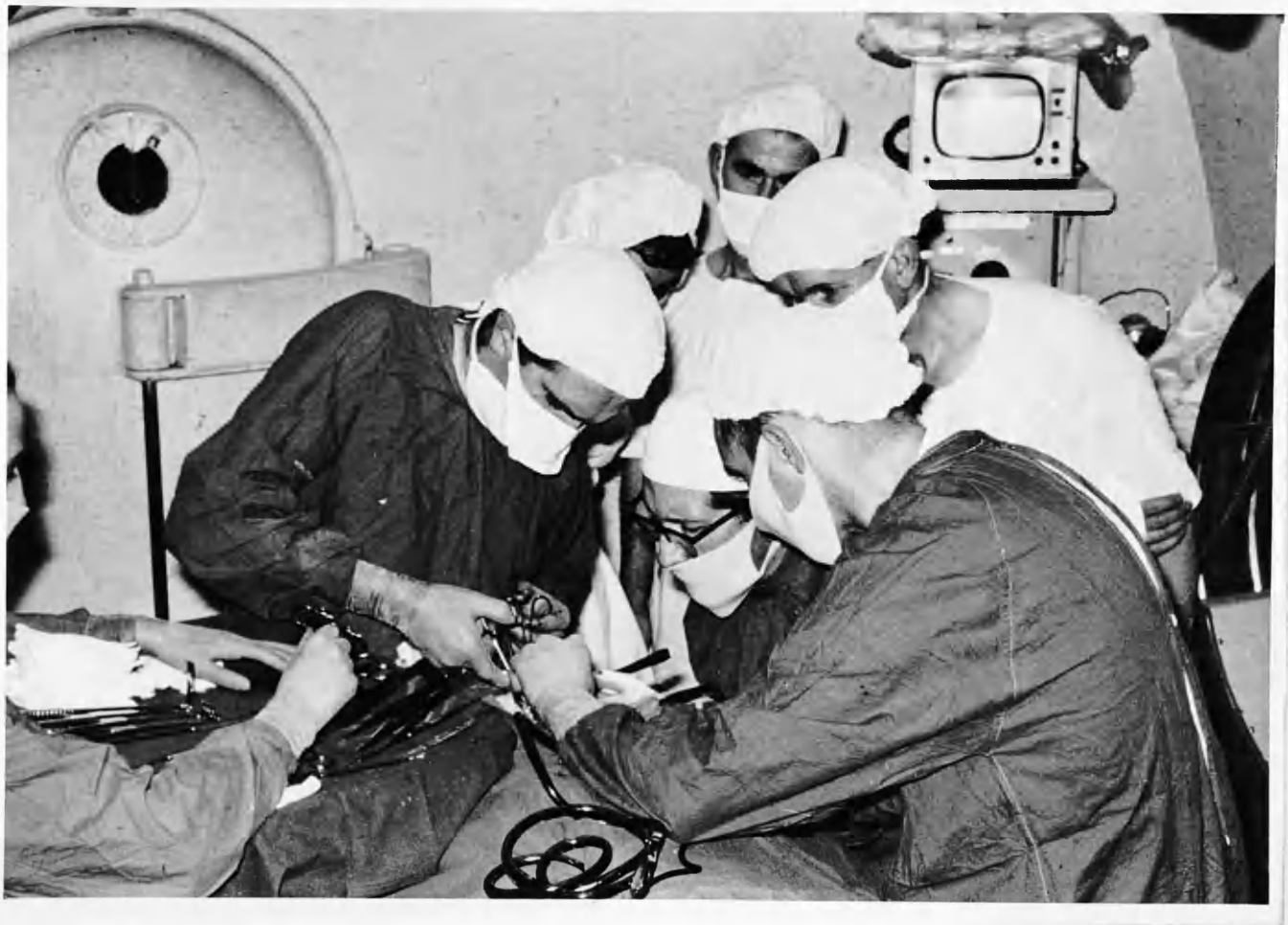


Figure 1.15. Large compressed-air hyperbaric chamber - exterior and interior views.

system at increased pressure (MacDowall et al, 1965) it was shown that the system of oxygen administration depicted in Figure 1.16 regularly achieved values for end-expiratory oxygen concentration of 83%. The incorporation of a humidification system into the latter circuit did not significantly alter its efficiency and diminished the irritant effects of dry oxygen administered over prolonged periods of time. When the patient is anaesthetised or unconscious, oxygen administration is less of a problem since endotracheal intubation with or without controlled ventilation will normally guarantee a high inspired oxygen concentration.

The alternative method of hyperbaric oxygen administration is depicted in Figure 1.17 - the one-man pressure vessel. In a pressure chamber of this sort the compressing gas may be either oxygen or air, although the former gas is used almost exclusively. With oxygen as the compressing gas, high concentrations of inspired oxygen are easily achieved; moreover the surface of the patient is in contact with the high PO_2, a feature of clinical importance in the treatment of certain types of infection.

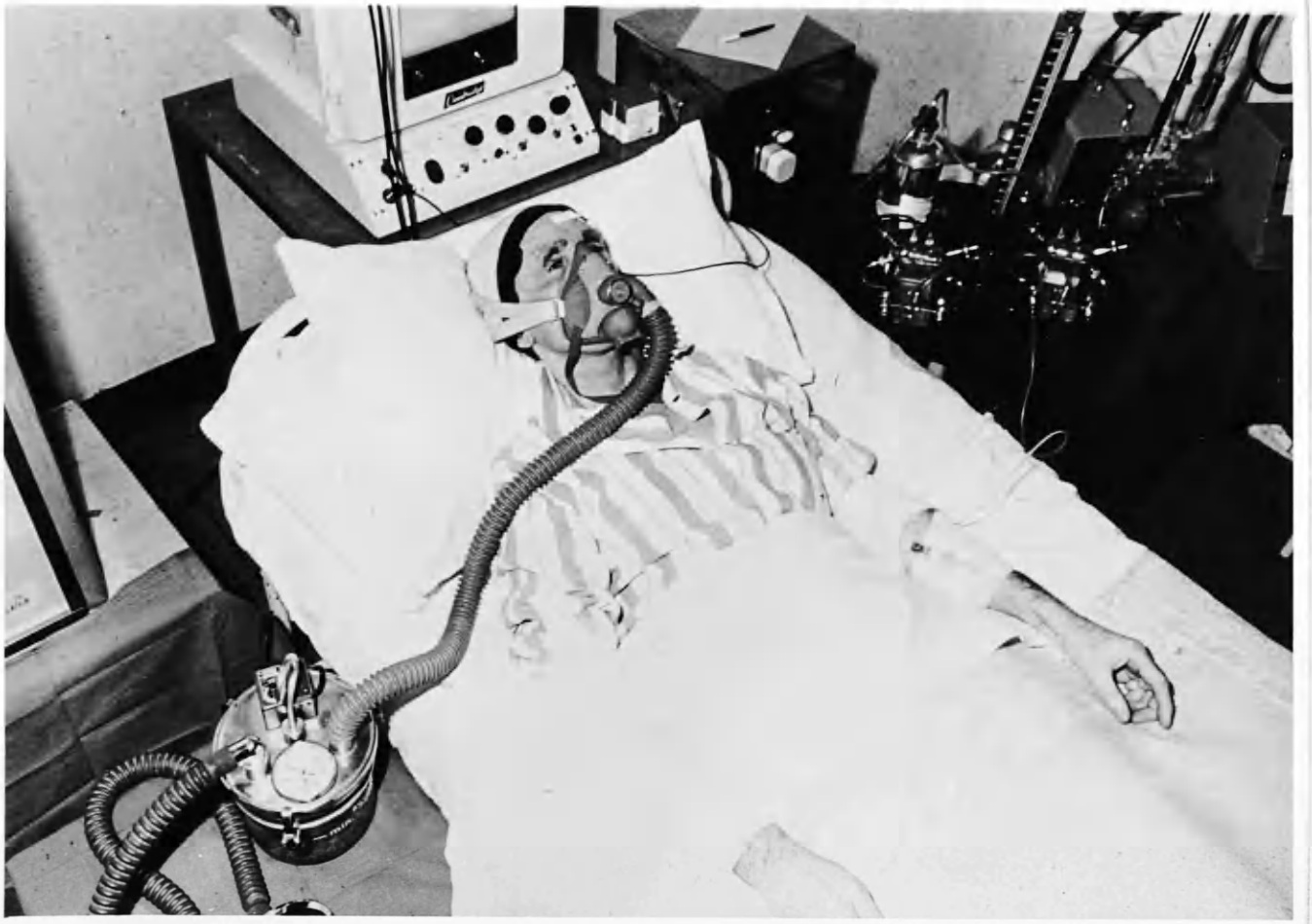


Figure 1.16. Oxygen mask system used in hyperbaric chamber.

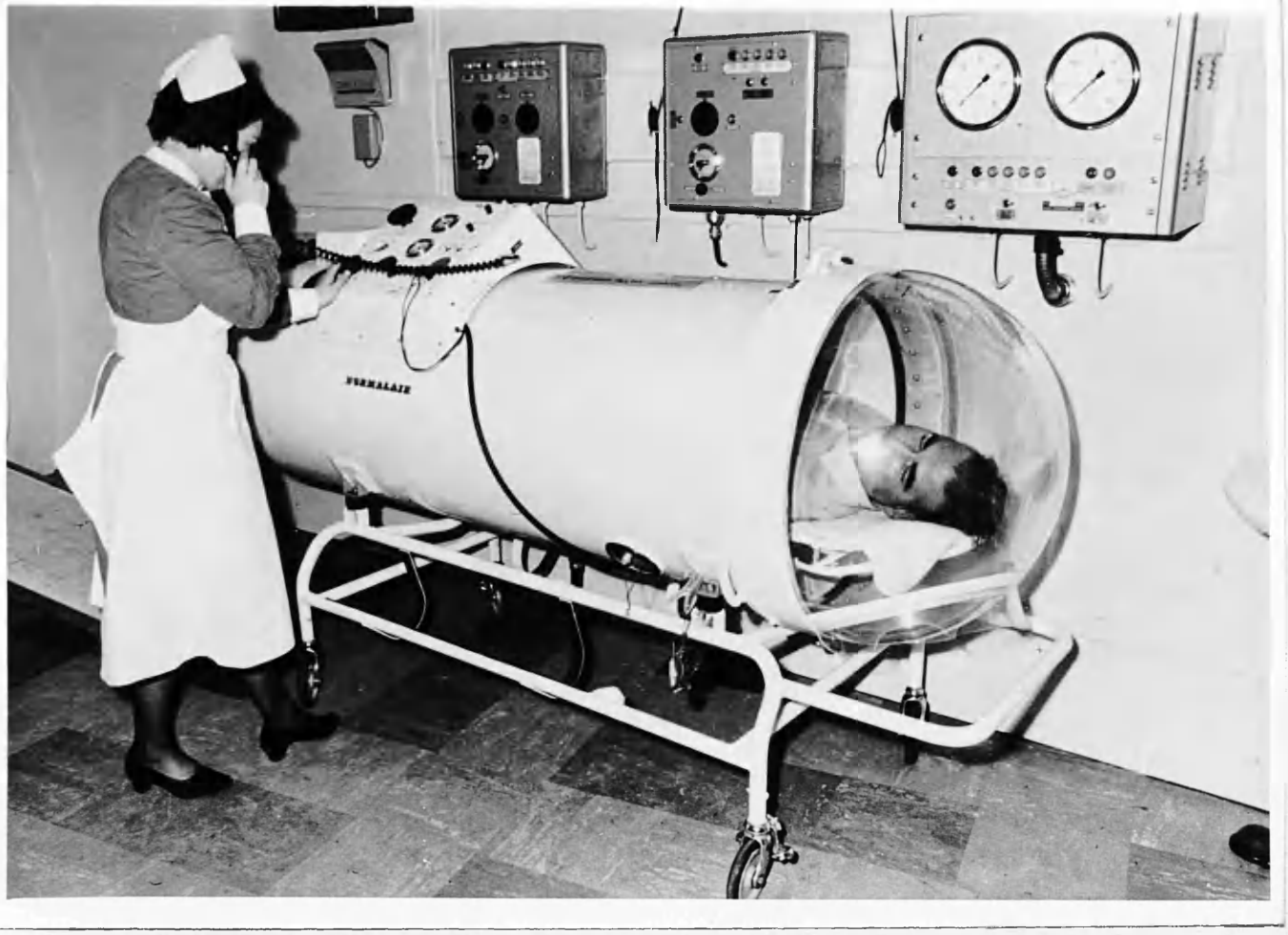


Figure 1.17. One man pressure chamber.

Both the large air-compressed and the smaller oxygen-compressed pressure vessels have inherent advantages and disadvantages. The larger pressure chamber is a more versatile piece of apparatus in which hyperbaric oxygen therapy is simply added to the patient's routine management. The patient is at all times accessible to attendant staff. The financial outlay in establishing and maintaining such a facility, however, is prohibitive to all but the largest centres. The small one-man pressure chamber is much less expensive but has certain disadvantages the most important of which are the relative inaccessibility of patient to staff and the necessity of discontinuing most other forms of therapy and monitoring during the period of hyperbaric treatment. On the other hand, the small pressure chamber is the only practical proposition for the combined radiotherapy/hyperbaric oxygen treatment of malignant disease.

In both types of pressure vessel the patient is exposed to the potential hazards of barotrauma and oxygen toxicity. In the large "walk in" vessels the attendant staff are exposed to the usual dangers of a compressed air environment - barotrauma, decompression sickness (or 'the bends'),

avascular bone necrosis and nitrogen narcosis (Walder, 1965). Finally, any increase in the oxygen content of the atmosphere carries with it an increased risk of fire.

HYPOTHERMIA

Hypothermia is defined as a fall in deep body (or core) temperature below 35 deg C (Exton-Smith, 1973). 'Core' temperature tends to be maintained stable while 'shell' (or surface) temperature may fluctuate substantially in response to changes in environmental temperature (Aschoff and Wever, 1958; Cooper, 1969). Three temperature ranges are of both physiological and clinical importance (MacLean and Emslie-Smith, 1977a):

(1) 35 to 32 deg C. A fall in core temperature within this range promotes extensive vasoconstriction (particularly of the skin vessels) and shivering.

(2) 32 to 25 deg C. Vasoconstriction is maintained and blood viscosity increases; shivering disappears. Tissue metabolism is progressively depressed.

(3) Below 25 deg C. Physiological mechanisms for heat conservation are obtunded and heat is lost passively to the environment.

Patients are at risk when core temperature falls below

32 deg C, and below 28 deg C death may occur suddenly from ventricular fibrillation.

Clinical interest in hypothermia centres principally on two aspects. Induced hypothermia has been used over the years in a wide variety of clinical contexts - to reduce the risk of stagnant hypoxia during the course of surgical operations on the heart and blood vessels, to diminish the secondary effects of hypoxia e.g., brain swelling after cardiac arrest, and to preserve organs and tissues during transplantation. These are only some of the many applications which have been explored (Popovic and Popovic, 1974a). Accidental hypothermia is the other area of clinical interest and two main sub-divisions are recognised - exposure of otherwise healthy individuals to cold, wet or windy conditions (Pugh, 1966), and hypothermia occurring in the very young or the elderly (often secondary to some underlying illness), and in the general population (secondary to drugs and alcohol).

Advantages and Disadvantages

The main advantages of hypothermia to the body are reduced oxygen and substrate consumption and increased arterial oxygen content (resulting from the greater solubility of oxygen in

cooled plasma. Whole body oxygen consumption falls with temperature in an exponential fashion (Horvath et al, 1953; Horvath and Spurr, 1956), giving an initial Q 10 of about 2.3 which is in good agreement with Van't Hoff's law (1884) (Fig. 1.18), in other words, a fall in temperature of 10 deg C approximately halves oxygen consumption (Cooper, 1961; Rosomoff, 1964). Extrapolation of this general observation to individual organs and tissues has to be made with caution. The degree of cooling may not be uniform throughout the body, largely because of variation in blood flow responses from one region to another, and not all biological processes are equally affected by temperature changes. Metabolic and rhythmic processes are particularly depressed, but most physical processes, e.g., diffusion, have a Q 10 of one (MacLean and Emslie-Smith, 1977a). Coincident with the reduction in oxygen consumption there is a fall in carbon dioxide production; depending on a number of factors respiratory quotient may fall (Blair, 1969), rise (Bickford and Mottram, 1958) or remain unchanged (Prakash et al, 1978).

The physical solution of oxygen in plasma and body water follows Henry's law which states that the amount of gas in physical solution is proportional to the partial pressure of

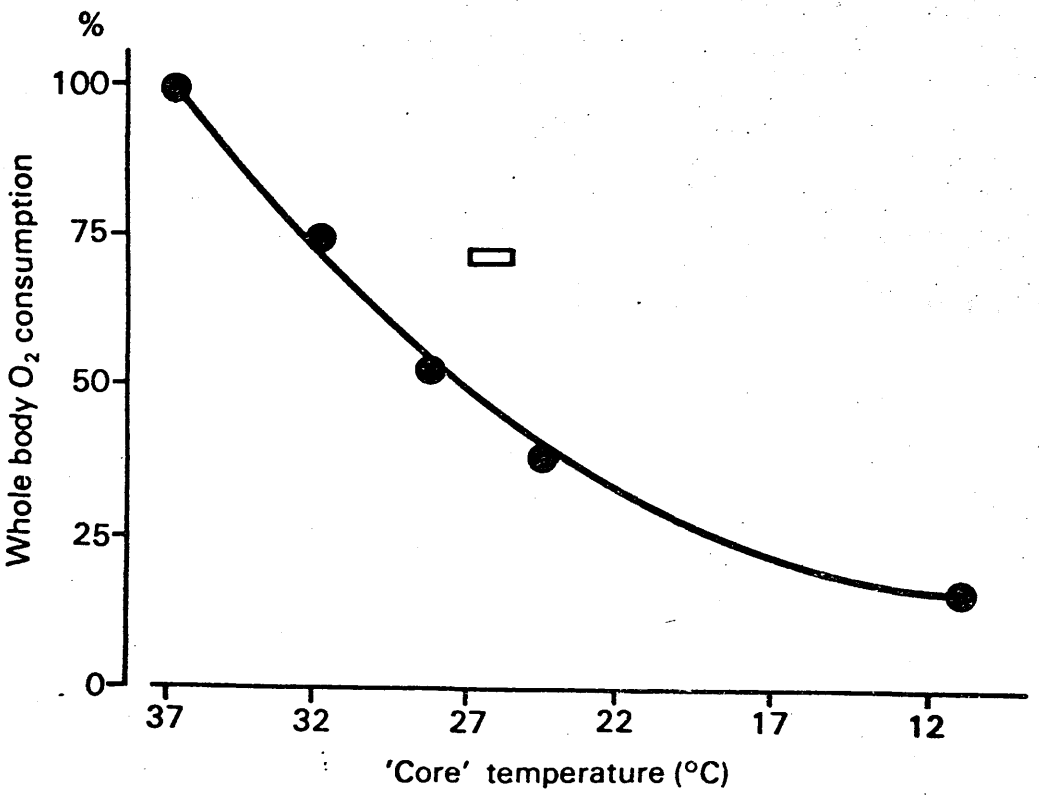


Figure 1.18. Curve showing the reduction in whole body oxygen consumption during hypothermia in man. (Data cited by Rosomoff, 1964: the small rectangle represents alternative data from Blair, 1969: After MacLean and Emslie-Smith, 1977).

the gas and its solubility constant. The importance of partial pressure has been mentioned in relation to hyperbaric oxygen (p.51). The solubility constant is temperature dependent:

> At 37 deg C the value for oxygen is 0.024 ml at 101 kPa (760 mm Hg) per ml H_2O. (The corresponding values at 28 deg C and 20 deg C are 0.027 and 0.031 respectively).

At an arterial PO_2 of 13.3 kPa (100 mm Hg), there is a 20% increase in dissolved oxygen at 30 deg C and a 59% increase at 20 deg C (Fairley, 1961).

The principal disadvantages of hypothermia are the shift to the left of the oxygen dissociation curve and reduction in blood flow. The effect on oxygen dissociation (Fig. 1.19) results from changes both in temperature and in pH (Brown and Hill, 1923; Dill and Forbes, 1941; Severinghaus, 1959). pH is influenced both by changes in pK, which rises 0.005 for each degree centigrade of fall in temperature (Severinghaus, Stupfel and Bradley, 1956; Severinghaus, 1959), and in the solubility of carbon dioxide, which also rises with falling temperature (Rosenhain and Penrod, 1951). A correction factor (Rosenthal, 1948), based on <u>in vitro</u> estimations in anaerobic blood, indicates a rise of 0.0147 pH units per degree centigrade

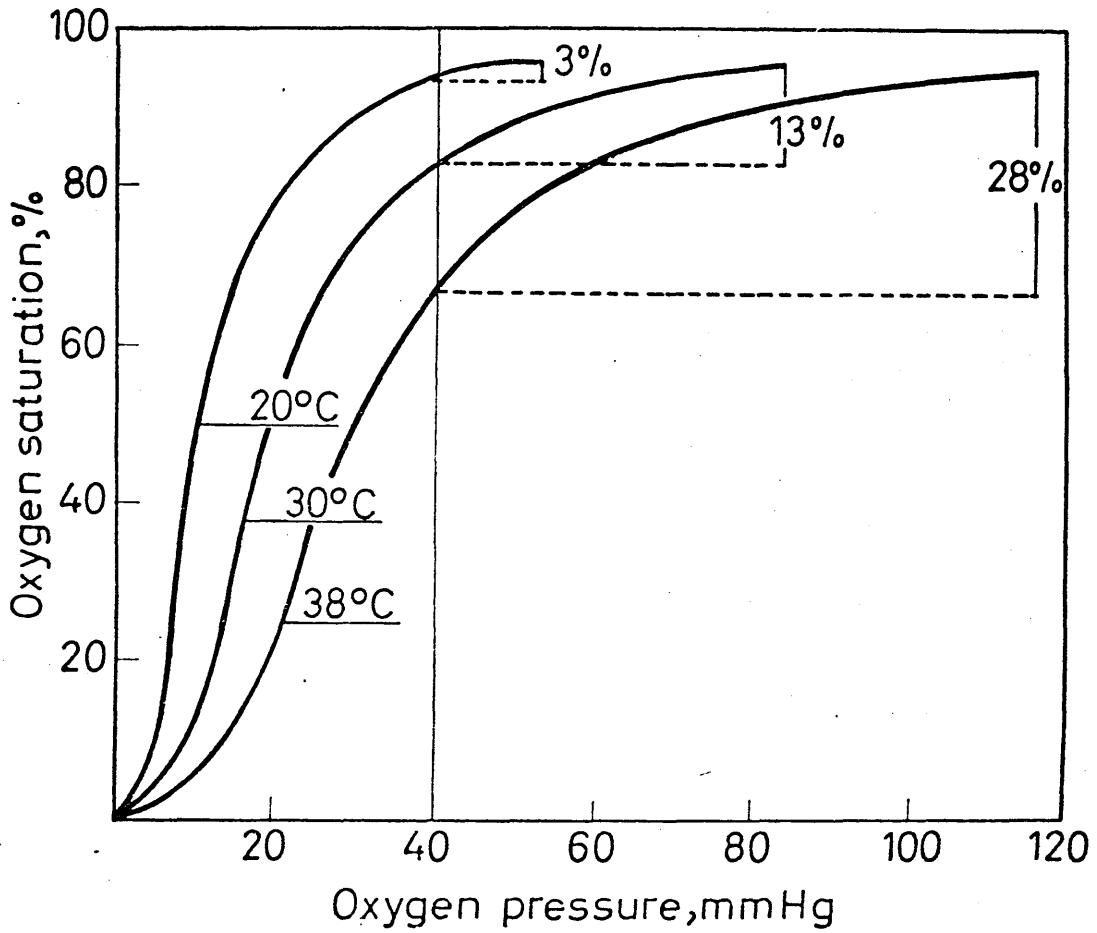


Figure 1.19. Dissociation curve of oxyhaemoglobin as related to temperature (After Blades Pierpoint, 1954).

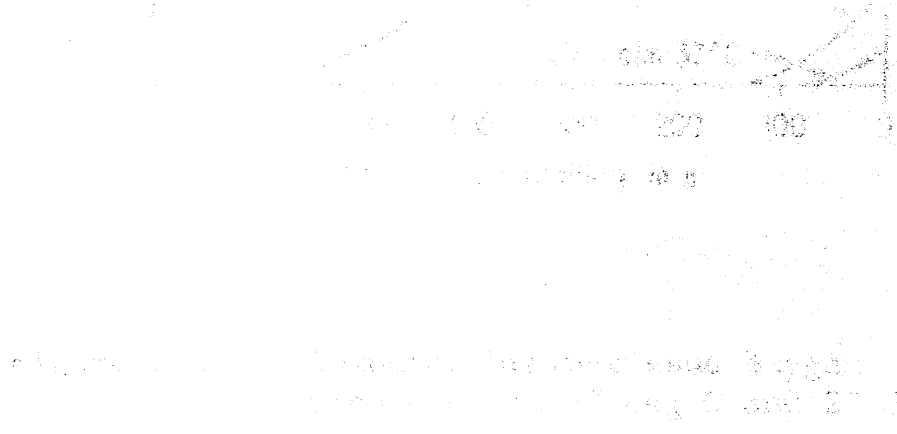
fall in temperature. More recently, calculation of the changes produced in pH, PO_2 and PCO_2 by temperature, taking into account other factors such as haemoglobin concentration, has been facilitated by the development of the Severinghaus slide rule (Severinghaus, 1966).

Reduction in blood flow in hypothermia is a consequence of increased viscosity and vasoconstriction. The viscosity effects are due to a combination of the normal change in fluid characteristics with temperature, and haemoconcentration. Agents which reduce the latter effects have been shown to improve perfusion during hypothermia (Mohri et al, 1968). Vasoconstriction is the usual response to cold with temperatures above 25 deg C; lower temperatures may produce vasodilatation.

Effects on Hypoxia

In spite of the aforementioned disadvantages, hypothermia of brief duration is generally considered to produce no significant harmful effects of itself and there is evidence of an increase in oxygen reserve of sufficient magnitude to be of significance during circulatory standstill. The

combination of hypothermia and hyperbaric oxygen was seen to offer additional advantages in this context (Fig. 1.20). The quantitative assessment of these advantages varied widely but several groups calculated that the gains would be considerable (Richards, Pinto and Coombs, 1963; Edwards, Holdefer and Dimick, 1965). The degree to which these theoretical estimates were substantiated in experimental and clinical practice will be indicated in subsequent chapters. Further amplification of the physiological consequences of hypothermia will also be presented together with the relevant therapeutic implications.



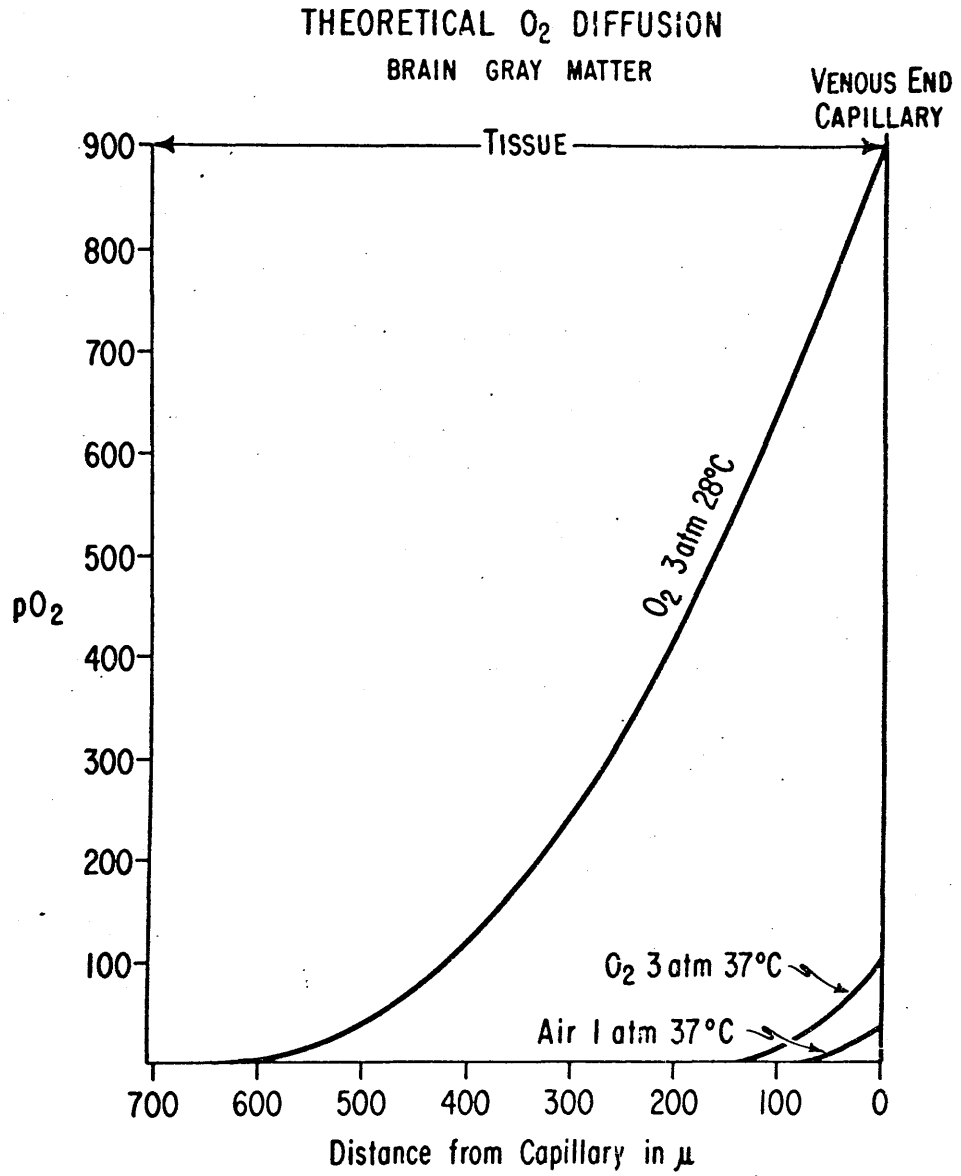


Figure 1.20. Computed brain-tissue oxygen pressures at 37 deg C and 28 deg C.

EXPERIMENTAL SECTION

Chapter 2

Apnoeic oxygenation and total circulatory arrest; preliminary studies using hyperbaric oxygen (2 ATA) at normothermia

The aim of the studies in the next five chapters was to determine the maximum period of total arrest of the circulation consistent with survival of the organism. The latter was defined as complete return to normal function and was distinguished from revival, a state associated with at least some degree of functional impairment. It was assumed that the central nervous system would be the principal limiting factor in determining survival. Clearly survival was expected to relate to the capacity of the oxygen stores of the body and to the ability of oxygen to diffuse into the tissues in the presence of a stagnant circulation. The effect of hyperbaric oxygen could thus be assessed in quantitative terms.

The studies in this chapter were subdivided as follows :-

A. Apnoeic oxygenation

B. Total circulatory arrest

(I) Air at normal atmospheric pressure

(II) Oxygen at normal atmospheric pressure < no acid-base correction / acid-base correction / carbogen inhalation

(III) Oxygen at 2 ATA

Discussion of both subdivisions (A and B) is presented at the end of the chapter.

A. APNOEIC OXYGENATION

The size of the oxygen stores may be estimated using a modification of the procedure known as 'apnoeic oxygenation' which consists simply of arresting ventilation and allowing the body to utilize the oxygen made available from the lungs, blood and tissues. (A similar procedure is used under certain circumstances by anaesthetists but oxygen is continuously supplied via the trachea to maintain a normal arterial PO_2). It was instructive to compare the results of this technique, in which the circulation remained intact and functional, with those of the subsequent studies which involved circulatory standstill.

Materials and Methods (15/5/62 - 19/6/62; 3/8/66)

Six adult mongrel dogs weighing from 8.2 to 20.9 kg were lightly anaesthetised with intravenous sodium thiopentone and an endotracheal tube placed in situ. Measurements included heart rate, systemic arterial blood pressure, pupillary size, electrocardiograph (ECG), electroencephalogram (EEG - two animals), calibre of cerebral vessels through a trephine hole (two animals), mucosal colour changes and arterial blood gases. The technique for recording the

the EEG was developed in this laboratory and is described in detail elsewhere (Smith et al, 1961). The blood gases were measured using one of the first two Micro-Astrup apparatuses to become available in this country. PO_2 was derived from directly measured oxygen saturation, pH and base excess.

After initial stabilisation of the animal, manual hyperventilation was performed with four gases in random sequence:

(I) Air at normal atmospheric pressure

(II) Oxygen at normal atmospheric pressure

(III) Air at 2 ATA

(IV) Oxygen at 2 ATA

All six animals were subjected to hyperventilation with each of the four gases for a period averaging 15 minutes. When anaesthesia was judged to be stable (absent palpebral reflex and no ventilatory response to 15% carbogen gas) the endotracheal tube was clamped and a time-clock started. The time to onset of hypoxia was noted precisely, the endotracheal clamp removed and the animal allowed to recover for at least half an hour prior to repeating the procedure with the next gas mixture. Although the duration of apnoea coincident with a deterioration in

each of the measured variables was more or less similar, the most consistent and clearcut end-point proved to be the onset of progressive pupillary dilatation. This was used as the indicator for immediate termination of apnoea; it was noted to coincide with the appearance of cyanosis and severe slowing or inactivity of the EEG.

A single animal was studied later when the development of a reliable, accurate PO_2 electrode facilitated examination of the time relationship between pupillary dilatation and arterial PO_2 changes. Halothane was used as the anaesthetic agent but otherwise the technique was identical to that of the main series.

Results

The principal positive findings for the main series of animals are indicated in table 2.1 and figure 2.1.

There was a four- and twelve-fold increase in the time to onset of hypoxia (pupillary dilatation) with oxygen at normal pressure and oxygen at 2 ATA respectively. Pupillary dilatation occurred when haemoglobin oxygen saturation was becoming critical. Apnoea was associated with a fall in arterial pH

Table 2.1 The onset of hypoxia in apnoea with associated arterial blood gases (mean of 6 animals)

	Period of apnoea	pH (units)		PCO_2 (mm Hg)		base excess (meq/l)		PO_2 (O_2 sat%) (mm Hg)	
	(min: mean/range)	start	end	start	end	start	end	start	end
AIR	1.78 (1.20-2.40)	7.46	7.34	23	32	-2.8	-4.0	104(98)	37(65)
AIR at 2ATA	2.90 (2.30-5.20)	7.44	7.28	19	34	-7.0	-8.0	>140(100)	38(61)
OXYGEN	7.74 (6.00-10.30)	7.49	7.24	23	58	-2.8	-4.2	- (99)	46(72)
OXYGEN at 2ATA	21.06(14.00-33.30)	7.48	7.01	17	110	-6.0	-12.0	- (100)	50(59)

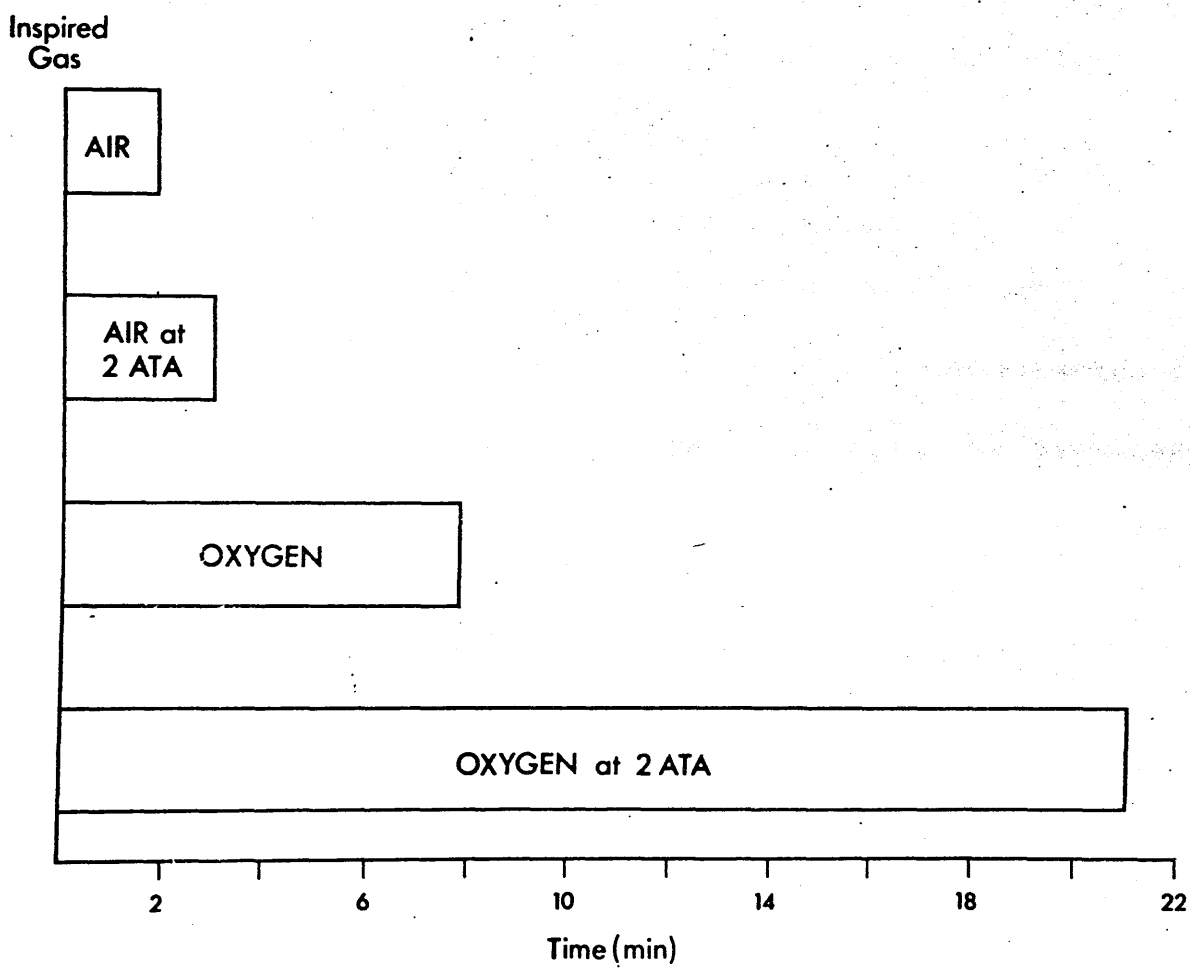


Figure 2.1. Time to pupillary dilation during apnoea after breathing each of the four gases indicated.

(range 0.02 - 0.07 units/min of apnoea), an increase in PCO_2 (range 4.4 - 5.2 mm Hg/min) and an increase in base deficit (0.17 - 0.67 meq/l/min). The rate of increase in base deficit per minute of apnoea was greatest with the short period of apnoea (air at normal pressure) and least with the long period of apnoea (oxygen at 2 ATA).

The relevant data for the single additional animal are illustrated in figure 2.2. Arterial PO_2 remained elevated for a few minutes then fell precipitously. Progressive pupillary dilatation occurred at a PO_2 of 38 and 55 mm Hg with oxygen at normal pressure and oxygen at 2 ATA respectively.

Comment

This study confirmed that hyperbaric oxygen could be used to increase the available oxygen stores in the apnoeic animal with an intact circulation. Pupillary dilatation was a reasonably valid and consistent indicator of the onset of hypoxia under these circumstances.

B. TOTAL CIRCULATORY ARREST

In contrast to the previous study, hypoxia was induced in the next three studies by arrest of both ventilation and

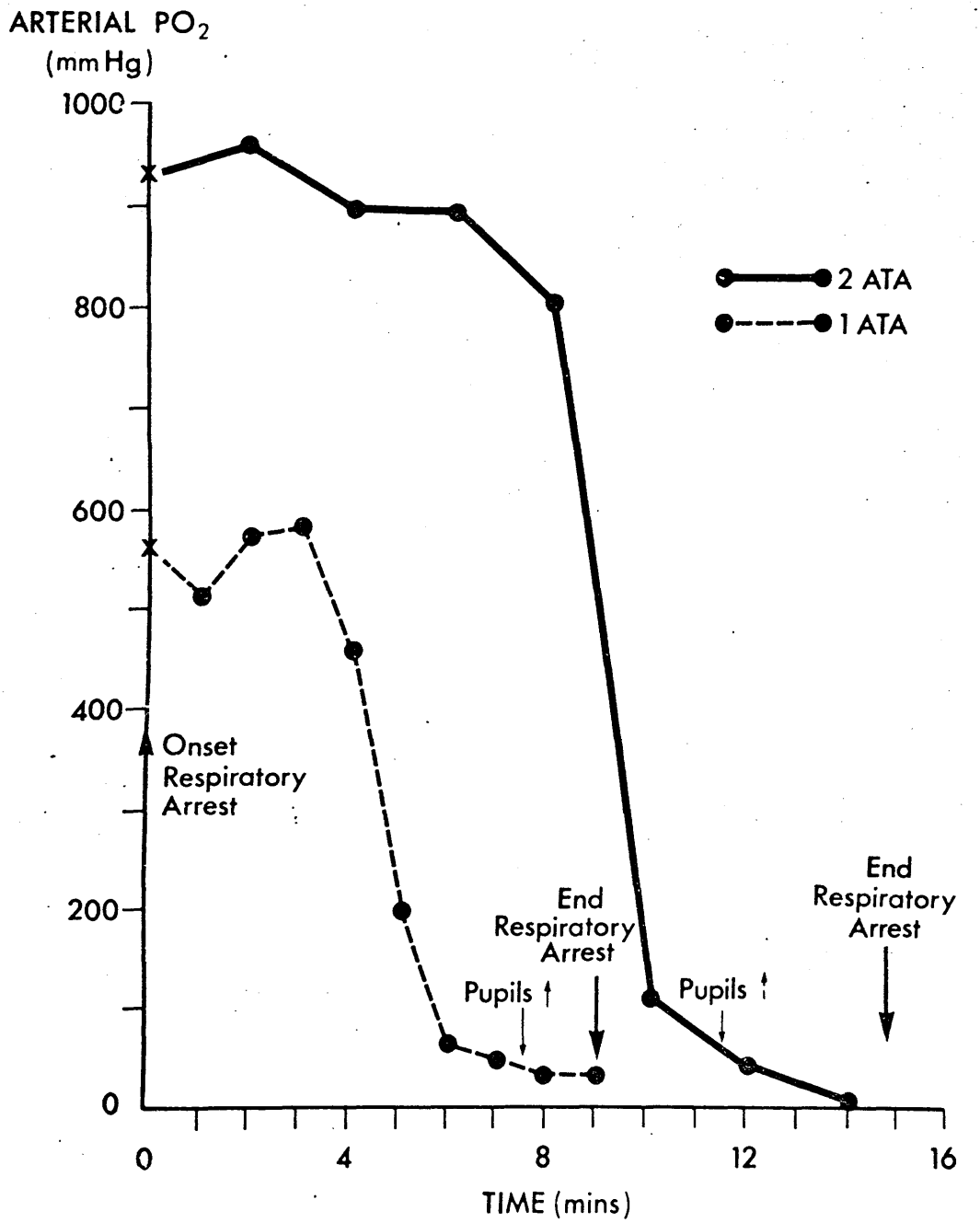


Figure 2.2. Fall in arterial PO2 during apnoea after a single animal breathed first oxygen at normal pressure and later oxygen at 2 ATA.

circulation. Return to normal activity was assessed during long-term follow-up studies extending over a period of days and, in some cases, weeks.

Material and Methods (27/2/62 - 7/11/62)

Adult mongrel dogs were anaesthetised with the smallest effective dose of intravenous sodium thiopentone and a cuffed Magill endotracheal tube was inserted. Anaesthesia was maintained with incremental doses of thiopentone. Ventilation was carried out with :

(I) Air at normal atmospheric pressure (five dogs; weight range 10.9 - 23.0 kg)

(II) Oxygen at normal atmospheric pressure (17 dogs; weight range 11.0 - 23.0 kg)

(III) Oxygen at 2 ATA (seven dogs; weight range 8.2 - 22.8 kg)

using a Starling ventilator except for about 10 minutes immediately before the period of circulatory arrest and for a few minutes after the arrest phase when ventilation was performed manually. Using an aseptic technique, thoracotomy was performed through the bed of the fifth rib, and snares placed round the venae cavae and the vena azygos. Immediately

prior to the period of arrest, sodium bicarbonate was administered by the intravenous route (see section (II) for background and details). Circulatory arrest was established by occlusion of the veins followed a few seconds later by cross-clamping of the aorta and pulmonary artery via the transverse sinus (Fig. 2.3). At the end of the predetermined period of arrest the snares and clamp were removed in the reverse order and, if required, the heart given a few gentle squeezes to encourage coronary filling. No drugs were used during the phase of cardiac resuscitation. Once satisfactory myocardial action was restored, the chest was closed and the animals allowed to recover in the laboratory overnight before being returned to their cages. In the ensuing days and weeks, the clinical condition of the dogs was carefully observed, particularly with respect to evidence of damage to the central nervous system.

Measurements performed during the acute phase of the study included the basic cardiovascular and respiratory variables described in the previous study of apnoeic oxygenation. In addition, serum electrolytes, urea, haematocrit and serum glutamic oxaloacetic transaminase and serum glutamic pyruvic

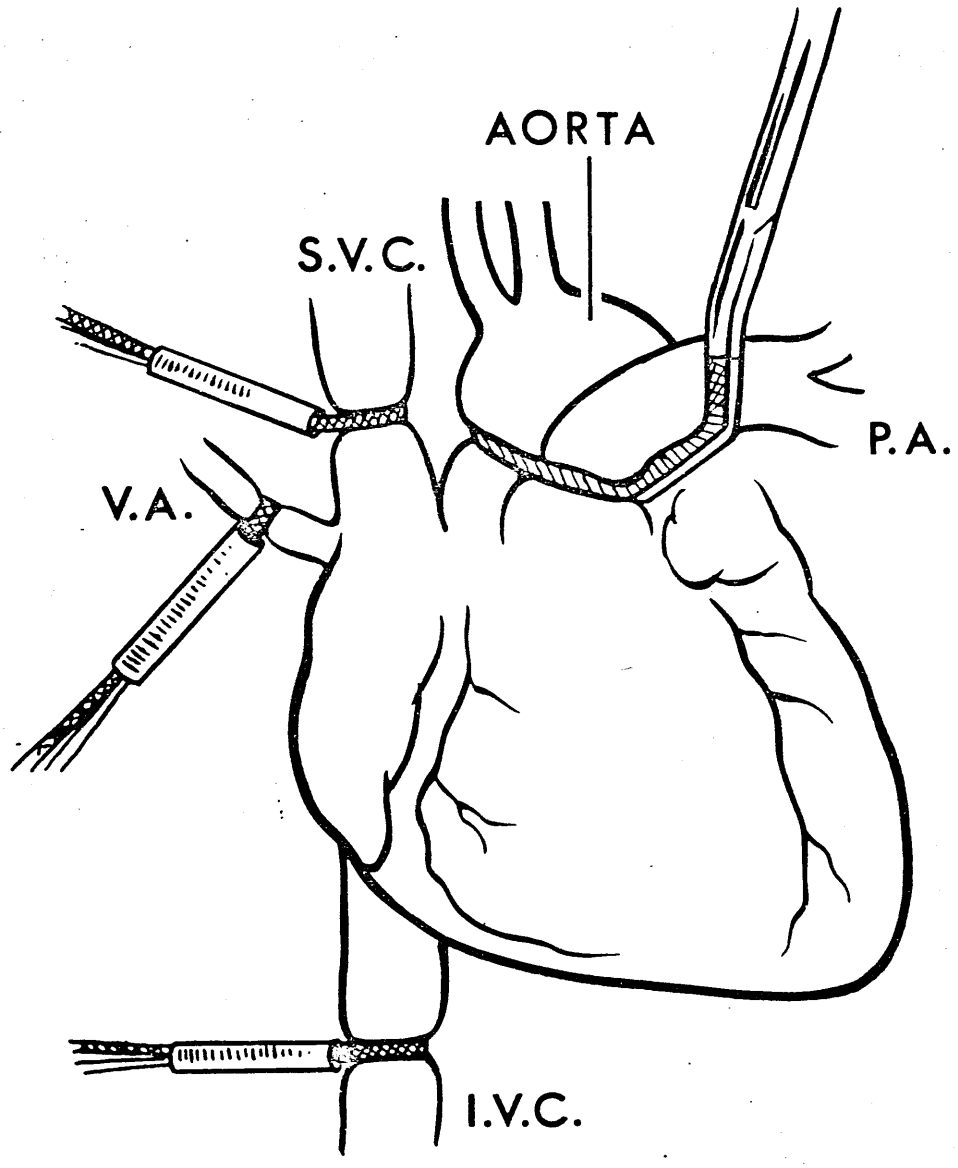


Figure 2.3. Occlusion of great vessels.

transaminase were estimated, using standard laboratory techniques, before induction of anaesthesia and daily thereafter, for from eight to 10 days. At various times after arrest the dogs were sacrificed.

Pilot studies not included in this report indicated that animals subjected to three minutes of total circulatory arrest whilst breathing air at normal atmospheric pressure recovered promptly and without neurological sequelae. In the animals of the present series the period of arrest was increased by one or two minute intervals from four to five minutes (air at normal pressure), from four to seven minutes (oxygen at normal pressure) and from six to 10 minutes (oxygen at 2 ATA). The series of time increases was randomised although, for ease of understanding, the data are presented as if obtained in sequence.

Results

(I) Air at normal atmospheric pressure

The main cardiac and neurological findings during and immediately after the period of arrest are summarised in Table 2.2

Table 2.2 Cardiac and neurological responses to total circulatory arrest breathing air

	ARREST PERIOD			POST-ARREST PERIOD		
DOG	Duration of arrest (min)	Cardiac action	Time to pupillary dilatation (min)	Time to effective cardiac action (min)	Time to pupillary constriction (min)	Postoperative neurological condition
A1	4	Sinus rhythm ↓ Sinus bradycardia	1.5	immediate	2	normal next morning
A2	4	"	2.0	"	3	standing next morning normal at 2 days
A3	4	"	2.0	"	3	normal next morning
A4	5	"	1.5	3	4	opisthotonic next morning - sacrificed
A5	5	"	2.0	immediate	2	decerebrate rigidity at 2 days - sacrificed

In five other dogs not here reported in detail, tris-hydroxymethylamino-methane (TRIS) was administered prior to the period of arrest instead of sodium bicarbonate. No difference between the effects of the two alkalis was observed.

Comment

The maximum safe circulatory arrest time with air at normal pressure would appear to be four minutes.

(II) Oxygen at normal atmospheric pressure

In the animals studied whilst breathing oxygen at normal pressure (p.74), detailed investigation was made of the acid-base disturbances associated with circulatory arrest, particularly with respect to restoration of cardiac function. It was realised that proper assessment of neurological recovery from the period of hypoxic arrest depended on the rapid establishment of an adequate cardiac output. One possible reason for a delay in restoration of normal cardiac function was the increase in blood lactic acid and potassium during the arrest period (Fig. 2.4 and 2.5). The metabolic acidosis could be anticipated by the prior intravenous administration of sodium bicarbonate using the following formula to calculate dose:

animal weight (kg) x 0.43 (recorded base excess immediately before arrest (meq/l) +

(1 meq Na HCO_3 x duration of arrest (min))

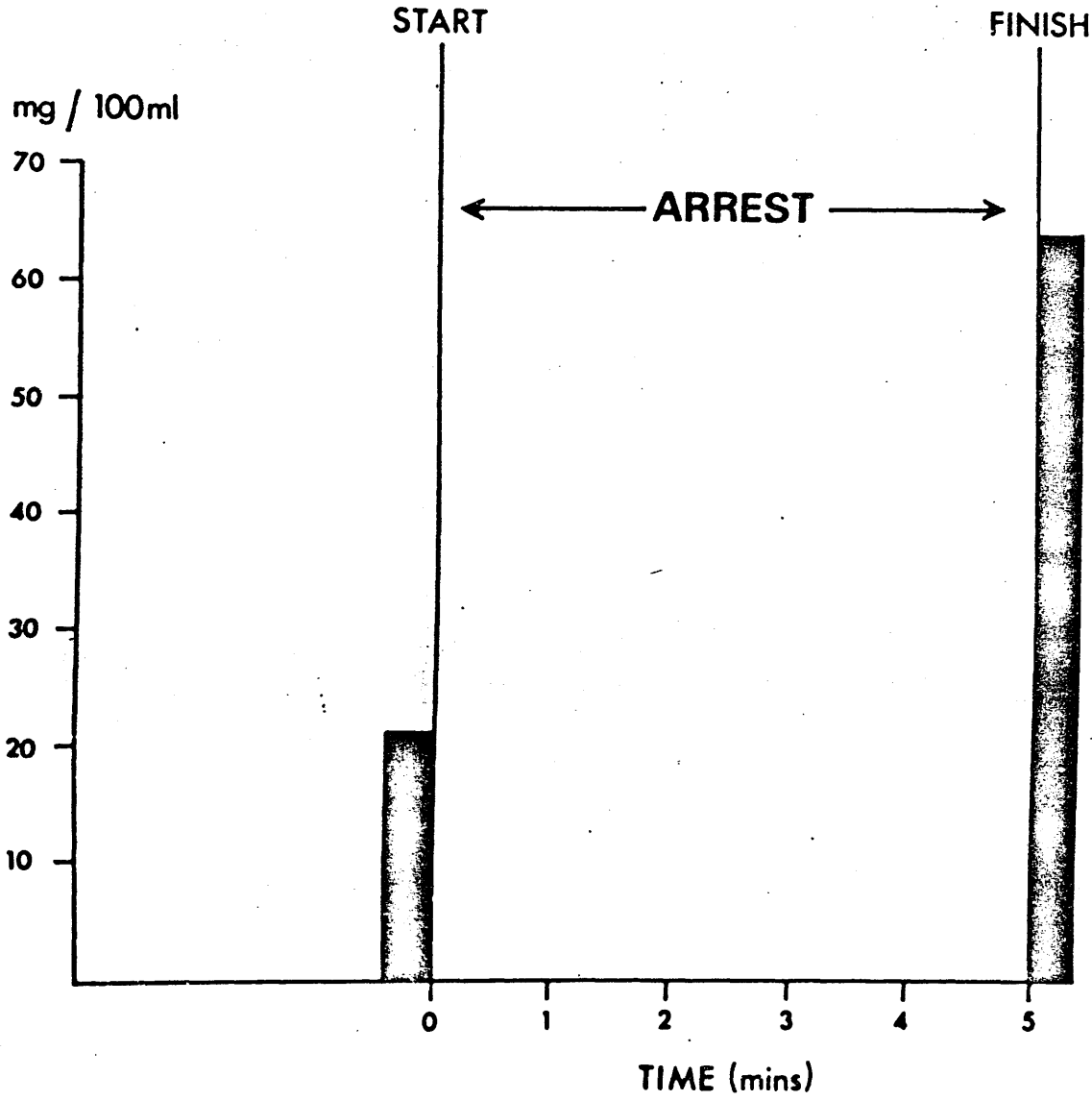


Figure 2.4. Blood lactic acid values in an animal subjected to a five minute period of total circulatory arrest.

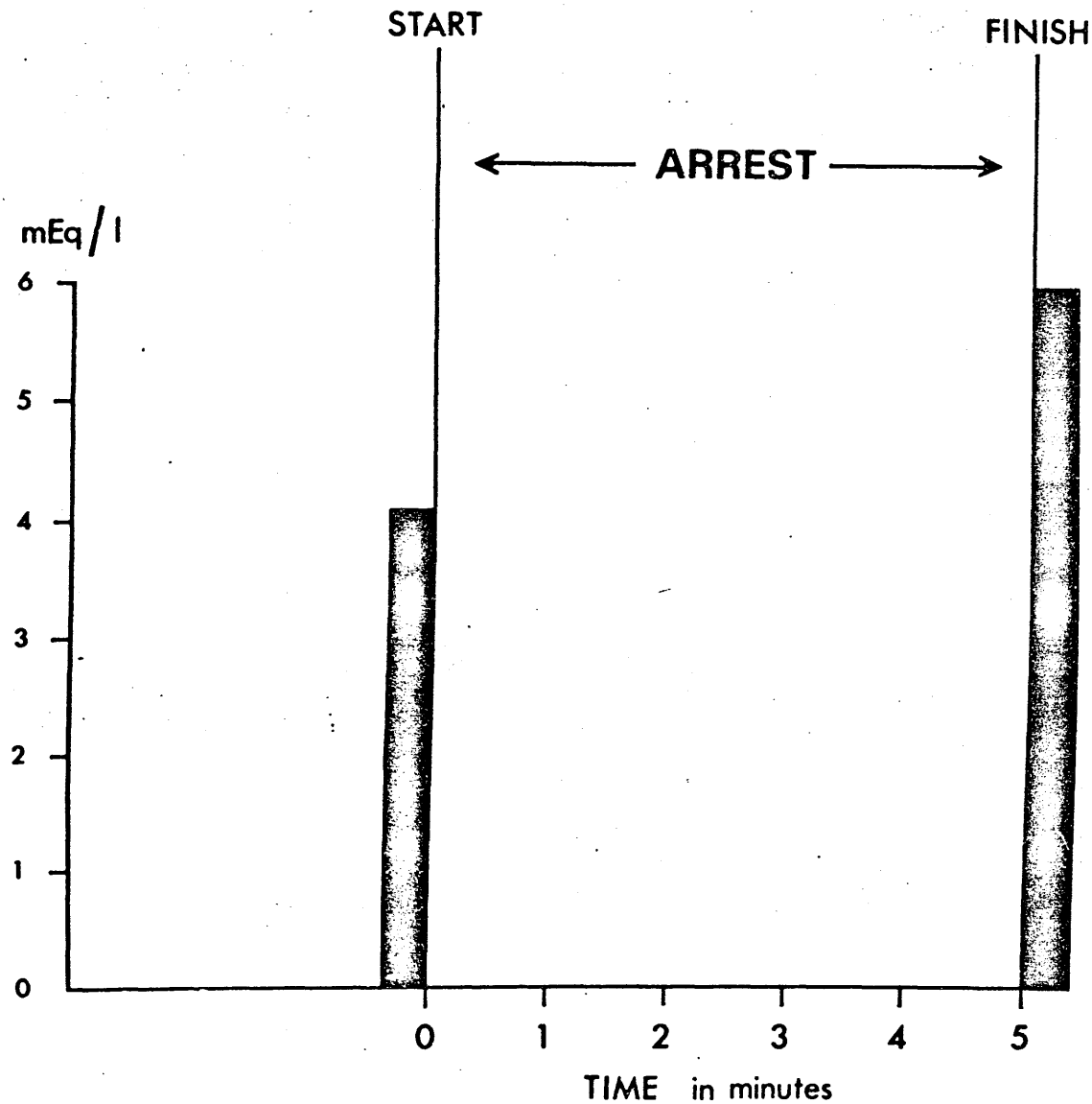
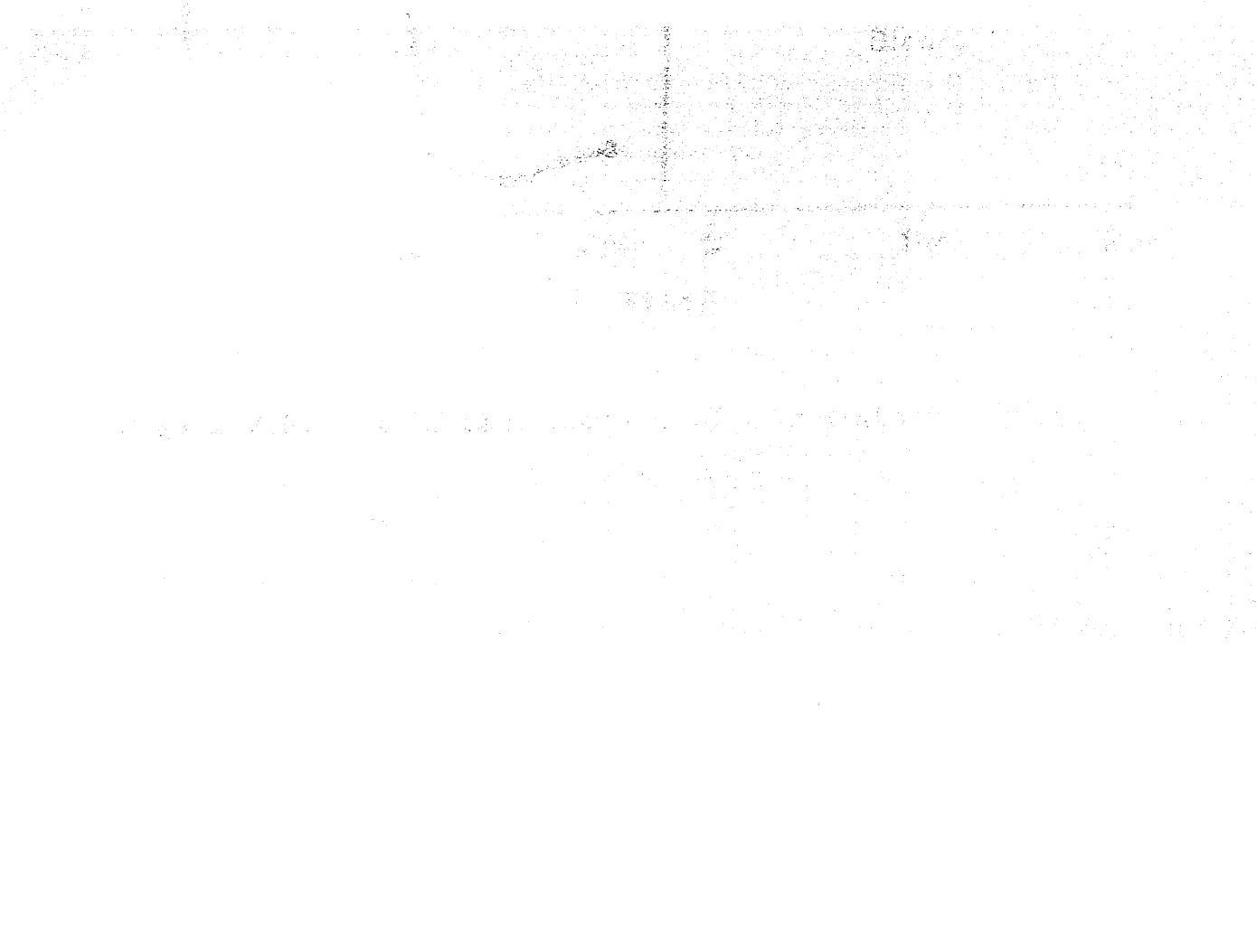


Figure 2.5. Serum potassium values in an animal subjected to a five minute period of total circulatory arrest.

The factor 0.43 was derived empirically and fell between that given by Astrup et al (1960) for the extracellular body space and that given by Palmer and Van Slyke (1918) for the whole body in corrections for non-respiratory disturbances of acid-base balance. The effect of this manoeuvre on the base excess level is illustrated in figure 2.6.

The details of the oxygen studies together with the results of the associated acid-base manipulations are presented in the reprint which follows.



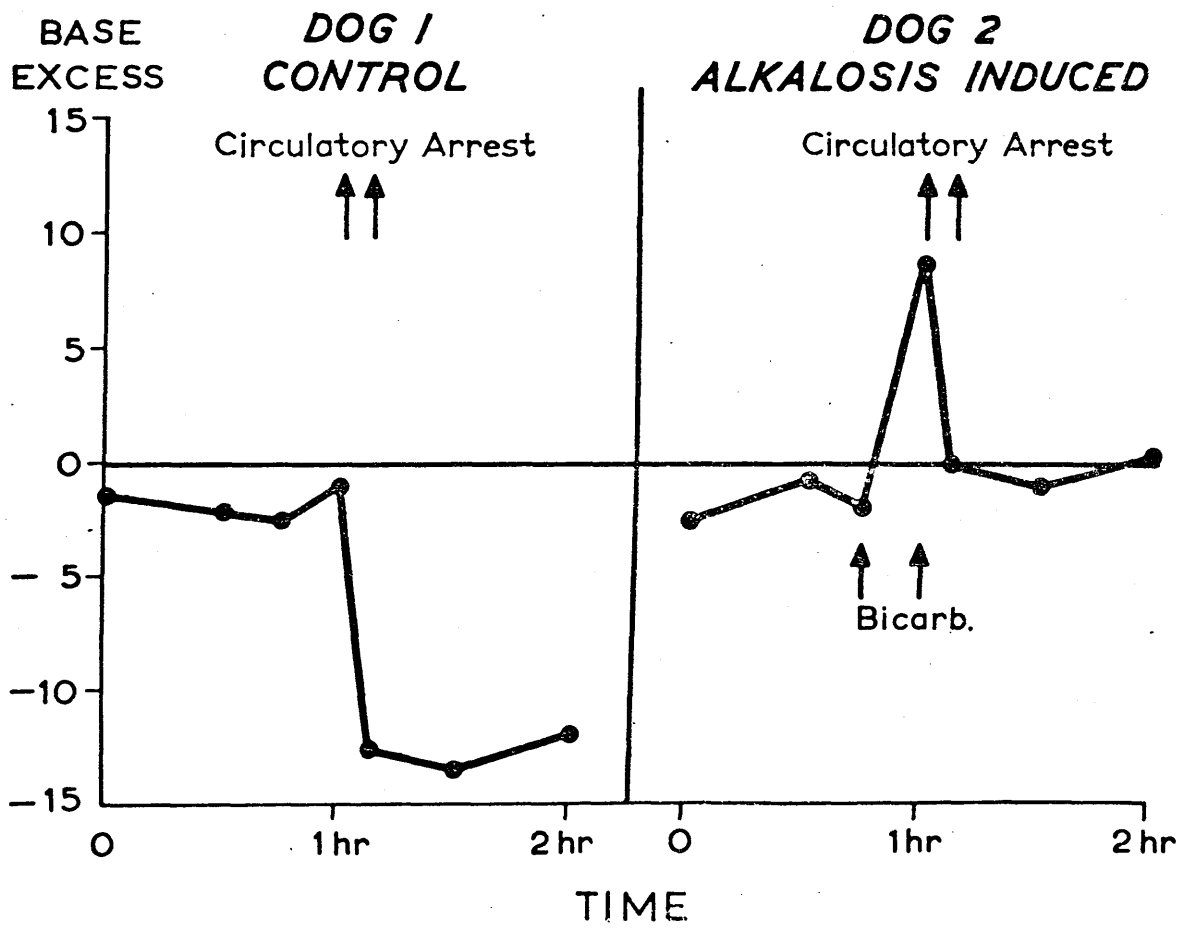


Figure 2.6. Acid-base control of circulatory arrest.

Preliminary Communication
reprinted from THE LANCET, *November* 10, 1962, *pp.* 967-969

ACID-BASE STUDIES IN EXPERIMENTAL CIRCULATORY ARREST

SAFE and complete resuscitation of an animal from a period of circulatory arrest without cardiopulmonary bypass apparatus is dependent upon rapid and complete recovery of adequate myocardial function. An inadequate cardiac output, whether or not accompanied by cardiac arrhythmias (in particular, ventricular fibrillation), may produce cerebral damage not associated with the period of arrest itself.

This well-known hazard has led to the development of methods of determining the degree of anoxia which can be withstood by the brain, either without arresting the systemic circulation [1,2] or by maintaining the pulmonary and coronary circulations in an isolated manner.[3-7] These techniques are not applicable to open-heart surgery. But during a recent study of oxygen at increased pressure in total circulatory arrest in dogs, the importance of achieving rapid recovery of myocardial function has become obvious.

The present experiments were designed to investigate the importance of acid-base control in the prevention of inefficient myocardial action and the resultant neurological damage after circulatory arrest.

METHODS

Adult mongrel dogs weighing from 11 to 23 kg. were anæsthetised with the smallest effective dose of intravenous sodium thiopentone, and a cuffed Magill endotracheal tube was inserted. Ventilation was carried out with 100% oxygen by a positive-pressure apparatus throughout each experiment, except for the 5 minutes immediately before the period of circulatory arrest and for a few minutes after the arrest phase, when ventilation was performed manually. Thoracotomy was

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3. Brockman, S. K., Jude, J. R. *Bull. Johns Hopk. Hosp.* 1960, 106, 74.
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6. Gunn, C. G., Williams, G. R., Parker, I. T. *J. surg. Res.* 1962, 2, 141.
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performed through the bed of the fifth rib, and snares were placed around the venæ cavæ, proximal to the vena azygos, and around the roots of the aorta and pulmonary artery. Total circulatory arrest was then established for a predetermined length of time. Once satisfactory myocardial action was restored, the chest was closed and the animals allowed to recover.

The dogs were divided into two groups, A and B. In each, the acid-base status was followed from samples of central aortic blood obtained by means of a catheter introduced through a femoral artery. The pH, Pco_2, standard bicarbonate, and base excess in this arterial blood were measured by the micro-Astrup apparatus.[8] In the animals of group A no attempt was made to correct any acid-base imbalance, but in those of group B the acid-base status was carefully controlled. 8·4% sodium bicarbonate (1 mEq. per ml.) was used, and the dose given was calculated by the formula: body-weight (kg.) × 0·43 × base excess. This is a modification of the formula suggested by Astrup [9] for man, which we found to be more accurate in the dog.

A similar experiment was performed on a third group of animals (group C), but, for 5 minutes before the arrest of the circulation ventilation was performed with various carbogen mixtures (carbon dioxide in oxygen). The metabolic component of the acid-base balance was controlled as carefully as in the animals of group B.

In all groups, standard lead-II electrocardiograph (E.C.G.) tracings were recorded intermittently, and the blood-pressure was recorded with a mercury manometer. Samples of venous blood were removed from the dogs of groups B and C before and after circulatory arrest and for several days postoperatively. These samples were analysed for sodium, potassium, chloride, urea, serum glutamic-oxaloacetic transaminase (S.G.O.T.) and serum glutamic-pyruvic transaminase (S.G.P.T.), and the packed-cell volume was determined.

RESULTS

Table I shows the occurrence of arrhythmias after the period of circulatory arrest in the dogs of groups A and B, together with the time taken to achieve adequate ventricular output (effective beat) as determined by direct inspection of the heart, by measurement of the blood-pressure, and by examination of the E.C.G. The time taken for the pupil, dilated by anoxia, to constrict is also shown, and the condition of the dog 24 hours later.

Table II shows the acid-base parameters of the dogs of group A together with the duration of the circulatory

8. Anderson, O. S., Engel, K., Jorgensen, K., Astrup, P. *Scand. J. clin. lab. Invest.* 1960, 12, 172.
9. Astrup, P., Andersen, O. S., Jørgensen, K., Engel, K. *Lancet*, 1960, i, 1035.

TABLE I—RESULTS IN DOGS OF GROUPS A AND B

Group	Dog	Duration of arrest (min.)	Time to effective beat (min.)	Time to pupillary constriction (min.)	Postarrest arrhythmia	Postoperative condition 24 hours later
A	1	4	0 (Immediate)	3½	Supraventricular tachycardia with persistent extrasystoles	Semiconscious and spastic
	2	5	½	3½	Frequent ventricular extrasystoles with paroxysmal ventricular tachycardia	Unconscious and spastic
	3	5	3	6½	Ventricular extrasystoles and supraventricular tachycardia	Unconscious and spastic
	4	6	3	9	Ventricular fibrillation; heart-block; ventricular extrasystoles	Unconscious and spastic
	5	6	9	12	Ventricular extrasystoles; heart-block	Unconscious and spastic
	6	7	3	8	Heart-block; paroxysmal tachycardia; numerous ventricular extrasystoles	Unconscious and spastic
B	7	4	0 (Immediate)	2½	Supraventricular tachycardia	Conscious, walking, seeing, lapping
	8	5	0 (Immediate)	3	Auricular fibrillation	Conscious, drinking, seeing
	9	5	1½	5½	None	Conscious, lapping, spastic
	10	6	0 (Immediate)	12 (when noted)	None	Conscious, lapping, seeing
	11	6	0 (Immediate)	3	Supraventricular tachycardia	Conscious, lapping, trying to stand
	12	7	0 (Immediate)	13 (when noted)	None	Conscious, lapping, seeing

TABLE II—ACID-BASE MEASUREMENTS IN ANIMALS OF GROUP A AT THE BEGINNING OF THE EXPERIMENT, JUST BEFORE ARREST OF THE CIRCULATION, AND WHEN EFFECTIVE BEAT RESTORED

Dog	Body-weight (kg.)	Duration of arrest (min.)	Stage of experiment	pH	P_{CO_2} (mm.Hg)	Standard bicarbonate (mEq. per l.)	Base excess (mEq. per l.)
1	16·4	4	Start	7·30	38	18·0	− 6·7
			Prearrest	7·56	11·5	18·5	− 6·5
			Postarrest	7·25	31	14·6	−11·8
2	15·5	5	Start	7·33	33	20·5	− 3·5
			Prearrest	7·51	19	20·5	− 3·0
			Postarrest	7·23	43	16·7	− 9·8
3	10·9	5	Start	7·26	45	18·5	− 6·0
			Prearrest	7·39	27	18·3	− 6·6
			Postarrest	7·29	26	15·4	−11·8
4	23·7	6	Start	7·30	33	16·6	− 8·5
			Prearrest	7·43	18	15·2	−10·2
			Postarrest	7·15	34	12·6	−16·8
5	15	6	Start	7·24	39	16·3	−11·0
			Prearrest	7·13	60	14·8	−13·5
			Postarrest	7·15	32	12·5	−18·0
6	15·5	7	Start	7·31	34	17·6	− 7·2
			Prearrest	7·44	24	19·0	− 5·4
			Postarrest	7·14	55	14·0	−13·2

arrest. These values were measured at the beginning of the experiment, immediately before the arrest of the circulation, and upon re-establishment of adequate myocardial function. The figures for standard bicarbonate and base excess, measured before and after the period of circulatory arrest, show that a state of metabolic-acidosis developed to a degree dependent on the length of the arrest. Table III shows the fall in base excess during each period of arrest in the dogs of group A. The calculated fall per minute of arrest is also shown, the mean rate of fall being 1·1 mEq. per litre of blood per minute of circulatory arrest.

On the basis of this information, the dogs of groups B and C were given calculated doses of 8·4% sodium bicarbonate: the first was given early in the experiment to

TABLE III—BASE EXCESS IN DOGS OF GROUP A SHOWING FALL PER MINUTE OF CIRCULATORY ARREST

Dog	Duration of arrest (min.)	Prearrest base excess (mEq. per l.)	Postarrest base excess (mEq. per l.)	Fall in base excess per minute of arrest (mEq. per l. per min.)
1	4	−6·5	−11·8	1·3
2	5	−3·0	− 9·8	1·4
3	5	−6·6	−11·8	1·0
4	6	−10·2	−16·8	1·1
5	6	−13·5	−18·0	0·8
6	7	−5·4	−13·2	1·1
		Mean		1·1

correct any pre-existing acidosis, and the second was given 10 to 15 minutes before the arrest of the circulation to create a metabolic alkalosis of such magnitude that the animals would be in acid-base balance at the end of the period of arrest. Thus, if the arrest were to last 7 minutes, the animal was given an amount of bicarbonate calculated to raise its base excess to +7. Table IV shows the acid-base parameters of the dogs of group B and the amounts of bicarbonate given.

The acid-base measurements of the dogs of group C, recorded before and after the circulatory arrest, are shown

TABLE IV—ACID-BASE MEASUREMENTS IN ANIMALS OF GROUP B TOGETHER WITH THE BICARBONATE REPLACEMENT GIVEN

Dog	Body-weight (kg.)	Duration of arrest (min.)	Time from start of experiment* (min.)	pH	P_{CO_2} (mm. Hg)	Standard bicarbonate (mEq. per l.)	Base excess (mEq. per l.)	Bicarbonate given (mEq.)
7	16·4	4	0	7·36	33	19·7	−4·8	10
			63					
			73	7·45	31	24·0	+1·8	
			86	7·43	31	22·4	−0·8	
8	23·0	5	0	7·42	38	24·0	+1·4	50
			60					
			75	7·54	34	29·5	+8·8	
			81	7·39	43	24·5	+2·3	
9	12·3	5	0	7·32	41	20·2	−3·8	20
			43					
				7·40	39	23·4	+0·8	23
			83					
			91	7·62	21	26·5	+5·0	
			103	7·32	47	21·7	−1·5	
10	15·5	6	0	7·34	36	19·5	−5·0	34
			22					
			40	7·36	40	21·5	−1·8	53
			51					
			59	7·55	28	26·0	+3·7	
			75	7·40	34	20·8	−3·0	
11	17·3	6	0	7·33	39	19·7	−5·0	12
			61					
			71	7·29	49	20·3	−4·0	80
			78					
			83	7·46	39	27·2	+6·2	
			92	7·38	41	23·0	+0·5	
12	10·9	7	0	7·36	35	20·8	−4·0	19
			50					
			70	7·36	44	22·9	0	33
			100					
			105	7·50	36	27·7	+6·3	
			123	7·50	17	22·0	−1·5	

*Point of circulatory arrest indicated by dotted lines.

TABLE V—ACID-BASE MEASUREMENTS BEFORE AND AFTER CIRCULATORY ARREST IN ANIMALS (GROUP C) BREATHING CARBOGEN MIXTURES FOR 5 MIN. BEFORE ARREST

Dog	Duration of arrest (min.)	P_{CO_2} of respired gas (mm. Hg)	pH	P_{CO_2} of (mm. Hg)	Standard bicarbonate (mEq. per l.)	Base excess (mEq. per l.)	Pre-arrest arrhythmias
13	6	31	7·54 7·41	30 36	27·3 22·9	+6·0 0	None
14	7	43	7·42 7·29	52 51	30·0 21·7	+9·0 −2·0	None
15	7	115	7·19 7·43	170 27	26·0 21·0	+4·5 −2·9	None
16	7	115	7·22 7·30	92 51	28·5 22·5	+7·0 −0·5	None
17	7	112	7·23 7·28	105 50	31·8 20·3	+11·5 −4·0	None

in table V, together with the P_{CO_2} of the carbogen breathed. No cardiac arrhythmias occurred while the gas mixture was being inhaled.

The figures obtained for the blood-electrolytes, blood-urea, and packed-cell volume showed changes consistent with slight hæmoconcentration but remained otherwise normal. The S.G.O.T. and S.G.P.T. levels did not rise above those shown to be consistent with thoracotomy alone.[10]

DISCUSSION

Metabolic acidosis is known to develop in association with hypoxia since anaerobic glycolysis occurs in the absence of adequate oxygenation.[11] Tissue oxygenation may be inadequate when respiration is controlled during general anæsthesia [12] when there is sustained hypotension from any cause,[13] and when flow-rates are low during cardiopulmonary bypass procedures.[14 16] Complete circulatory arrest must therefore be associated with a metabolic acidosis of this type which must quickly become profound since the anoxic stimulus is as great as it can be. The degree of acidosis produced in different animals should be the same for the same period of circulatory arrest and should alter only with alteration in metabolic rate, such as

10. Nydick, I., Wróblewski, F., LaDue, J. S. *Circulation*, 1955, **12**, 161.
11. Huckabee, W. E. *J. clin. Invest.* 1958, **37**, 264.
12. Bunker, J. P. *Anæsthesiology*, 1962, **23**, 107.
13. Root, W. S., Allison, I. B., Cole, W. H., Holmes, L. H., Walcott, W. W., Gregersen, M. I. *Amer. J. Physiol.* 1947, **149**, 52.
14. Paneth, M., Sellers, R., Gott, V. L., Weirish, W. L., Allen, P., Reed, R. C., Lillehei, C. W. *J. thorac. cardiovasc. Surg.* 1957, **34**, 570.
15. Litwin, M. S., Panico, F. G., Rubini, C., Harken, D. E., Moore, F. D. *Ann. Surg.* 1959, **149**, 188.
16. Glover, J. L. *ibid.* 1962, **155**, 360.

might be produced by hypothermia; and, in this instance, the degree of acidosis should vary with temperature.

In the dogs of group A (tables I and II), the hypoxic acidosis produced is associated with delay in the establishment of an adequate circulation and with the development of dangerous arrhythmias after the longer periods of circulatory arrest.

Since a consistent degree of acidosis develops per minute of complete circulatory arrest, the degree of acidosis likely to result from a given period of arrest can be estimated; then an amount of sodium bicarbonate calculated to neutralise the acid produced can be administered. The frequency with which this amount could be accurately forecast can be seen from table IV. At the end of the period of circulatory arrest, the base excess in all the animals of group B lay within the normal range (±2·3 mEq. per litre of blood). In this group, long periods of arrest were withstood without troublesome arrhythmias and, more important, an adequate blood-pressure was quickly achieved and sustained when the circulation was restored. Ebert et al.[17] demonstrated increased ventricular efficiency in the presence of alkalosis and decreased ventricular efficiency in the presence of acidosis. In our experiments, the degree of alkalosis produced in the immediate prearrest phase in the dogs of groups B and C was not associated with any deterioration in ventricular function nor with any upset in the serum-sodium, serum-potassium, and serum-chloride figures. We have since given intracardiac adrenaline in the immediate postarrest phase to a small number of dogs (not included in this series), and in the alkalotic state, this has produced a rapid ventricular response without arrhythmia. This corresponds with the experience of others.[17 18]

24 hours postoperatively the neurological condition of the animals of group B was much better than those of group A (table I), and this difference is presumed to be related to the prompt recovery of myocardial function in group B. A moderately severe acidosis was present in four of the animals of group A on the day after operation, showing that they were unable to overcome the effects of hypoxia efficiently. Clowes et al.[19] in a clinical review of patients undergoing thoracotomy, felt that the presence of acidosis limited their ability to compensate for hypoxia.

Increasing tensions of carbon dioxide have been shown

17. Ebert, P. A., Greenfield, L. J., Austin, W. G., Morrow, A. *Surg. Gynec. Obstet.* 1962, **114**, 357.
18. Thrower, W. B., Derby, T. D., Aldinger, E. E., *Arch. Surg.* 1961, **82**, 56.
19. Clowes, G. H. A., Alichniewicz, A., DelGuereio, L. R. M., Gillespie, D. *J. thorac. cardiovasc. Surg.* 1960, **39**, 1.

to increase the rate of cerebral blood-flow [20 21] and to displace the dissociation curve of oxyhæmoglobin to the right.[22] The dogs of group C were therefore ventilated with carbogen mixtures of various concentrations for 5 minutes before the arrest of the circulation in an attempt to fix the Pco_2 at a high level while, at the same time, achieving full oxygenation. Thus, when the circulation was arrested, these dogs were in a state of respiratory acidosis combined with metabolic alkalosis; but, when the Pco_2 of the gas mixture used was nearer 40 mm. Hg, the resultant blood pH either remained within the normal range or was high. In none of the dogs of group C was there any arrhythmia associated with the high blood-Pco_2 in the prearrest phase, and in one only was there delay in restoring an adequate blood-pressure after the arrest. In this animal the Pco_2 of the blood rose to 170 mm. Hg before the circulation was arrested and this was presumed to be due to inadequate ventilation.

Apparently, therefore, a vital factor in the restoration of efficient myocardial function after circulatory arrest and in the prevention of dangerous arrhythmias is the avoidance of a hypoxic acidosis. Neither a high Pco_2 nor variation of pH over a wide range (7·2–7·6) seems responsible for inadequate myocardial function provided there is no accompanying metabolic acidosis.

We wish to thank Sir Charles Illingworth and Prof. George Smith for constant help and encouragement. Dr. T. A. Douglas allowed us to use his laboratory facilities for the estimation of the serum-electrolytes and serum-transaminases and kindly criticised the paper. We would also like to thank Mr. I. Jacobson and Dr. E. H. Bates for their helpful criticism and participation in some of the experiments, and Mr. C. Henderson and Mrs. R. Hume for able technical assistance.

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21. Harper, W. M., Bell, Ruth, Glass, H. To be published.
22. Barcroft, J. The Respiratory Function of the Blood; part II. Hæmoglobin. London. 1928.

The Lancet Office,
7, Adam Street, Adelphi, London, W.C.2

Comment

The maximum period of safe circulatory arrest with oxygen at normal pressure would appear to be five minutes. The importance of rapid restoration of an adequate cardiac output was established. The adverse effect of metabolic acidosis could be diminished by the prior administration of sodium bicarbonate.

(III) Oxygen at 2 ATA

The main cardiac and neurological findings during and immediately after the period of arrest are summarised in Table 2.3.

Arterial pH decreased during the arrest by a mean of 0.006 units/min and PCO_2 and base deficit increased by 1.9 mm Hg and 1.0 meq/l/min respectively.

Comment

The maximum period of safe circulatory arrest with oxygen at 2 ATA would appear to be eight minutes.

GENERAL DISCUSSION

The effects of asphyxia (apnoeic oxygenation) during air and oxygen breathing at normal atmospheric pressure are in

Table 2.3 Cardiac and neurological responses to total circulatory arrest breathing oxygen at 2ATA

	ARREST PERIOD			POST-ARREST PERIOD		
DOG	Duration of arrest (min)	Cardiac action	Time to pupillary dilatation (min)	Time to effective cardiac action (min)	Time to pupillary constriction (min)	Postoperative neurological condition
OHP 1	6	SR→ ST→ SB	2	immediate	3	Rapid/complete neurological recovery
" 2	8	SR→SB →ST	1.5	2	18	Rapid/complete neurological recovery
" 3	8	SR →ST →SB	3	immediate	17	Slow initial recovery but full/complete at day 14
" 4	9	ST→ 5/1 HB	2	5	6	Slow initial recovery but full/complete at day 6
" 5	9	SR→ST →SB	3	4	11	Slow incomplete recovery Ataxia at day 22
" 6	10	SR→ST→SB →ST	2	immediate	4	Slow incomplete recovery high-stepping gait at day 15
" 7	10	SR	2	19	-	Remained unconscious 2 days - sacrificed

reasonable agreement with other studies (Richards, Pinto and Coombs, 1963; Nunn, 1977b). The extended period of apnoea with oxygen at 2 ATA indicates a substantial increase in utilisable oxygen stores. Pupillary dilatation occurred in three of four animals at an arterial PO_2 level remarkably similar to that associated with the onset of unconsciousness in hypoxic man (Nunn, 1977e). During apnoea carbon dioxide accumulated at a rate within the predicted range. The decrease in the rate of formation of fixed acids with longer periods of apnoea may have two explanations; lactic acid formation will tend to decline as the body's glucose reserve is consumed and the presence of a greater oxygen reserve may also have contributed to a certain extent.

Using an identical model of circulatory arrest as that of the present studies, Ledingham (1962 - unpublished observations) confirmed that the method of vessel clamping was effective; radioiodinated serum albumin (RISA) injected into the left ventricle was not detected in subsequent assays of brain tissue. In fact, earlier work (Kaplan et al, 1956) showed that cross-clamping of the pulmonary artery and aorta was unnecessary since this did not affect the rate of fall of brain tissue PO_2 after inflow occlusion. Prolongation of

the safe circulatory arrest time would, therefore, appear to depend upon the increased PO_2 breathed prior to arrest, since the observed values of pH, PCO_2 and bicarbonate were comparable at that time in all groups of dogs.

The periods of safe circulatory arrest at normothermia reported here were confirmed by later studies (Edwards, Holdefer and Dimick, 1965; Moor et al, 1966; Takahashi et al, 1970). The latter workers used recovery of normal EEG activity as their criterion of survival and considered that seven minutes was the maximum tolerable duration of arrest with oxygen at 3 ATA. The relatively small difference in safe arrest time, and the negligible differences in time to pupillary dilatation and rate of increase in fixed acid, between these normothermic dogs hyperventilated with air, oxygen, and oxygen at 2 ATA was initially puzzling but on reflection understandable. It is now known that during hyperbaric oxygenation tissue PO_2 is considerably lower than was originally supposed (Richards, Pinto and Coombs, 1963) and oxygen diffusion capacity is poor (see p. 56). Furthermore, if, as was stated by Moor et al (1966), only the oxygen storage capacity of <u>blood</u> could influence cerebral oxygenation during circulatory arrest, a modest increase in safe arrest was all that could be expected - of the order of 25% with oxygen at 2 ATA.

Experiments on the cerebral circulation of dogs (Jacobson, Harper and McDowall, 1963; Ledingham, McDowall and Harper, 1966) showed that cerebral venous PO_2 was elevated by only a small amount during oxygen breathing at 2 ATA and there was no protective effect in animals subjected to middle cerebral artery occlusion (Jacobson and Lawson, 1963). Visual persistence time studies in retinal ischaemia have shown that dimness of vision occurs in five seconds with air at normal pressure and 50 seconds with oxygen at 4 ATA. This represents a tissue penetration extension of only 0.073 mm in critical PO_2 (Carlisle, Lanphier and Rahn, 1964; Lanphier and Brown, 1966). In patients undergoing carotid artery surgery, oxygen at 2 ATA provided a comparatively minor degree of protection to the brain during periods of arterial occlusion (Jacobson et al, 1963; Jennett et al, 1970); the choice of anaesthetic agent is of particular importance under these circumstances because of their variable influence on cerebral oxygenation (McDowall et al, 1966).

Comparison of the respective effects of ventilatory and circulatory arrest was of interest although complicated by the different methods of assessing the hypoxic end-point. The longer period of circulatory arrest with air breathing (four min versus 1.8 min during 'apnoeic oxygenation') is

presumably largely explained on this basis. On the other hand, the shorter period of circulatory arrest with oxygen, particularly at 2 ATA, must be a reflection of the static circulation and perhaps problems arising during re-establishment of normal cardiac function. Certainly the rate of change in base deficit was greater (1.12 $\pm$ 0.09 meq/l/min) during circulatory arrest than during asphyxia (0.17 $\pm$ 0.08 meq/l/min; $p < 0.001$).

The importance of rapid restoration of adequate post-arrest myocardial function in assessing neurological recovery was discussed in the reprint. The beneficial action of prior administration of sodium bicarbonate was also reviewed. A number of other possible ways of determining the relationship between oxygen storage and neurological function independent of cardiac action were considered (see also p106). One possibility which seemed worth exploring involved occlusion of the inferior vena cava, the superior vena cava (excluding the azygos vein), the brachiocephalic and subclavian arteries, and the descending aorta (Brockman and Jude, 1960). Five animals were thus studied. The small amount of recirculation via the azygos vein appeared to provide reasonable coronary perfusion and the heart continued to beat in sinus rhythm for

periods in excess of one hour at normothermia (three of the five dogs). Radioisotope studies of the brain, however, indicated the presence of a collateral circulation although the precise anatomical route could not be demonstrated by angiographic techniques. These studies were not further pursued.

Chapter 3

Total circulatory arrest; preliminary studies with hyperbaric oxygen (2 ATA) at hypothermia (28 deg C)

In view of the minor differences in the periods of safe circulatory arrest with air, oxygen and hyperbaric oxygen at normothermia, the possibility that increased protection might accrue from a combination of hyperbaric oxygen and hypothermia was next considered. A substantial decrease in oxygen consumption with hypothermia was assured. The question was whether the increase in solubility of oxygen with reduced blood temperature could be augmented to a significant degree by hyperbaric oxygen.

Material and Methods (3/5/61 - 18/10/61)

Twenty-eight adult mongrel dogs were anaesthetised, ventilated and monitored as described in the previous chapter. Cooling was effected by immersion in an ice water bath (Figs. 3.1 and 3.2) so that the nasopharyngeal and midoesophageal temperatures at the start of circulatory arrest were 28 $\pm$ 1 deg C. The circulation was arrested without preliminary acid-base correction. The inspired gas throughout cooling, arrest and rewarming was either:

(I) Oxygen at normal atmospheric pressure (14 dogs; weight range 7 - 25 kg)

or

(II) Oxygen at 2 ATA (14 dogs; weight range 6 - 26 kg)

Figure 3.1. Animal being cooled in bath of iced water.

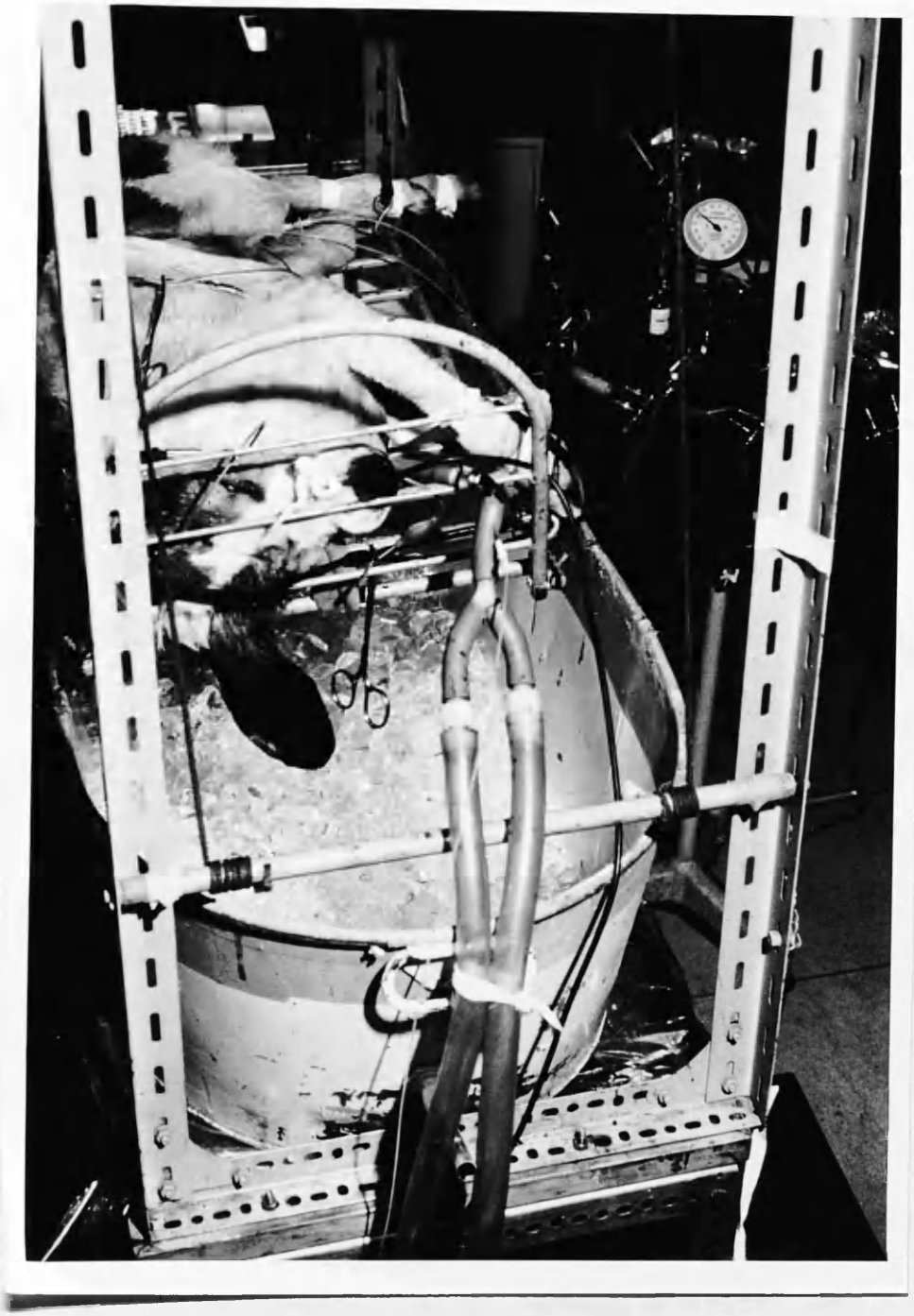

Figure 3.2. Elevation from water bath effected by cradle suspended from dexion frame.

Animals which recovered were returned to their cages on the following day and biochemical estimations carried out on a daily basis as in the normothermic series. Thereafter the dogs were sacrificed at various intervals up to 134 days after operation.

Detailed histological examination (Dr F.D. Lee) was made of the myocardium, kidneys, lungs, liver, pancreas, and gastro-intestinal tract. The brains were removed intact and, after fixation, sections were examined naked eye; tissue was obtained for histological examination from the cerebral cortex, the basal ganglia, and the cerebellum. Fixation was effected with 10% formol saline immediately after death with subsequent postfixation in mercuric chloride-formol. Paraffin sections were stained with haemalum-eosin and, in addition, haematoxylin-van Gieson, Masson's trichrome, Mallory's phosphotungstic acid haematoxylin, Heidenhain's iron haematoxylin, and the van Kossa technique for calcium deposition were used when necessary, particularly for elucidating the nature of the changes in the heart muscle. A standard block was taken from the apex of the left ventricle muscle in all dogs.

Pilot studies indicated that animals subjected to 10 minutes of total circulatory arrest at 28 deg C whilst breathing oxygen at normal pressure recovered promptly and without neurological sequelae. In the animals of the present series the period of arrest was increased by three to 10 minute intervals from 12 to 25 minutes (oxygen at normal pressure) and from 17 to 40 minutes (oxygen at 2 ATA). As in the normothermic series of animals the safe circulatory arrest period was considered as that from which all the dogs in any one group recovered without permanent neurological damage. The earliest evidence of damage appeared to be minor degrees of ataxia and head "weaving" which frequently disappeared within a few days. More severe damage was permanent ataxia and blindness.

Results

The number of animals surviving the period of arrest and the neurological outcome may be seen in tables 3.1 and 3.2. The safe period of circulatory arrest appeared to be 20 minutes with oxygen at normal pressure and 30 minutes with oxygen at 2 ATA.

The biochemical changes were, in general, slight and consistent only with haemoconcentration. The changes in transaminase

Table 3.1

Circulatory arrest at 28°C
with oxygen at normal pressure

Period of arrest (min)	No. dogs	No. recovered	Sequelae
12	4	4	Nil
15	1	1	Nil
20	4	4	Nil
25	5	3	Lethargy and Ataxia

Table 3.2

Circulatory arrest at 28°C
with oxygen at 2ATA

Period of arrest (min)	No. dogs	No. recovered	Sequelae
17	1	1	Nil
20	2	2	Nil
30	4	4	Nil
35	5	3	Lethargy and Ataxia
40	2	0	Coma and G.I. haemorrhage

levels in the animals which survived the longer periods of arrest are illustrated in figures 3.3 and 3.4.

Histological examination of the heart revealed that in two of three dogs in which arrest had been effected for 25 minutes with oxygen at normal pressure and in two of four in which it was continued for 35 minutes with oxygen at 2 ATA, numerous focal lesions were scattered irregularly throughout the whole thickness of the myocardium. This was not true with shorter periods of arrest. The lesion consisted of aggregations of necrotic muscle cells associated with marked histiocytic infiltration (Fig. 3.5). Phagocytosis of necrotic muscle debris by histiocytes was a prominent feature. No polymorphonuclear infiltration was noted. At a later stage in the evolution of this lesion, the necrotic foci were replaced by connective tissue. Remnants of necrotic muscle fibres could, however, persist for a considerable period of time and were observed 55 days post-operatively in one dog (Fig. 3.6). The necrotic muscle showed a marked affinity for calcium salts, but their deposition was not constant and did not appear to depend on the age of the lesion. Furthermore, the lesions were not all found at the same stage

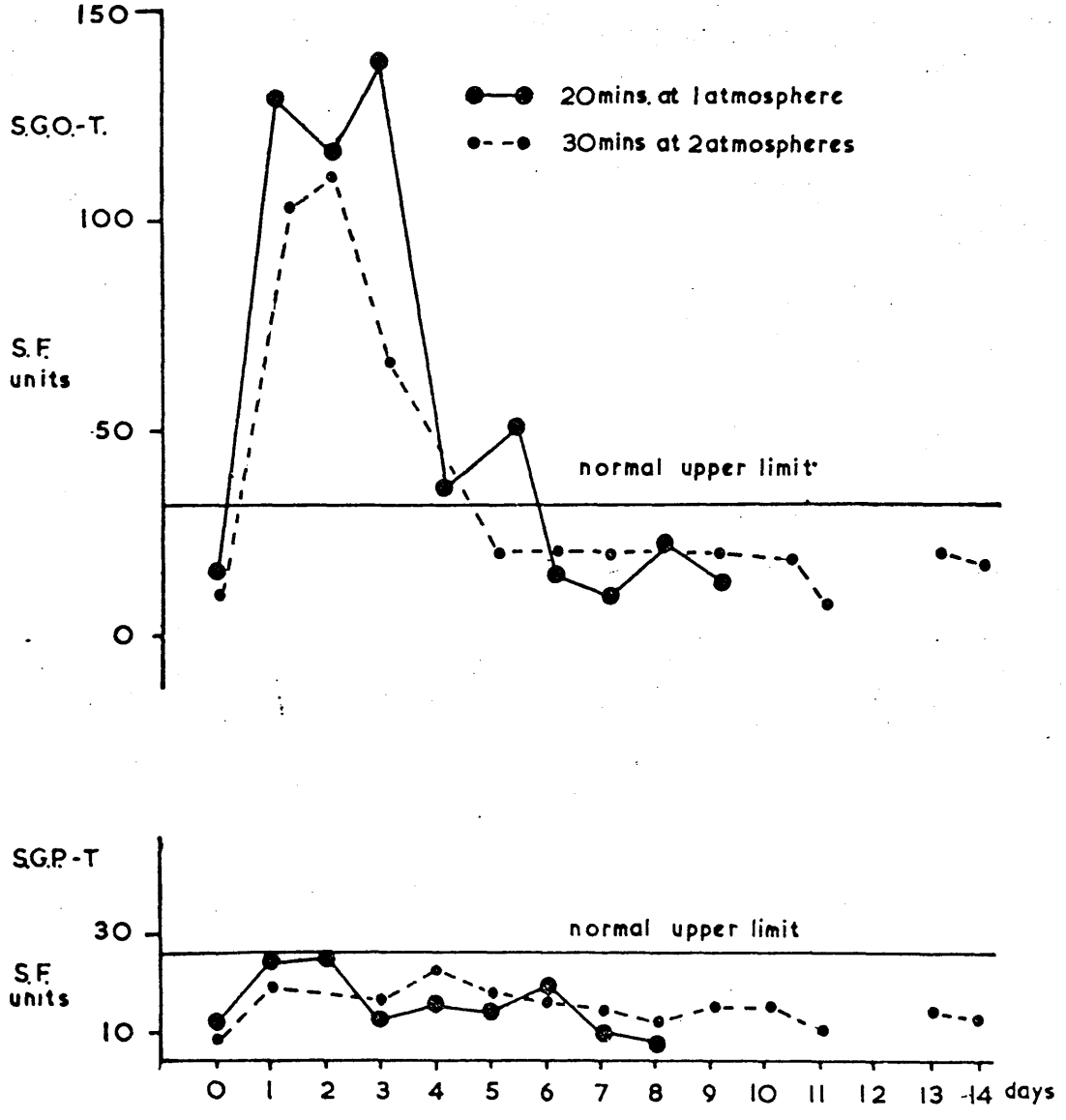

Figure 3.3. Mean changes in serum glutamic oxalacetic transaminase and serum pyruvic transaminase in 4 dogs subjected to circulatory arrest for 20 minutes after ventilation with oxygen at normal pressure and in 4 dogs for 30 minutes after oxygen at 2 ATA.

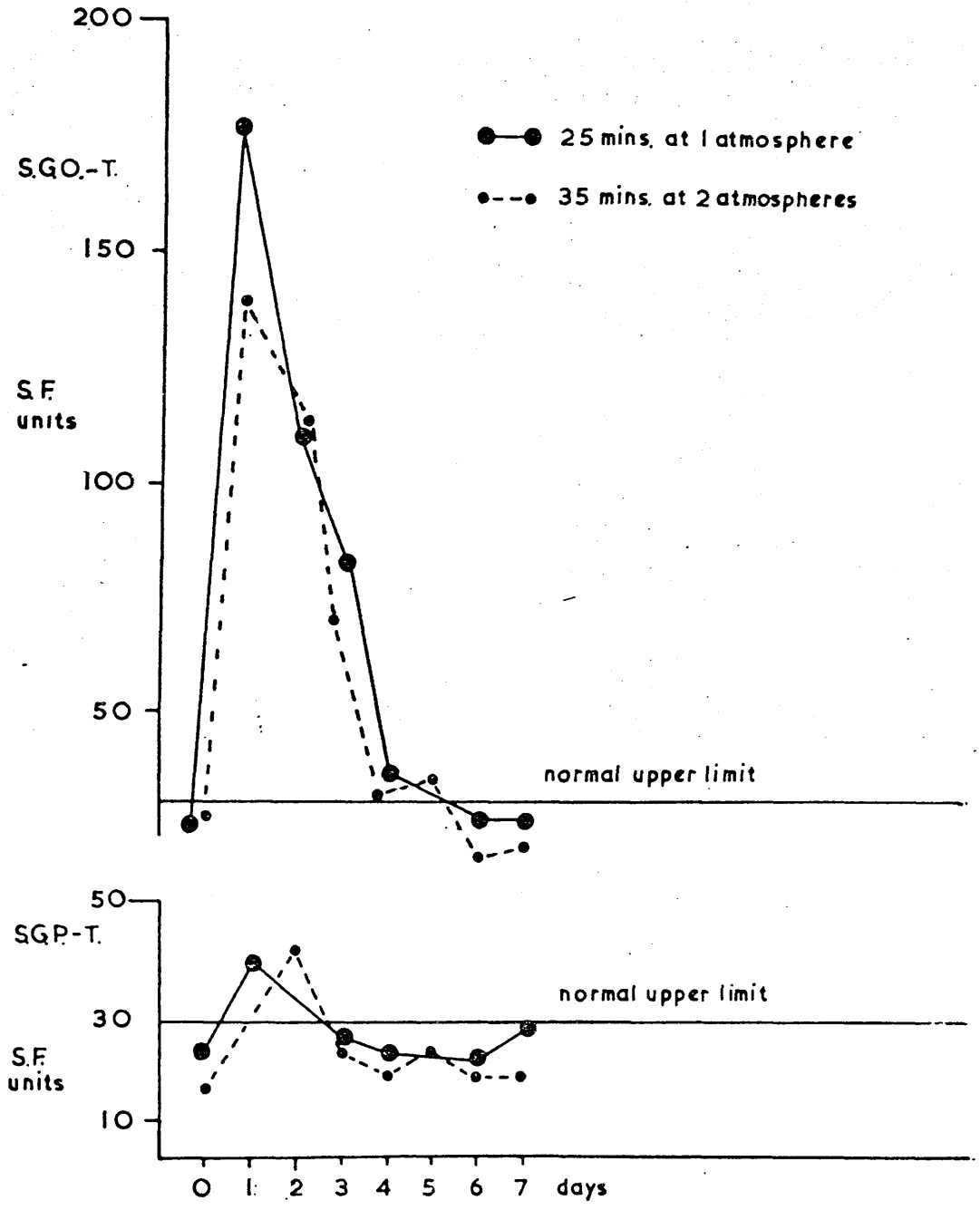

Figure 3.4. Mean changes in serum glutamic oxalacetic transaminase and serum pyruvic transaminase in 4 dogs subjected to circulatory arrest for 25 minutes after ventilation with oxygen at normal pressure and in 4 dogs for 35 minutes after oxygen at 2 ATA.

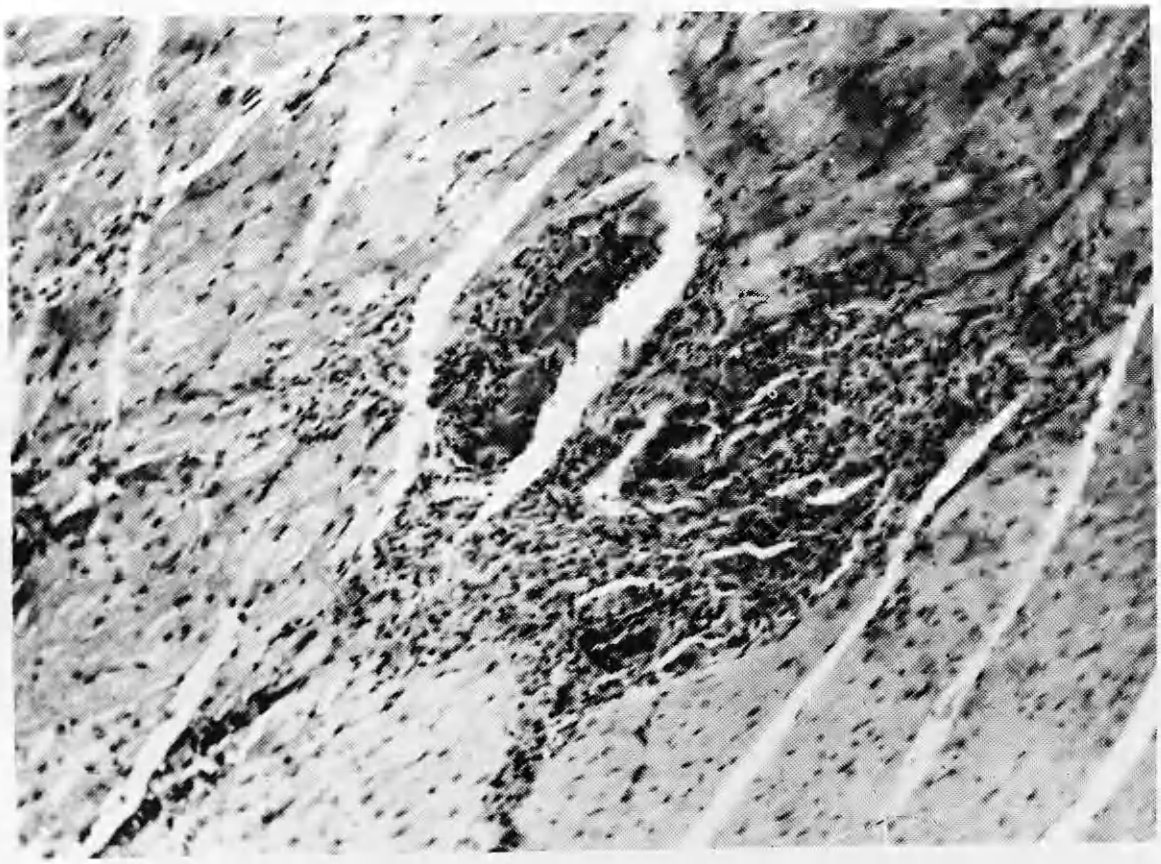

Figure 3.5. Aggregations of necrotic muscle fibres with marked histiocytic infiltration x 7¼.

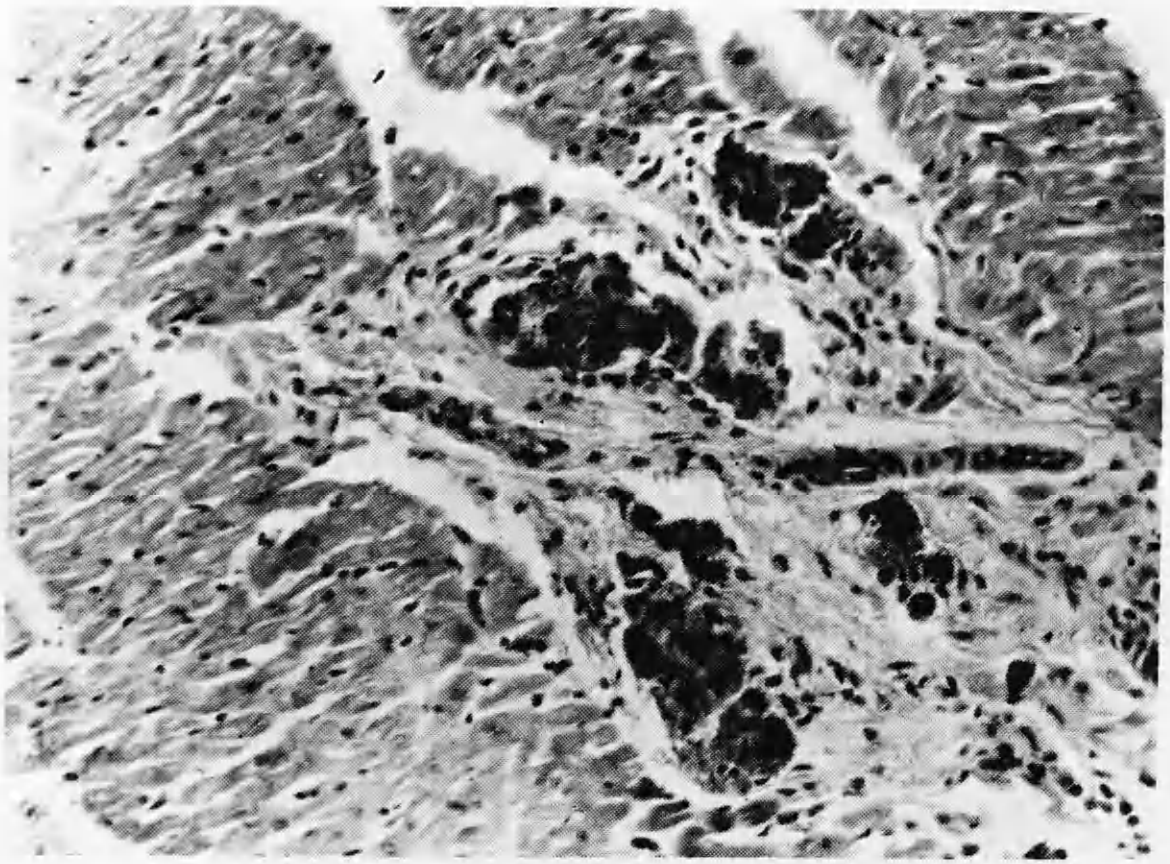

Figure 3.6. Remnants of necrotic cardiac muscle fibres with calcium deposition 55 days after operation x 116.

of evolution in any one case. The term microinfarct was applied to this lesion.

Additional evidence of myocardial damage was present. Necrotic muscle fibres, singly or in groups, were scattered throughout the heart. The affected cells showed markedly eosinophilic protoplasm with partial loss of striation and pyknotic nuclei. There was no histiocytic reaction (Fig. 3.7). The term necrobiosis was applied to this change. It was seen not only in three of the four dogs with micro-infarction but also in the remaining dog in which arrest had been effected for 25 minutes with oxygen at normal pressure and in the four dogs arrested for 30 minutes at 2 atmospheres of pressure.

No evidence of brain damage was found with an arrest period of 20 minutes with oxygen at normal pressure and 30 minutes at 2 ATA. In one dog in which the period of arrest was 35 minutes at 2 ATA there was a microscopic focus of necrosis in the cerebral cortex.

Since the two dogs arrested for 40 minutes at 2 ATA showed severe neurological damage, they were sacrificed one and two days post-operatively. Only in these two dogs did significant

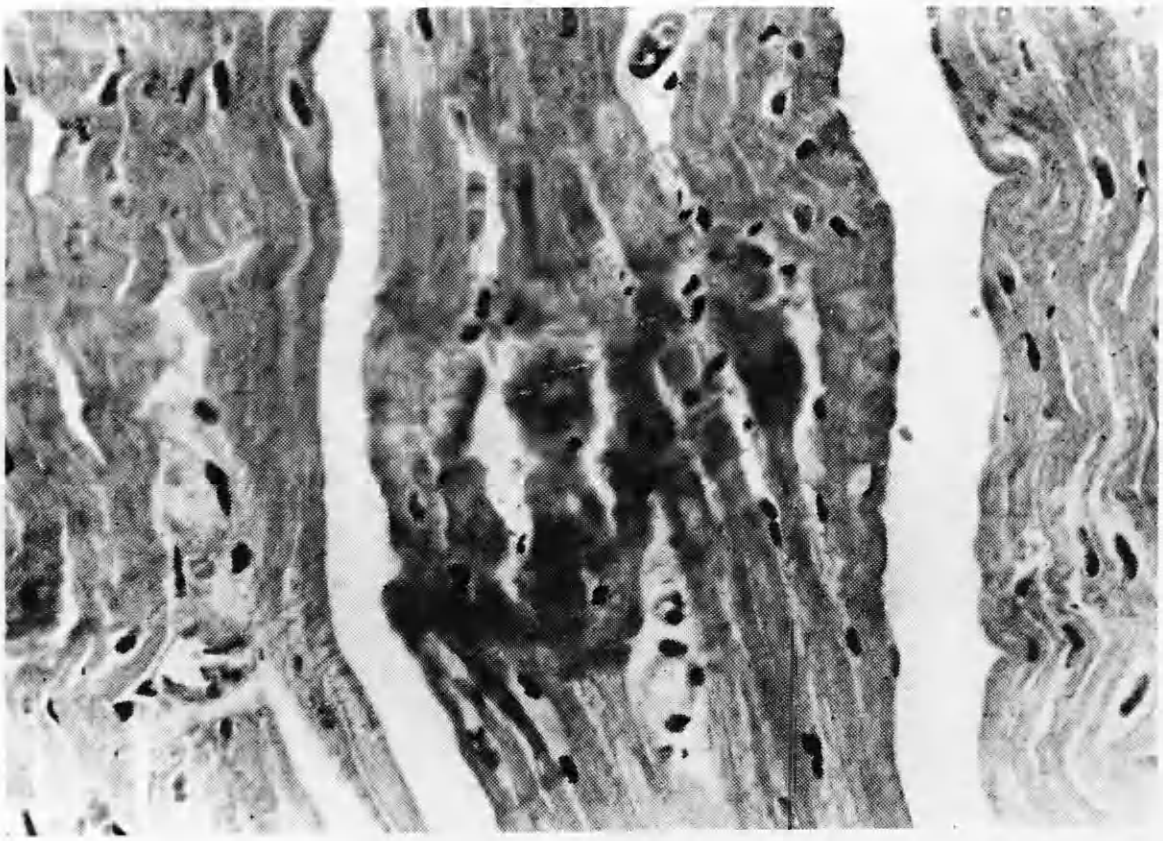

Figure 3.7. Necrobiosis of cardiac muscle fibres with deeply eosinophilic cytoplasm, partial loss of striations, and pyknotic nuclei. Note lack of histiocytic infiltration.

pathological lesions develop in the pancreas (one dog), and in the intestines (both dogs). At autopsy, intestinal haemorrhage was found, and on histological examination necrosis of the tips of the villi and of the superficial parts of the intestinal mucosa was evident without marked leucocytic infiltration. The necrotic process extended into the large intestine, but not into the stomach, in one animal. In one of these dogs haemorrhagic pancreatic necrosis was found. In this latter dog, acute tubular necrosis of the kidneys was also noted which was the only significant lesion detected in the kidneys of any of the dogs examined. Examination revealed that no damage had occurred in the liver and lungs of any of the dogs.

Discussion

With a reduction of the body temperature to 28 deg C the metabolic requirements of the brain should be reduced to about one third (Rosomoff and Holaday, 1954). Assuming that the safe circulatory arrest times in the normothermic dogs were correct, the expected arrest times at 28 deg C would therefore be roughly 15 and 24 minutes with oxygen at normal pressure and 2 ATA respectively. At this temperature, however, the increased solubility of oxygen should produce a greater prolongation of the safe arrest time; this expectation was realised. Furthermore, as the temperature

of the body is lowered, the benefit accruing from oxygen dissolved in the body fluids and cells should be correspondingly enhanced (see later chapters).

The safe circulatory arrest periods of 20 and 30 minutes with oxygen at normal pressure and 2 ATA respectively seemed to be substantiated both by the recovery rates and by the biochemical and pathological findings. It appeared that the degree of cell damage indicated by the transaminase levels was about the same in the 20 and 30 minute groups. When these times were exceeded by periods of five minutes, the transaminase elevations were again comparable in the two groups but at higher levels.

The myocardial microinfarcts closely resembled those reported to occur in dogs with hypothermia alone (Sarajas, 1956; Sarajas et al, 1956). Duguid and his associates (1961) have reported similar lesions in human accidental hypothermia. The absence of polymorphonuclear infiltration may have been due to the relatively late stage at which these lesions were examined after operation. The cause of myocardial necrobiosis in uncertain. It may merely represent a less severe form of

microinfarction but it may indicate progressive muscle damage since it was seen for as long as 134 days after operation.

The absence of histological evidence of cerebral damage in all but one of the animals subjected to prolonged arrest is curious and may simply indicate the scattered nature of any lesions which do occur (however, see chapter 6).

The intestinal lesions reported in this study were comparable with those which have been found in shocked dogs (McArdle et al, 1975) and occasionally in man.

These results at 28 deg C were reproduced by Edwards, Holdefer and Dimick (1965) and by McSherry, Patterson and Lanphier (1966). The latter used isolated occlusion of the cerebral circulation thus avoiding the problems of cardiac resuscitation at the end of the period of arrest. After occlusion of the cerebral circulation at 28 deg C EEG activity disappeared almost as quickly as it had done at normothermia (about 26 sec) and clearly bore no relationship to survival which was reported as 30 minutes with oxygen at 3 ATA. On the other hand,

Anabtawi and Brockman (1962) and Moor et al (1966) could only produce safe arrest for 15 minutes at 28 - 30 deg C and the latter demonstrated extensive neuronal loss amongst 50% of the animals which survived the operation.

As in the normothermic dogs (chapter 2), consideration was given to other ways of examining the relationhip between oxygen storage and neurological function which did not depend so critically on rapid post-arrest restoration of cardiac output. A pilot study was performed on nine dogs using the technique of isolated, hypothermic (28 deg C) perfusion of the brain (Bjork, 1948; Kristiansen, Krog and Lund, 1960). After a 30 minute period of cerebral circulatory arrest with oxygen at normal pressure, four of the nine dogs appeared to recover normal cerebral function (as judged short-term). The remaining five died as a result of various technical problems mostly related to bleeding with the heparinised perfusion circuit. However, enough information was gleaned from this brief study to indicate that cerebral dysfunction after total circulatory arrest relates not only to the duration of arrest but also to any degree of hypoperfusion which may occur during the acute phase of resuscitation.

Chapter 4

Deep hypothermia (20 deg C); pathophysiological aspects and total circulatory arrest

The preliminary studies described in the previous chapter indicated that whereas at normothermia OHP had little to offer in protecting tissues deprived of their blood supply, the combination of hypothermia and OHP might prove valuable. Furthermore, it followed that this effect might be accentuated by increasing the depth of hypothermia or the pressure of oxygen, or both. In the first instance, increasing the depth of hypothermia was more attractive. Not only would there be a further reduction in oxygen consumption and increase in the amount of oxygen carried in physical solution but the adverse effects of any hypoperfusion associated with reduced temperature might be assuaged. The alternative of further increasing the partial pressure of oxygen was less appealing because of the uncertain risk of oxygen toxicity (Thomas et al, 1966).

Increasing the depth of hypothermia was not without its problems, perhaps the most obvious being the development of serious cardiac arrhythmias and progressive hypotension

(Bigelow, Lindsay and Greenwood, 1950; Bigelow, Callaghan and Hopps, 1950; Hegnauer, Shriber and Haterius, 1950; Covino and Hegnauer, 1956). In the absence of a pump-oxygenator, these hazards were considered to limit total body cooling in the human to temperatures above 28 deg C. Moreover, even if the problems of hypothermia itself could be overcome there was uncertainty as to the ability of the cooled heart to resume normal rhythm and function after a period of circulatory standstill. It was, therefore, decided to examine the pathophysiological changes of deep hypothermia with the aim of evolving a technique which would produce consistent recovery after induced total circulatory arrest. Thereafter the ability of OHP to support prolongation of the period of safe circulatory arrest at deep body temperature could be investigated (see following chapter).

This chapter reflects the above considerations and the experiments were designed to identify and, if possible eliminate, some of the factors which might contribute to the cardiovascular disturbances of deep hypothermia.

Materials and Methods (4/7/62 - 3/8/62)

Thirty-eight mongrel dogs weighing from 7 to 27 kg were

anaesthetised, intubated with a cuffed Magill endotracheal tube and ventilated by means of a Starling intermittent positive pressure ventilator. The minute volume was initially adjusted until the arterial PCO_2 was within the range 35 to 45 mm Hg. The inspired gas was either oxygen or, in some animals at low temperature, oxygen combined with 2 or 5% carbon dioxide. Hypothermia was induced in a bath of iced water and shivering prevented using gallamine, d-tubocurarine or suxamethonium.

Measurements were made of arterial blood pressure, heart rate and the acid-base state together with recordings of the ECG at regular intervals throughout the procedure. To avoid the problems of acid-base correction at different temperatures (about which there was considerable controversy at the time of these studies) the micro-Astrup apparatus was cooled commensurate with the animals.

There were four major experimental groups and the procedures undertaken in each are shown in table 4.1.

The five dogs of Group A were cooled to 28 deg C and the

Table 4.1 The procedures carried out in the 4 groups of dogs.

Group	No. of dogs	Procedure	Circulatory Arrest		Anaesthetic agent
			Duration (min)	Temp. (°C)	
A	5	Hypothermia, circulatory arrest, and rewarming	15/20	28	Thiopentone
B	4	Hypothermia and rewarming	none	20	Thiopentone
C	14	Hypothermia, circulatory arrest, and rewarming	20/30	20	Thiopentone
D	14	Hypothermia, circulatory arrest, and rewarming	30/20	20	Halothane
	1	Hypothermia and rewarming	none	20	Halothane

circulation arrested for 15 or 20 minutes to determine changes in acid-base balance. Three of these animals were rewarmed, and later recooled and subjected to a further period of circulatory arrest at 28 deg C to assess the effect of prophylactic administration of sodium bicarbonate in a manner similar to that described in the normothermic experiments (chapter 2).

The four dogs of Group B were cooled to 20 deg C and rewarmed without circulatory arrest. One of these animals was not given relaxants in order to assess the effect of shivering on acid-base balance.

The 14 dogs of Group C were cooled to 20 deg C and the circulation arrested (in the manner previously described) for 20 minutes in 12 dogs, and for 30 minutes in the remaining two animals. Occasional use was made of aramine to maintain an adequate arterial blood pressure below 25 deg C, and atropine when the heart rate fell below 30 beats per minute. Sodium bicarbonate was administered during cooling and as indicated during the rewarming phase. Adrenaline and electrical defibrillation were used when required to expedite restoration of normal cardiac function at the end of the arrest period.

Fourteen of the 15 dogs in Group D were cooled to 20 deg C and the circulation arrested for 20 minutes in one animal, and for 30 minutes in 13 animals. The remaining dog in this group was simply cooled and rewarmed without circulatory arrest to observe the effect at deep hypothermia of altering the inspired carbon dioxide concentration by varying either the ventilatory volume or the inspired gas. Unlike the animals of Groups A, B and C, the dogs in Group D were given sodium thiopentone only to achieve intubation. Thereafter anaesthesia was maintained with halothane until the temperature was 28 deg C at which level anaesthesia was reduced. It did not prove necessary to use aramine or atropine.

Those dogs in Group C and D which recovered from the period of circulatory arrest were examined 24 hours later to determine their neurological status.

Results

In the five dogs of Group A the base deficit increased by a mean of 0.31 meq/l/min of circulatory arrest at 28 deg C. Three of the dogs were subjected to a further 15 minute period of arrest to assess the effect of sodium bicarbonate but no difference in the speed of myocardial resuscitation

was observed. All the animals of this group survived.

The base deficit changes in the four dogs of Group B are illustrated in figure 4.1. It can be seen that uncontrolled shivering during cooling was associated with the development of metabolic acidosis; this was corrected spontaneously in the later stages of rewarming. When shivering was eliminated significant acidosis did not develop during cooling; during the early stages of slow surface rewarming, however, bradycardia and hypotension occurred with the development of an associated acidosis - again correcting spontaneously in the later stages of rewarming. In the fourth dog, shivering was prevented, and bradycardia and hypotension avoided by the initiation of rapid rewarming; metabolic acidosis did not develop.

Only four of the animals of Group C survived the whole procedure (Table 4.2). The cause of death in three was faulty technique. In dog 9 spontaneous ventricular fibrillation occurred during cooling attributable to inadequate control of shivering. Haemothorax accounted for the deaths of dogs 12 and 13 during rewarming. The remaining animals died of cardiac causes during resuscitation after arrest. In the animals which died,

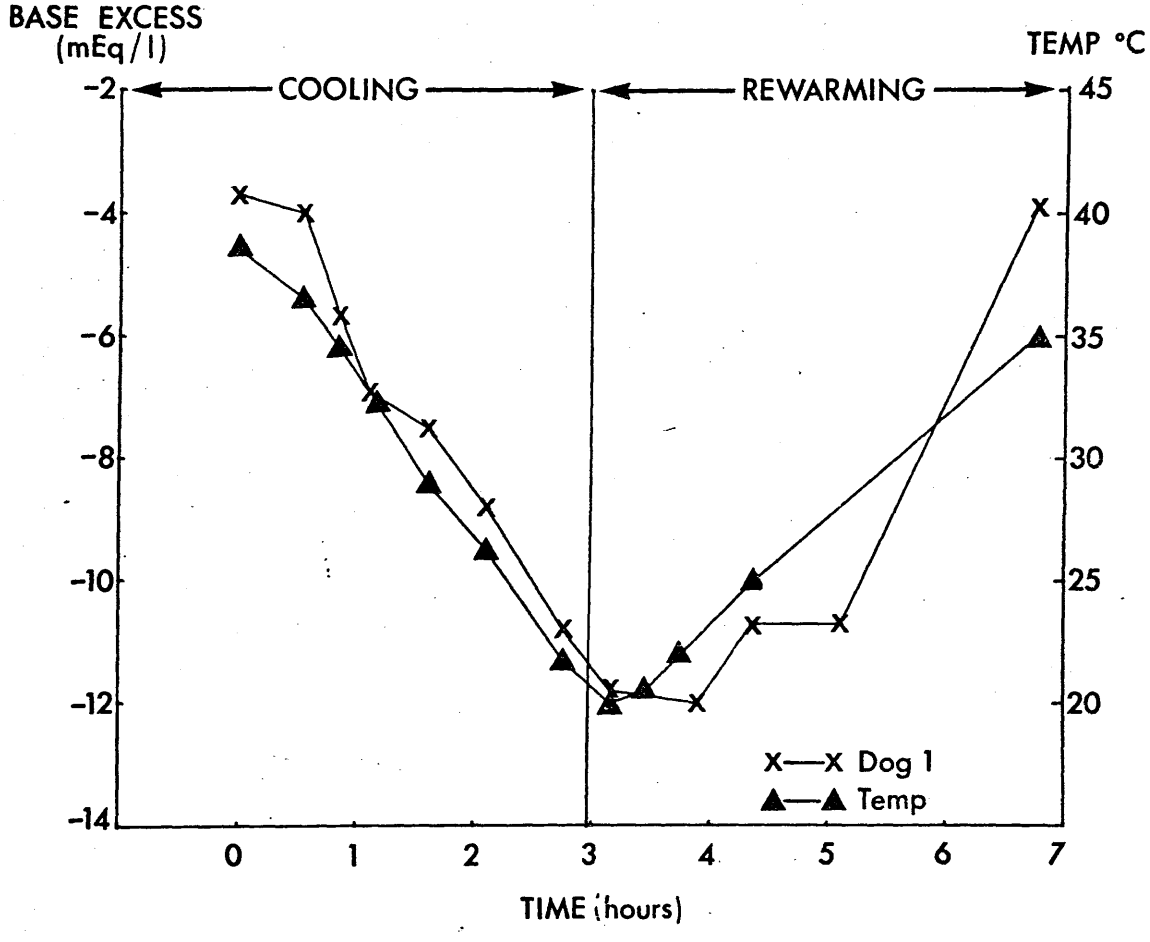

Figure 4.1a. Acidosis of uncontrolled shivering.

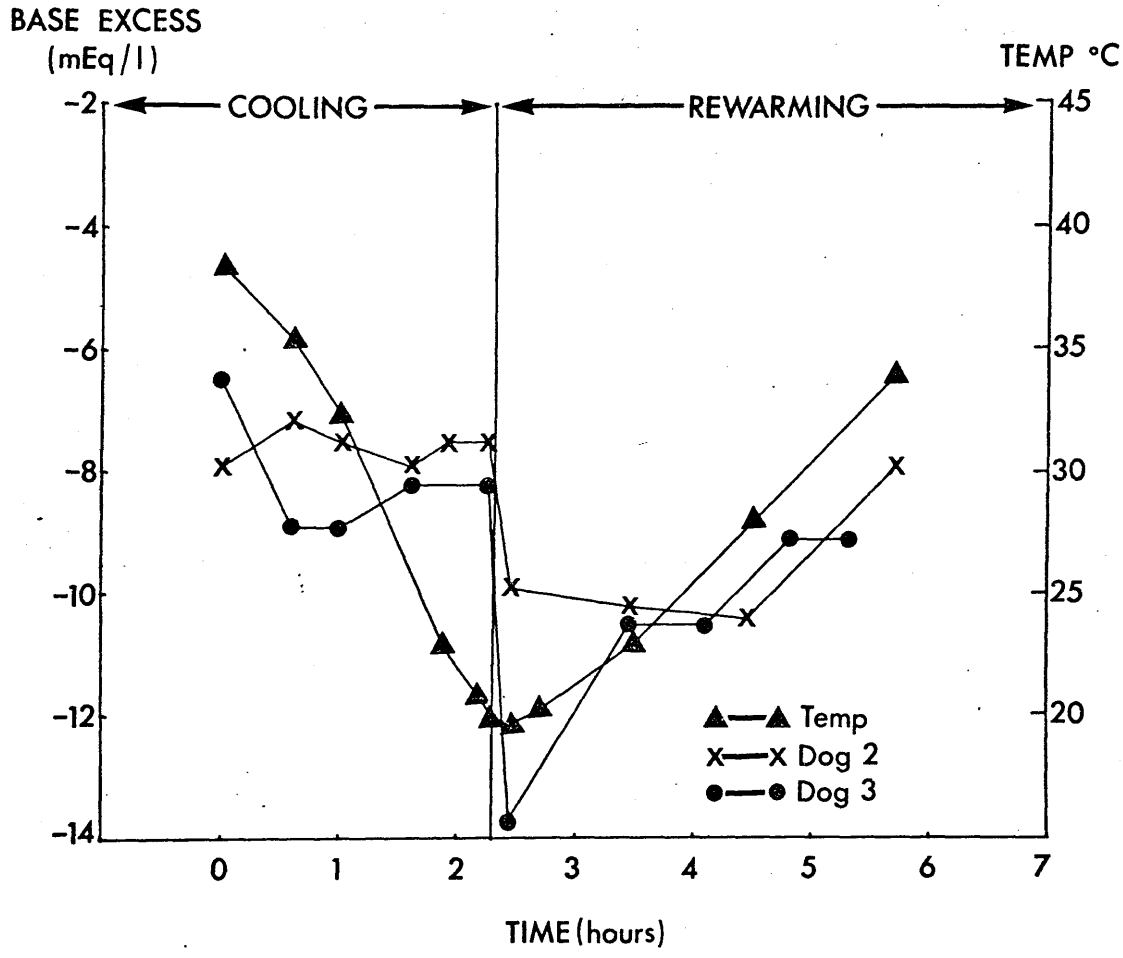

Figure 4.1b. Shivering and acidosis eliminated during cooling.

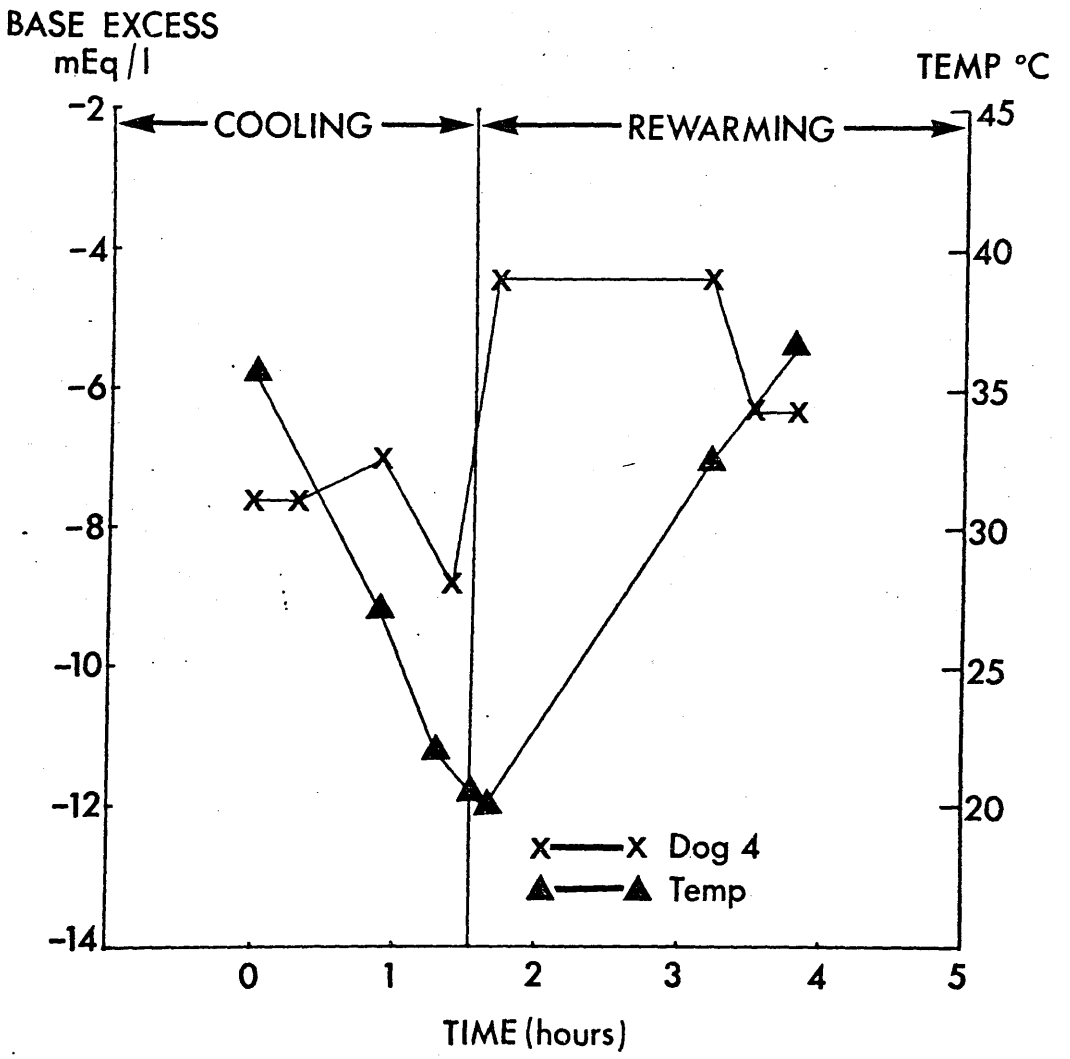

Figure 4.1c. Shivering and acidosis absent throughout cooling and rewarming.

Table 4.2 Values obtained from the dogs of group C. The figures in brackets are those which obtained before vasopressors were used. An asterisk indicates that the cause of death was technical.

Dog	wt kg	Period of Arrest min	Cooling time min/kg	Pre-arrest mean B.P. mmHg	Pre-arrest H.R. beats/min	Fate	Temp of Arrest °C
1	16.4	20	12.9	-	27 (22)	Died	20.3
2	26.4	20	10.2	-	VF	Died	20.3
3	29.0	20	10.4	75	46	Recovery	20.6
4	13.7	20	22.3	55 (30)	50 (9)	Died	20.7
5	11.8	20	15.4	125 (15)	22 (9)	Died	19.6
6	16.4	20	11.8	50	35	Recovery	20.6
7	22.9	20	13.5	30	37	Died	21.1
8	18.2	20	11.6	55 (50)	25	Recovery	20.8
9*	11.8	20	13.6	- (50)	VF	Died	23.0
10	15.3	20	12.2	80	27	Recovery	20.8
11	15.9	20	12.2	60 (35)	37	Died	21.2
12*	11.8	20	13.9	45	37	Died	21.1
13	13.6	30	13.8	70 (30)	33 (25)	Died	20.3
14*	14.5	30	16.6	100 (95)	37	Died	20.8
Mean	16.9		13.6 $\pm$ 0.8	68 $\pm$ 8.1 (44 $\pm$ 9.7)	34 $\pm$ 2.4 (16 $\pm$ 4.2)	-	20.8

the rate of cooling and the pre-arrest mean blood pressure and heart rate were lower than in the survivors. All the dogs which failed to recover from the period of arrest had a mean blood pressure of 35 mm Hg or less during the terminal stages of cooling but this was artificially raised using aramine to a level indistinguishable from that in the animals which recovered (Fig. 4.2; Table 4.4).

In Groups A, B and C, seven animals received gallamine, eight d-tubocurarine and seven suxamethonium in order to prevent shivering. Gallamine and d-tubocurarine caused varying degrees of hypotension whereas suxamethonium was effective without adversely affecting blood pressure. Seven animals were ventilated with oxygen during the cooling phase and seven with oxygen/carbon dioxide mixtures. No difference between the two groups in respect of cardiac arrhythmias or recovery was observed.

Survival in Group D exceeded that in Group C (Table 4.3) in spite of a 10 minute increase in the period of circulatory arrest. The difference in survival between the two groups, however, was not significant. The cause of death in Group D dogs was to be found in the resuscitation phase. Two of the

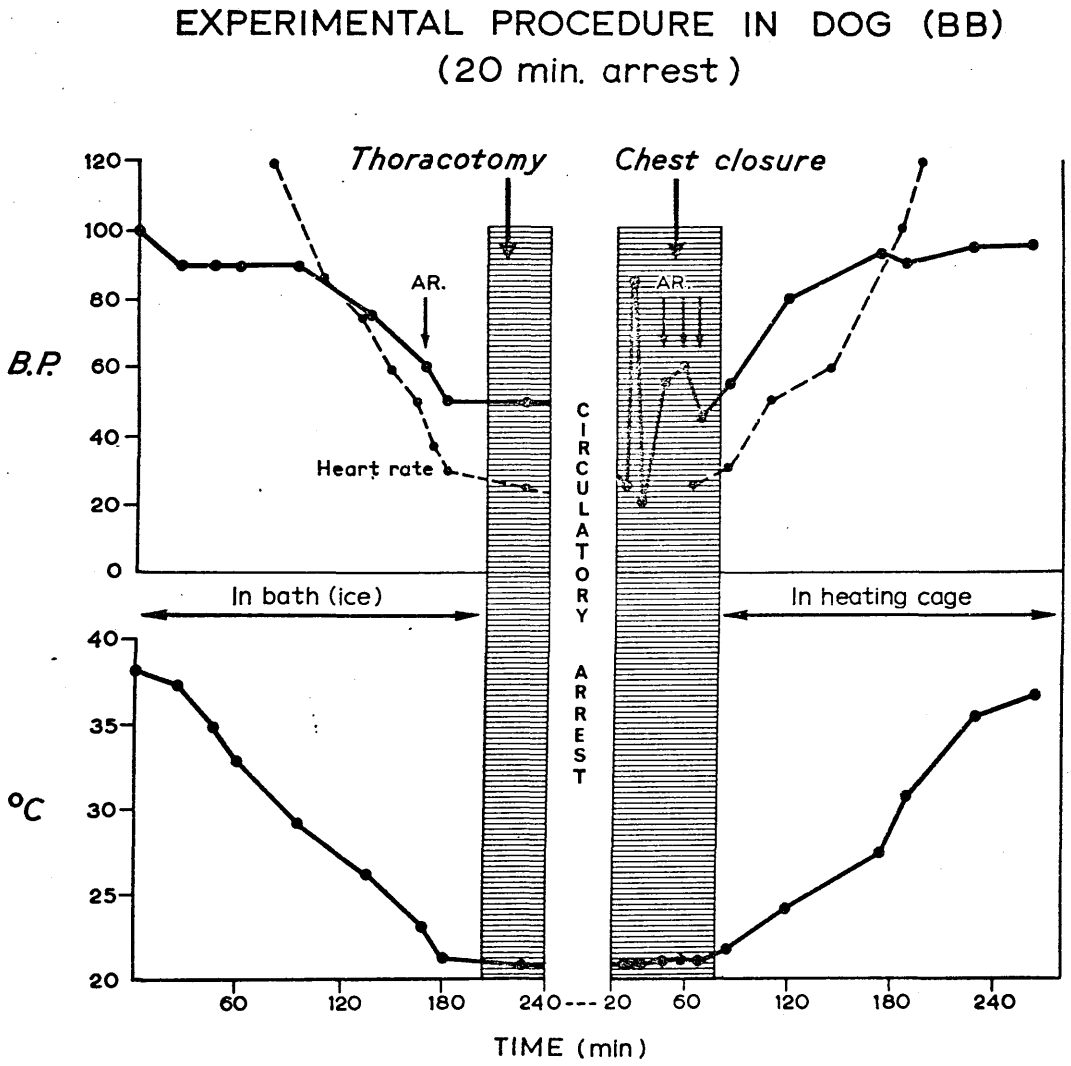

Figure 4.2. Animal of Group C anaesthetised with thiopentone and subjected to 20 minute circulatory arrest. Note prolonged cooling, slow resuscitation and use of aramine (AR).

Table 4.3 Values obtained from the dogs of group D. Vasopressors were not used in this group before circulatory arrest. An asterisk indicates that the cause of death was technical.

Dog	wt kg	Period of arrest min	Cooling time min/kg	Pre-arrest mean B.P. mmHg	Pre-arrest H.R. beats/min	Fate	Temp. of arrest °C
1	20.0	20	7.6	50	34	Recovery	19.9
2	14.5	30	11.4	60	30	Recovery	20.0
3*	10.9	30	12.1	80	37	Died	19.9
4	10.9	30	10.7	90	27	Recovery	20.0
5	14.5	30	8.6	70	46	Recovery	21.2
6	15.4	30	11.4	55	33	Died	19.5
7	9.1	30	11.6	65	27	Died	19.2
8*	20.9	30	4.2	100	26	Died	19.5
9	12.7	30	9.2	125	60	Died	21.4
10	20.0	30	6.5	90	25	Died	19.1
11	18.2	30	5.4	80	33	Recovery	20.3
12	16.4	30	6.8	70	30	Recovery	20.2
13	16.4	30	5.6	100	30	Recovery	21.2
14	9.1	30	13.0	70	28	Recovery	20.7
Mean	14.9	-	8.8 $\pm$ 0.8	79 $\pm$ 5.5	33 $\pm$ 2.5	-	20.2

Table 4.4 Mean values obtained from those dogs of Groups C and D which recovered and those which died. The figures in brackets are those which were obtained before vasopressors were given.

Group	No. Dogs	Fate	Period of Arrest min	Cooling Time min/kg	Pre-arrest mean BP mm Hg	Pre-arrest HR beats/min
C	4	Recovery	20	11.5	65	33
	10	Died	20	14.4	69 (44)	35 (16)
D	8	Recovery	30	8.6	74	32
	6	Died	30	9.2	86	38

Table 4.5 The base excess and blood pressure on 5 occasions before and whilst breathing carbogen mixtures.

Before Breathing Carbogen			Whilst Breathing Carbogen		
Base excess mEq/L	Mean blood pressure mm Hg	PCO_2 mm Hg	Base excess mEq/L	Mean blood pressure mm Hg	PCO_2 mm Hg
+2.1	100	30	-3.5	95	57
-3.5	95	27	-7.8	70	67
+3.0	85	10	-6.2	70	55
+4.5	90	28	-6.0	70	53
+3.0	80	35	-2.5	60	54

deaths were due to technical factors - inadvertent cardiac distension during arrest in dog 3 and an aortic tear in dog 8. Dogs 6, 7, 9 and 10 died of cardiac causes during investigations into the importance of ventilation and the respiratory component of the acid-base state. In these animals the arterial PCO_2 was adjusted to remain between 30 and 40 mm Hg during the cooling stage either by progressive reduction of ventilatory volume or by the addition of carbon dioxide to the inspired gas, while in the post-arrest phase of cardiac resuscitation manual ventilation was replaced by mechanical ventilation. The unsatisfactory outcome of these manoeuvres prompted a return to the original method of ventilation with 100% oxygen at a constant volume throughout the procedure (other than during the stage of cardiac resuscitation). When this approach was adopted in the final four dogs of Group D the results were entirely satisfactory. The cooling, arrest and rewarming sequence using halothane anaesthesia is illustrated in figure 4.3; the rapid cooling and rewarming times and the absence of hypotension was in contrast to the animals of Group C (Fig. 4.2; Table 4.4).

In view of the apparently adverse effects observed in those dogs of Group D in which arterial PCO_2 was maintained between

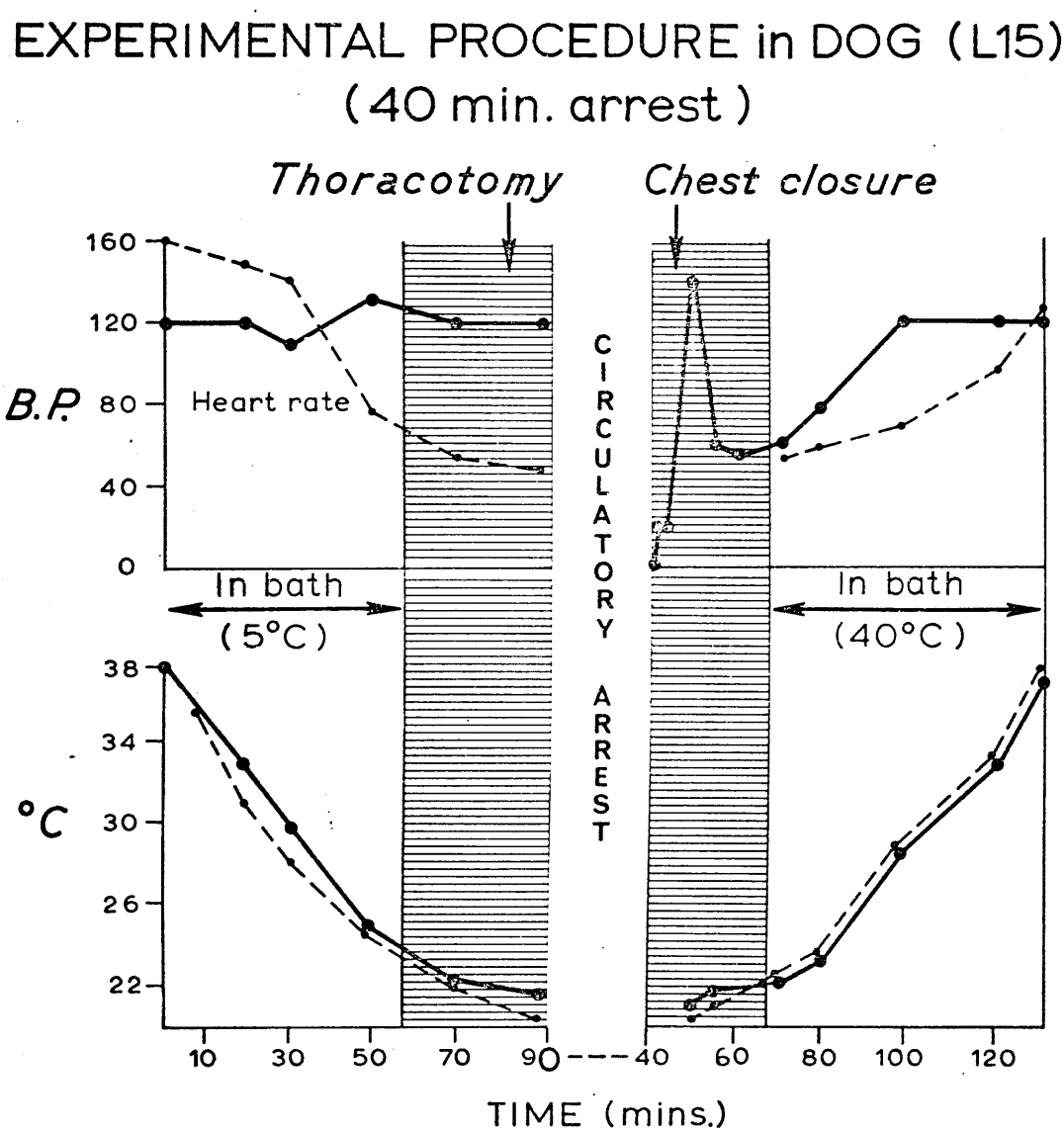

Figure 4.3. Animal anaesthetised with halothane (as in animals of Group D) and subjected to 40 minute circulatory arrest. Note rapid cooling, prompt resuscitation and avoidance of vasoactive agents.

30 and 40 mm Hg, one further animal was subjected to deep hypothermia and ventilated with various oxygen/carbon dioxide mixtures. In this animal raising the arterial PCO_2 was associated with hypotension and the development of metabolic acidosis at 20.3 deg C (Table 4.5).

Discussion

Prior to the studies reported in this chapter, attempts to subject animals to prolonged total circulatory arrest at around 20 deg C without the use of cardiopulmonary bypass had met with disappointing or indifferent results (Bigelow, Lindsay and Greenwood, 1950; Covino and Hegnauer, 1956). Using the technique described for the Group D animals most of the major problems were overcome and (as can be seen in the following chapter) the technique was successfully adopted for the studies with hyperbaric oxygen.

The basis for success in any procedure involving surface cooling is that cardiac output and tissue perfusion should be affected as little as possible. If either of these variables is adversely affected, particularly during cooling and the early stages of rewarming, metabolic acidosis and cardiac dysrhythmias develop leading to a progressive downward spiral in

cardiopulmonary function (Covino and Hegauer, 1956). If, on the other hand, cardiac output and perfusion are not substantially reduced, hypothermia by itself produces remarkably few acid-base disturbances.

Anaesthesia

The choice of anaesthetic agent is of considerable importance since many of these agents cause a diminution in cardiac output especially in the hypothermic animal, and some are more frequently associated with the onset of cardiac dysrhythmias than others (Bigelow et al, 1950; Covino and Hegnauer, 1956; Mohri et al, 1968). Volatile agents are generally to be preferred since they are not metabolised to any great degree as are the barbiturates, and both ether and halothane have been used extensively (Blair, 1969; Warner et al, 1970). In the present study there could be little doubt about the superiority of halothane over intermittent intravenous doses of thiopentone and some of the poor results previously reported with deep hypothermia might be explained on this basis (see also chapter 13).

Although halothane diminishes cardiac output, the dose used in this study would have produced minimal myocardial depression

(Shimosato, Tsung-Han and Etsten, 1963); the increased risk of ventricular fibrillation reported by some (Sprouse, Galindo and Morrow, 1963) was not confirmed. The main action of halothane was to increase skin and muscle perfusion resulting in an increase in the cooling rate; myocardial resuscitation after the period of circulatory arrest was also more rapid. At 28 deg C there is evidence that halothane requirement is about 40% of normal (Munson, 1970) and in the group D animals when halothane administration was reduced at this temperature, heart rate and arterial blood pressure returned almost to pre-cooling levels. These factors seemed to favour prompt resuscitation although there is clearly disagreement about the cardiac effects of the various levels of anaesthesia, some believing that deep anaesthesia should be avoided (Popovic and Popovic, 1974b) while others take the opposite view (Rittenhouse, Mohri and Merendino, 1970).

Ventilation

The dangers of spontaneous ventilation in induced hypothermia have been appreciated for a number of years (Bigelow, Callaghan and Hopps, 1950; Osborn, 1953; Fleming, 1954; Brewin, Nashat and Neil, 1956). Progressive respiratory failure and shivering (both leading to acidosis) are the two main problems, and the risk of ventricular fibrillation at higher temperatures

is also increased. The importance of mechanical ventilation, together with muscle relaxant drugs (see fig. 4.1), is not, therefore, in doubt but there remains controversy on matters of detail. Swan and his colleagues (1953) were convinced of the advantages of hyperventilation particularly in reducing the incidence of ventricular fibrillation during cooling, and others have drawn attention to the association of acidosis and ventricular fibrillation (Riberi et al, 1955; Covino and Hegnauer, 1956). The manoeuvre of reducing minute volume to maintain a constant arterial PCO_2 during hypothermia appeared to be associated with an increase in mortality in the present study and others have noted similar findings (Swan et al, 1953).

Perhaps the main debate concerns the advisability of adding carbon dioxide to the inspired gas. Respiratory alkalosis causes cerebral and coronary vasoconstriction (Mohri, Dillard and Merendino, 1972; Hägerdal, Harp and Siesjo, 1975; see also chapter 9) and a shift to the left of the oxygen dissociation curve. However, metabolic studies of the brain and the heart have not revealed evidence of hypoxia (Penrod, 1951; Carlsson, Hägerdal and Siesjö, 1976; see also chapter 9). Nevertheless, the addition of 5 to 10% carbon dioxide has been advocated by many who feel that the advantages outweigh the disadvantages

(Niazi and Lewis, 1956; Borst et al, 1963). In a recent reappraisal of this problem Prakash et al (1978) concluded that 'normothermic ventilation without CO_2 added to the inspired gas did not cause any apparent harm and is suggested as a simple and safe method for ventilation during cooling'. The present study indicated that the introduction of carbon dioxide during the late stages of cooling was associated with hypotension and metabolic acidosis, presumably caused by vasodilatation (Gollan, 1965), and suggested that if carbon dioxide were considered important it should be administered throughout cooling.

Drugs

The multiplicity of drugs which have been used to prevent the disturbances of cardiac rhythm produced by hypothermia suggests that no single agent has proved to be convincingly effective. Sympathetic discharge increases the tendency for ventricular fibrillation (Nielson and Owman, 1969) and sympathetic blockade, either by surgical or pharmacological means, reduces the incidence of ventricular fibrillation (Riberi et al, 1955; Warner et al, 1970; Falck et al, 1972). On the other hand, the intravenous infusion of catecholamines appears to have an unpredictable effect since both an increase (Angelakos and Daniels, 1969;

Falck et al, 1972) and a decrease (Covino and D'Amato, 1962) in the incidence of ventricular fibrillation have been reported. Procaine amide and quinidine seem to be effective anti-arrhythmic agents (Johnson et al, 1960).

The hypotension of induced hypothermia responds well to vaso-constrictors such as noradrenaline and aramine. Intravenous administration of aramine was effective in increasing blood pressure in the animals of Group C although the onset of response was delayed for several minutes. The use of this drug, however, did not alter the eventual outcome in hypotensive animals, an observation which confirmed the earlier work of Detterling and his colleagues (1955). Atropine was capable of increasing heart rate although its effect was inconsistent and delayed. During the course of cardiac resuscitation following circulatory arrest adrenaline proved to be a reliable drug not only in facilitating electrical defibrillation when required, but also in prompting vigorous cardiac contraction.

The value of bicarbonate could not be assessed in the animals of Groups C and D since all received the alkali as necessary during cooling, and routinely prior to the arrest period.

Acidosis during the early rewarming phase was a common occurrence but was self-correcting during the later stages, presumably because the liver becomes able to metabolise lactate above 28 deg C (Brewin et al, 1955).

Neurological Recovery

None of the animals of Groups C and D which survived the resuscitation phase showed neurological damage although recovery was considerably delayed in the barbiturate animals possibly because of the continuing effects of the drug mobilised from the tissues during rewarming.

Total Circulatory Arrest at Deep Hypothermia (20 deg C) with and without hyperbaric oxygen (2 ATA)

The studies reported in the previous chapter were essentially of an exploratory nature but provided much information which proved useful in the design of the more definitive experiments now to be presented. The two main aims of the experiments in this section were (1) to determine the maximum period of safe circulatory arrest at 20 deg C with oxygen at normal pressure and oxygen at 2 ATA, and (2) to investigate the role of prophylactic alkali administration in restoring adequate cardiac function after circulatory arrest.

Material and Methods (29/1/63 - 25/10/63)

Eighty mongrel dogs weighing from 8.2 to 29.1 kg were anaesthetised, ventilated and cooled to 20 deg C in the manner described for the animals of Group D in the previous chapter. The inspired gas was either oxygen at normal pressure (39 dogs) or oxygen at 2 ATA (41 dogs) and immediately prior to the period of circulatory arrest the animals were given either no alkali (37 dogs) or sufficient alkali to counteract the development of acidosis (43 dogs). The alkali took the form of sodium bicarbonate or sodium lactate.

The predetermined duration of arrest was 30, 35 and 40 minutes at normal pressure and 30, 35, 40 and 45 minutes at 2 ATA. Rewarming was carried out as before by immersion in a bath of water at 40 deg C.

The standard cardiorespiratory measurements were performed, in addition to which blood samples were removed at regular intervals throughout cooling, arrest and rewarming for estimation of blood gases, sodium, potassium, chloride calcium, phosphate, lactate, pyruvate, haemoglobin and packed cell volume. After rewarming the animals which recovered were returned to their cages for neurological assessment on the following day.

For the purposes of statistical analysis the five animals subjected to a 45 minute period of circulatory arrest at 2 ATA were eliminated; the analyses consisted of unpaired and paired t-test, chi-squared analysis, and F-test where appropriate; t-tests were performed unless otherwise indicated.

Results

Four of the five animals subjected to a 45 minute period of arrest at 2 ATA could not be resuscitated after arrest (Table 5.1)

Table 5.1

Total Circulatory Arrest at 20°C (30-45 min)

Mortality (%)

	Normal Atmospheric pressure			2ATA			
Duration of arrest (min)	30	35	40	30	35	40	45
No alkali	25	67	50	0	43	13	-
Alkali	-	0	16	-	50	20	80

and the fifth animal was comatose the following day. Clearly the upper limit for revival using this particular animal preparation had been defined. The data relating to mortality and the incidence of ventricular fibrillation and neurological damage refer to the 75 animals whose periods of arrest were of 30 to 40 minutes duration. Since no clearcut differences attributable to duration of arrest were observed between the animals subjected to 30, 35 and 40 minutes of arrest, the results were pooled and distinguished solely on the basis of whether or not the animals received hyperbaric oxygen and whether or not they received alkali.

Hyperbaric oxygen was associated with a reduction in mortality in the animals not receiving alkali (Table 5.2). The administration of alkali, however, reduced mortality in the animals breathing oxygen at normal pressure ($x^2 = 3.61$; $p < 0.05$) such that no beneficial effect of oxygen at increased pressure could be observed. Death in all cases was attributable to irreversible fibrillation which was completely absent during the cooling phase but did occur, on occasions, during the period of arrest (when its onset was spontaneous (Table 5.3)), or during the period of cardiac resuscitation (when its onset was

Table 5.2

Total Circulatory Arrest

at 20°C (30-40 min)

Mortality (%)

	Normal atmospheric pressure	2ATA	Totals
No alkali	9/18 (50%)	4/19 (21%)	13/37 (35%)
Alkali	3/21 (14%)	4/17 (24%)	7/38 (18%)
Totals	12/39 (31%)	8/36 (22%)	

Table 5.3

Total Circulatory Arrest

at 20°C (30-40 min)

Spontaneous Ventricular Fibrillation (%)

	Normal atmospheric pressure	2ATA	Totals
No alkali	6/18 (33%)	3/19 (16%)	9/37 (24%)
Alkali	1/21 (5%)	4/17 (24%)	5/38 (13%)
Totals	7/39 (18%)	7/36 (19%)	

Table 5.4

Total Circulatory Arrest

at 20°C (30-40 min)

'Induced' Ventricular Fibrillation (%)

	Normal atmospheric pressure	2ATA	Totals
No alkali	6/18 (33%)	9/19 (47%)	15/37 (41%)
Alkali	9/21 (43%)	8/17 (47%)	17/38 (45%)
Totals	15/39 (38%)	17/36 (47%)	

associated with handling of the heart (Table 5.4)). Spontaneous ventricular fibrillation occurred less frequently ($x^2 = 3.59$; $p < 0.05$) amongst animals given alkali at normal atmospheric pressure but occurred with equal frequency in the other groups. The incidence of induced fibrillation was equal in all groups.

Neurological damage was assessed as being absent, slight or gross, and 24 hours after operation (Fig. 5.1) it was clear that only in the hyperbaric oxygen group were there animals with no evidence of neurological damage, but nonetheless even gross neurological damage was not entirely absent. In the interests of brevity data from the alkali and non-alkali groups are presented together but the impression was gained that the alkali group made speedier and better recoveries than those without alkali (see page 133).

The haemodynamic and biochemical results are presented separately for the three phases of the study - cooling, arrest and rewarming.

Cooling

The changes occurring during cooling are indicated in table 5.5

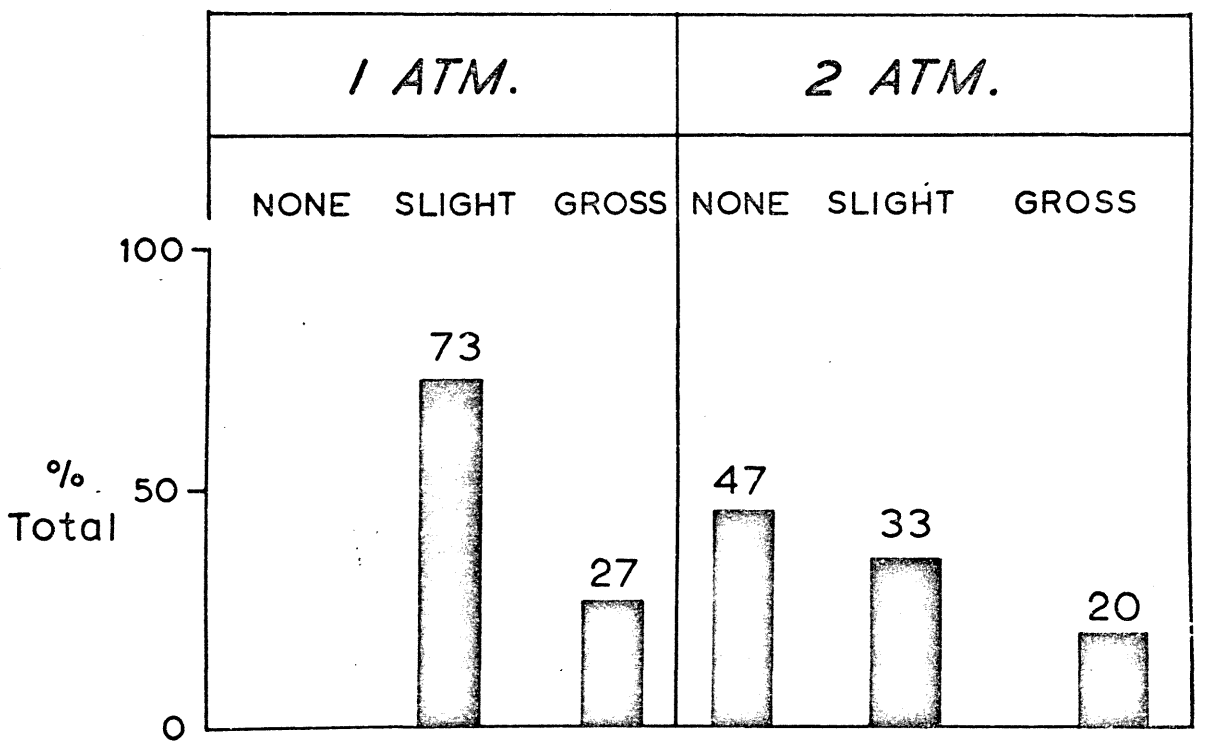

Figure 5.1. Incidence of neurological damage.

Table 5.5

Total Circulatory Arrest at 20°C
Biochemical and Haematological Data
(oxygen at normal pressure and 2ATA)

(30-40 min arrest)

Arterial blood	37°C		30°C		25°C		20°C PRE		20°C POST		25°C		37°C	
	NP	2ATA	NP	2ATA	NP	2ATA	NP	2ATA	NP	2ATA	NP	2ATA	NP	2ATA
pH (units)	7.35	7.33	7.45	7.47	7.49	7.49	7.57	7.54	7.42	7.48	7.28	7.22	7.16	7.10
PCO_2 (mmHg)	41	40	26	23	20	19	16	17	17	14	26	25	42	42
Base excess (meq/l)	-2.9	-4.0	-3.8	-3.8	-4.9 *	-6.6	-4.2	-6.5	-11.0	-11,6	-12.8	-16.1	-19.3	-15.5
Na (meq/l)	143	140	143	136	142	141	146	143	141	141	142	148	144	149
K (meq/l)	4.1	4.2	3.4	3.7	3.7	4.1	3.4 *	4.4	6.2	7.0	3.3	4.2	3.1	4.2
Cl (meq/l)	112	112	111	111	112	112	112	110	114	113	109	110	112	112
Ca (mg/100ml)	9.7	10.1	9.9	9.2	10.3	10.1	9.4	9.6	9.3	9.2	8.6	8.9	9.6	9.1
PO_4 (mg/100ml)	5.6	5.8	4.9	4.2	4.3	5.0	3.4 *	5.4	6.0	7.4	7.0	8.2	8.2	8.7
Hb /g/100ml)	14.9	13.8	15.7 *	13.1	15.9 *	14.5	17.9	15.9	18.9	17.1	18.2	16.1	19.0	17.2
PCV (%)	44	44	46	43	48	47	52	47	55	51	49	52	52	54
Lactate (mg/100ml)	15	14	17 *	9	13	12	18	11	49	34	55	39	38	35
pyruvate (mg/100ml)	1.3	1.1	0.7	0.5	0.8	0.9	0.8	0.7	0.7	0.9	1.7	2.0	1.3	2.3

Only means presented to avoid undue complexity

Asterisks indicate sig. diff. between NP and 2 ATA groups

for all 80 animals in the two main groups breathing oxygen at normal pressure and at 2 ATA. Apart from the anticipated differences between the two groups in relation to arterial and venous PO_2 (Fig. 5.2) there was remarkably similarity in the data at all stages of cooling. The arterial blood pressure and heart rate changes, and the mean duration of cooling (Fig. 5.3), were identical to those previously described in this model (Group D, previous chapter). There was a consistent small rise in haemoglobin and packed cell volume which was not matched by changes suggesting haemo-concentration in the serum electrolytes (Fig. 5.4). Only minor fluctuations within the normal range occurred in potassium although the number of values was large enough for the difference between the normal pressure and 2 ATA animals to be significant at 20 deg C ($p < 0.05$).

Coincident with a fall in arterial PCO_2, there was a progressive rise in pH; the minor changes in base excess towards acidosis as cooling proceeded were significant ($p < 0.001$) in both groups down to 25 deg C at which temperature there was a slight but significant difference ($p < 0.05$) between the two groups. There was no significant increase in lactate

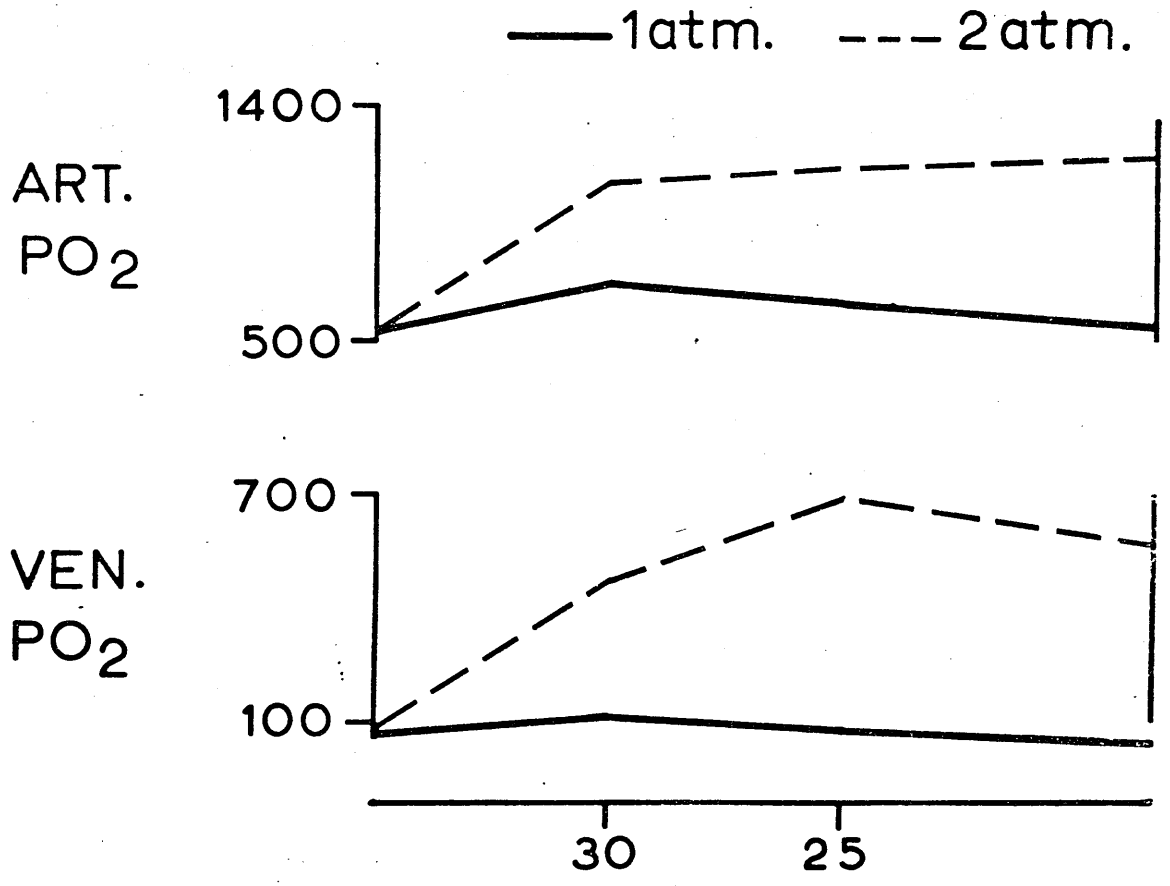

Figure 5.2. Mean arterial and venous PO2 values (mm Hg) during cooling from 37 to 20 deg C - oxygen at normal pressure (1 Atm) and oxygen at 2 ATA (2 Atm).

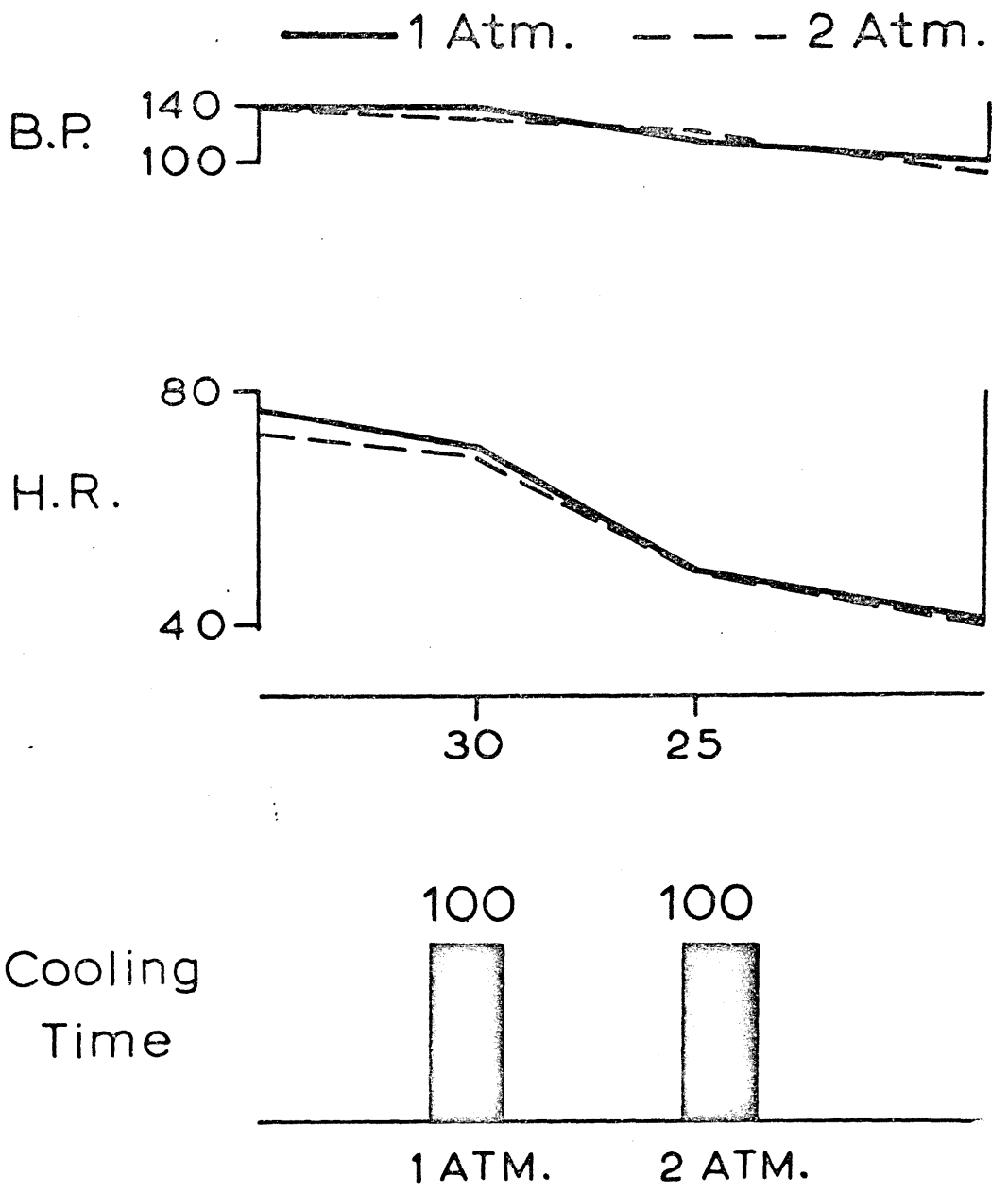

Figure 5.3. Mean arterial blood pressure, heart rate and cooling time to 20 deg C - oxygen at normal pressure (1 Atm) and oxygen at 2 ATA (2 Atm).

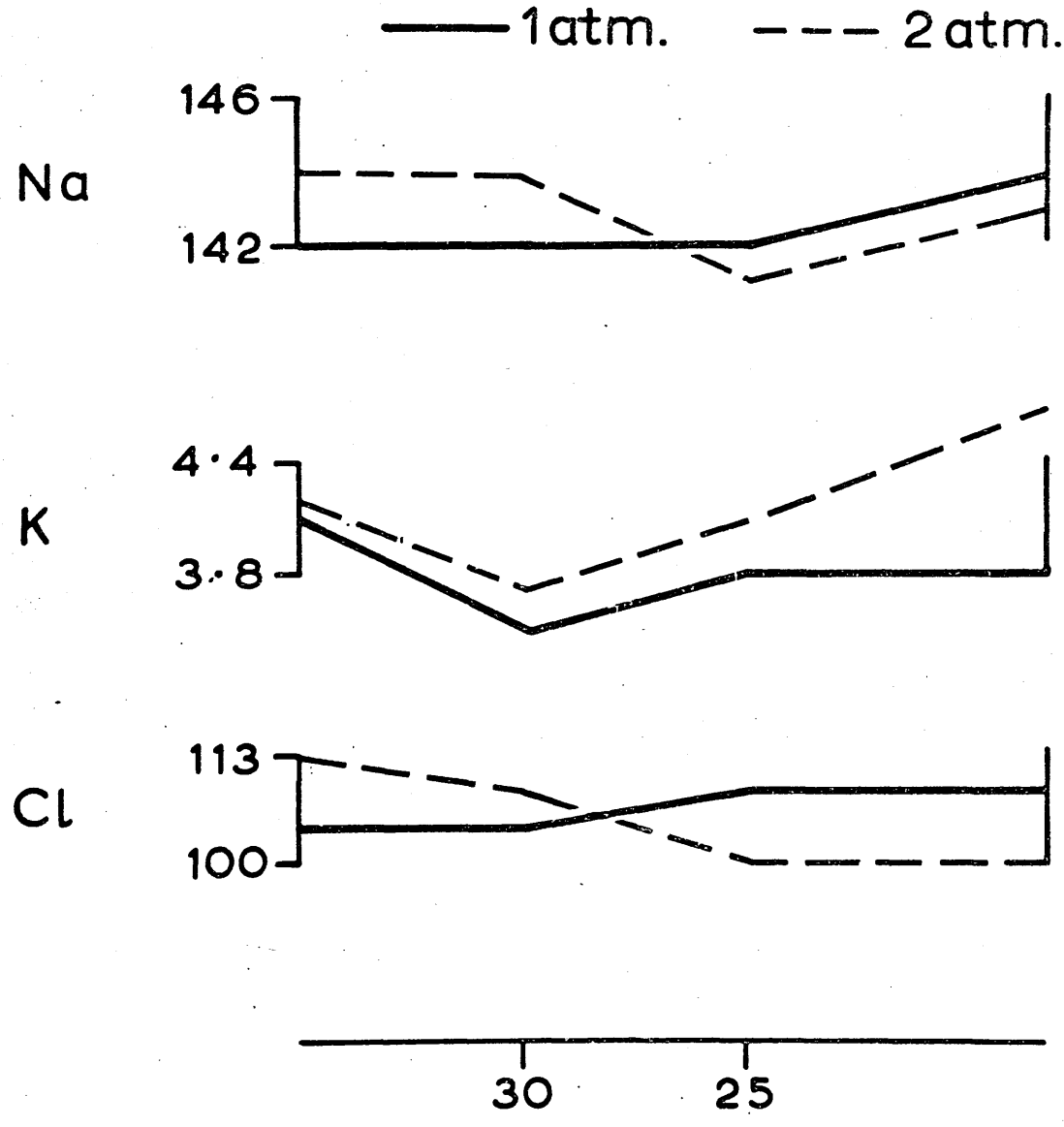

Figure 5.4. Mean serum electrolyte values (meq/l) during cooling - oxygen at normal pressure (1 Atm) and oxygen at 2 ATA (2 Atm).

with cooling although the slight difference between the normal pressure and 2 ATA groups at 30 deg C was significant ($p < 0.05$). Excess lactate rose slightly in the normal pressure group at 30 deg C.

Arrest

The biochemical changes during circulatory arrest are indicated in Table 5.5 for the normal pressure and 2 ATA dogs which did not receive alkali prior to arrest (16 animals). The expected decrease in pH and increases in base deficit, potassium, phosphate, lactate and excess lactate were observed (Fig. 5.5); base excess fell by a mean of 0.17 meq/l and 0.13 meq/l per minute of circulatory arrest in the normal pressure and 2 ATA groups respectively. Although the 2 ATA animals appeared to fare better in respect of all of these changes, there were no statistically significant differences between the two groups of dogs. Further statistical analysis also revealed that no unpredictable effects resulted from the administration of alkali in the pre-arrest period other than that those animals receiving sodium lactate showed a less marked increase in potassium ($F = 10.3$, $p < 0.01$).

Samples of arterial and venous blood withdrawn towards the

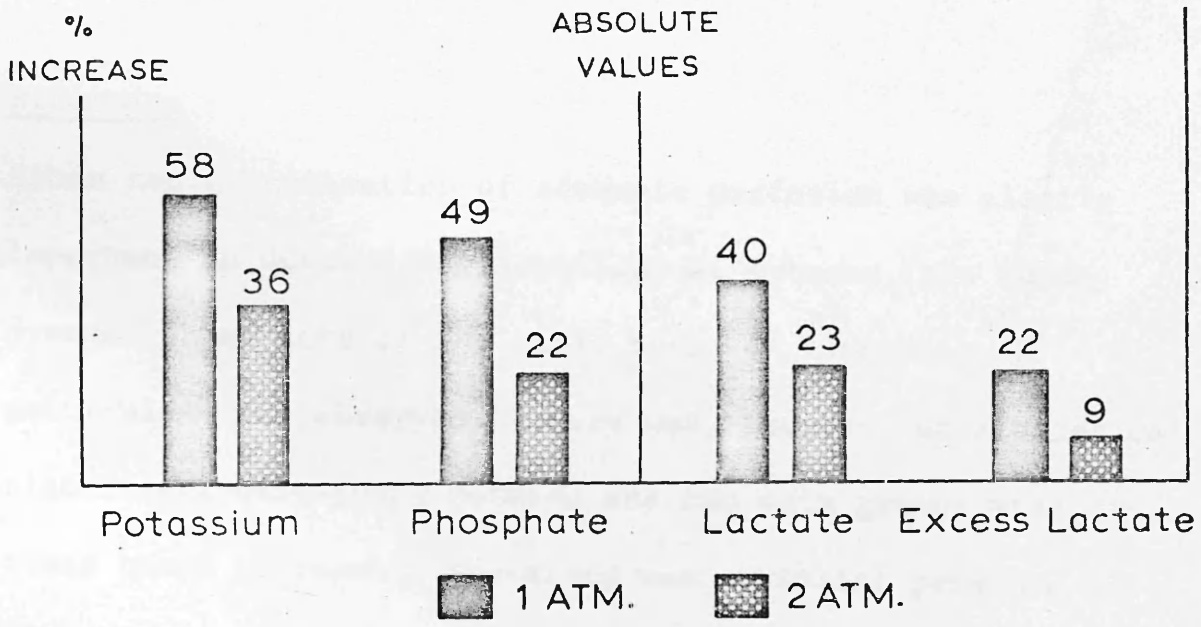

Figure 5.5. Per cent increase in serum values of potassium, phosphate, lactate and excess lactate during total circulatory arrest.

end of the period of arrest indicated mean PO_2 values as follows:

	Arterial	(no. dogs)	Venous	(no. dogs)
normal pressure	70	(3)	43	(3)
2 ATA	110	(8)	344	(9)

A typical example of the PO_2 changes with the passage of time during arrest is shown in figure 5.6.

Rewarming

Since rapid restoration of adequate perfusion was clearly important in determining neurological outcome, the haemodynamic parameters of the early stage of rewarming in particular were observed. There was, however, no statistically significant difference between the two main groups when the times taken to reach a sustained mean arterial pressure of 60 mm Hg were compared, and throughout the remainder of the rewarming phase cardiovascular recovery was equally satisfactory.

Reference to table 5.5 indicates that during rewarming, the animals which had not received alkali prior to arrest displayed a progressive decrease in pH as rewarming progressed. This trend was due to an increase both in lactate and in PCO_2 up to

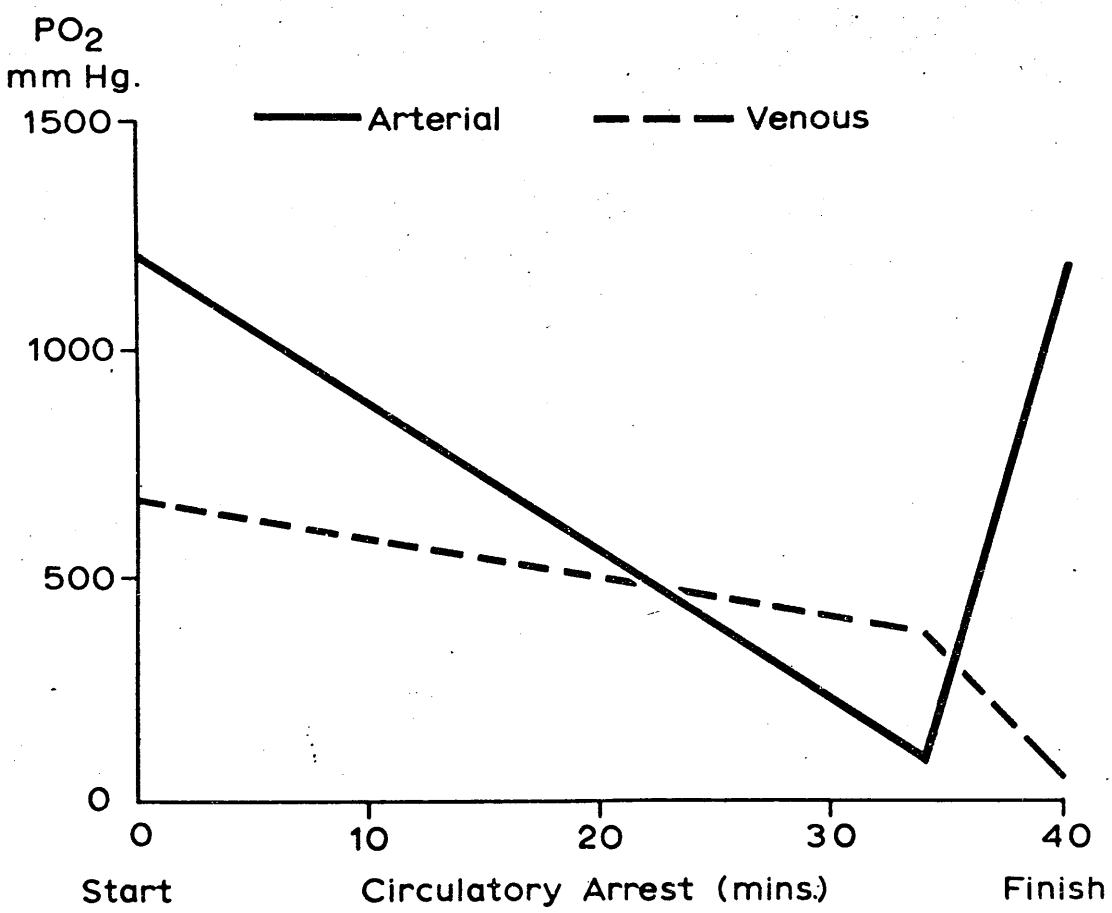

Figure 5.6. Arterial and venous PO2 values during a 40 minute period of total circulatory arrest.

a temperature of 25 deg C; thereafter the effect of the increase in PCO_2 predominated. Apart from a return to normal of serum potassium no other changes in the mean biochemical values during rewarming were noted and there were again no significant differences between the normal pressure and 2 ATA groups of animals. Examination of the effects of alkali revealed only one statistically significant difference - at 37 deg C arterial pH was 7.16 $\pm$ 0.14 (M $\pm$ S.E.) and 7.33 $\pm$ 0.11 in the no alkali and bicarbonate groups respectively ($p < 0.05$).

Half the hyperbaric group of animals were arbitrarily decompressed at a temperature of about 30 deg C (referred to as the early removal group) while the remainder were retained at increased oxygen pressure until normothermic (referred to as the late removal group). The latter appeared to make a more satisfactory biochemical recovery (Fig. 5.7) when the values at 37 deg C were compared.

Discussion

These data showed that the maximum period of safe circulatory arrest at 20 deg C using a surface-cooled experimental model was about 35 minutes. On the basis of numerous experimental

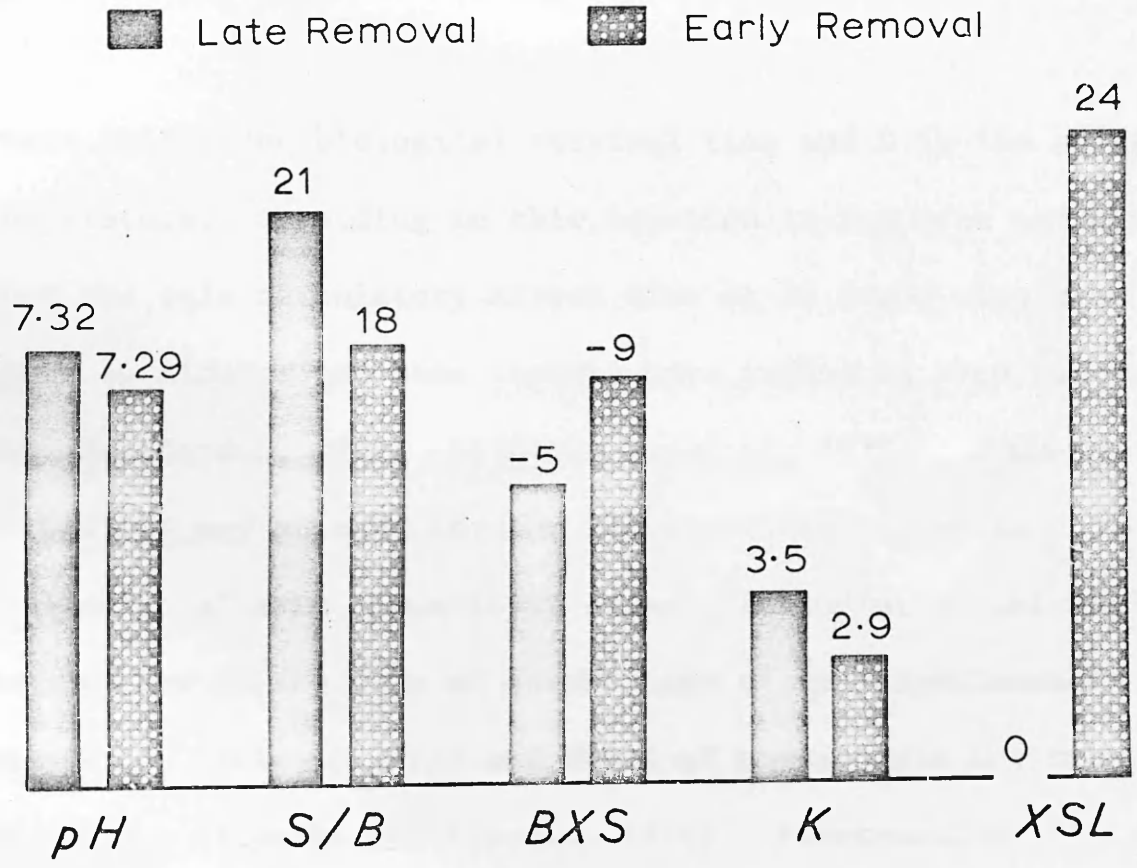

Figure 5.7. Biochemical data for hyperbaric animals after return to normothermia (pH - units; standard bicarbonate - meq/l; base excess - meq/l; potassium - meq/l; excess lactate - mg/100 ml).

results, Thauer (1965) suggested that the duration of safe circulatory arrest in dogs could be calculated from the following equation:

$$Bst = 150 \times E^{-b.0.108}$$

where Bst is the biological survival time and E is the rectal temperature. According to this equation it has been estimated that the safe circulatory arrest time at 18 deg C should be about 60 minutes and some reports have indicated even longer periods (Gordon, 1962; Rittenhouse et al, 1971). A number of factors may account for the reported differences in estimation of safe circulatory arrest, including actual brain temperature at the time of arrest, age of the experimental animal (or patient), type and depth of anaesthesia and method of cooling (Popovic and Popovic, 1974). Assessment of neurological recovery is also an imprecise technique.

In these studies, hyperbaric oxygen appeared to exert at most a marginal protective influence, and a detectable increase in the period of safe arrest using oxygen at 2 ATA was not achieved. During the late phase of rewarming hyperbaric oxygen may have made a minor contribution to the rate of restoration of normal cellular metabolism. No comparable study has been

performed at 20 deg C with hyperbaric oxygen but Thomas et al (1966) described circulatory arrest (with recovery) of more than two hours at 3 deg C using oxygen at 3 ATA; cardiopulmonary bypass was used to induce cooling and rewarming and there were no normal pressure control animals.

The most obvious explanation for the lack of effect of hyperbaric oxygen at this temperature was that the extra oxygen did not gain access to the tissues. Evidence in support of this contention came from the PO_2 data collected during the period of arrest, which showed that a substantial reserve of oxygen remained untapped (for further comment see Discussion in following chapter). The small increase in the duration of arrest in these experiments over that observed in animals at 28 deg C (30 minutes with oxygen at 2 ATA) is not easily explained although the two experimental methods were not identical and the cerebral metabolic rate of oxygen may not have been grossly different at the two temperatures. Another possible explanation is that hypoperfusion at the lower temperature may have reduced oxygen availability after the period of arrest.

Cooling per se was associated with remarkably few biochemical disturbances which is the usual pattern with uncomplicated

surface cooling (Cooper and Ross, 1960). Serum potassium fell slightly as did phosphate while calcium rose to a minor degree. Lactate formation did not occur during cooling. Acid-base balance presents special problems in hypothermia; physico-chemical changes occur in the ionic constituents of the body fluids, buffer capacity is reduced, and the kidney's ability to regulate hydrogen ion exchange is disturbed (Rosenfeld, 1963; Linton and Ledingham, 1966). The pH changes during cooling in the present study were attributable almost entirely to the fall in arterial PCO_2, the changes in base excess being negligible. An increase in packed cell volume has been reported in previous studies (Helmsworth, Stiles and Elstun, 1955; Kanter, 1968) and in the dog is likely to be due to splenic contraction possibly secondary to adrenergic discharge during induction of hypothermia. Shifts in water from plasma and interstitial compartments into the cells have been described but are usually trivial in the absence of shivering (D'Amato, 1954), and as long as hypothermia is not deep and prolonged (Popovic, 1960). If haematocrit levels exceed 50%, as in the post-arrest phase of the present study, yield shear stress increases to a significant extent (Marty et al, 1971) and rheological benefit accrues from the administration of colloid

solutions (Mohri et al, 1966).

As with the normothermic dogs (chapter 2), the administration of alkali immediately prior to the period of arrest proved to be of significant value (Benichoux et al, 1963). Not only was there a lower incidence of spontaneous ventricular fibrillation during arrest but successful defibrillation was the rule.

The absence of severe acidosis during rewarming in the bicarbonate-treated group was presumed to have contributed favourably to the speed of neurological recovery in these animals.

The metabolic changes produced by the period of arrest were comparable in character to those found during normothermic arrest. The overall magnitude of change in such variables as base deficit, potassium and lactate during a 35 minute arrest at 20 deg C were of the same order as that of a five to six minute arrest at normal body temperature. This observation was particularly obvious in relation to base excess, reductions in which were as follows (per minute of circulatory arrest):

Temperature	Normal Pressure	2 ATA
37°C	1.10 meq/l	1.0 meq/l
28°C	0.30 meq/l	-
20°C	0.17 meq/l	0.13 meq/l

The change in pH at hypothermia, however, was less marked than at normothermia apparently because of a negligible increase in PCO_2, and in spite of reduced buffering capacity at low temperature.

The conclusion was drawn that the predominent factor determining the duration of safe arrest in these experiments was the reduction in oxygen consumption consequent to hypothermia. The contribution of hyperbaric oxygen at 2 ATA was relatively minor.

Chapter 6

Observations on cerebral blood flow responses to oxygen at 3 ATA; total circulatory arrest combining deep hypothermia (20 deg C) and hyperbaric oxygen (3 ATA)

In the introduction to chapter 4 (p.107) it was suggested that increased protection against the hypoxic insult of circulatory arrest might accrue not only from deeper hypothermia but also from greater inspired oxygen pressures. The results obtained from the experiments described in chapter 5, however, suggested that any benefit arising from a further increase in inspired PO_2 could be expected to be small.

Coincidental with these experiments, a group of studies was in progress to determine the effects of oxygen at different pressure levels on cerebral blood flow and metabolism at normal body temperature. One of these studies, using oxygen at 3 ATA, had particular relevance to the circulatory arrest experiments and made it less easy to anticipate the results of arrest at 3 ATA.

This chapter, therefore, consists of two sections. The first section, in the form of the attached reprint, summarises the

the cerebral blood flow findings and the second section details the results obtained from a series of dogs subjected to total circulatory arrest after being ventilated with oxygen at 3 ATA.

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Cerebral Cortical Blood Flow Under Hyperbaric Conditions

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The response of the cerebral vasculature to high pressure oxygen is a subject of interest and controversy. A more detailed knowledge of the mechanism of this response might help to provide a rational basis for applying OHP in the treatment of cerebral hypoxia. In addition, the relationship between the cerebrovascular response to hyperbaric oxygen and oxygen toxicity is not well understood.

Previous workers have shown that conscious human subjects exposed to oxygen at 1 and 3.5 atm have cerebral vasoconstriction as determined by the nitrous oxide method for measuring total cerebral blood flow.[1,2] Lambertsen *et al.*[2] maintained that the cerebral vasoconstriction which occurred during oxygen-breathing at 3.5 atm was due to arterial hypocapnia resulting from associated hyperventilation. Previous work carried out in this laboratory on anesthetized dogs[3] demonstrated that oxygen at 2 atm was also associated with cerebral cortical vasoconstriction. These latter workers concluded, however, that the mechanism of vasoconstriction was based upon a direct effect of oxygen, because arterial pCO_2 was held constant throughout their experiments. Quite possibly, of course, physiologic differences may exist between conscious man and the anesthetized dog in this regard.

Further investigations on the anesthetized dog at 2 and 3 atm have made it apparent that the relationship between cerebral cortical blood flow and increased arterial pO_2 may be less simple than it first appeared.

Materials and Methods

One hundred and seven determinations of blood flow through the cerebral cortex were made in eight unselected mongrel dogs by the ^{85}Kr clearance method of Lassen and Ingvar.[4] By this method, the blood flow is calculated from the rate of clearance from the exposed brain cortex of ^{85}Kr after its injection into the carotid artery. The clearance rate is measured by an end-window Geiger counter, mounted 1 mm above the brain and connected to a ratemeter and recorder.

Anesthesia was induced with thiopentone and maintained with trichloroethylene and intermittent suxamethonium chloride. McDowall *et al.*[5] have established that trichloroethylene in the concentrations used in this experiment has no significant effect on cerebral cortical blood flow. In addition, it has been shown that when this preparation is used cerebral cortical blood flow remains stable for at least

6 hours during air-breathing at normal pressure.

Respiration was controlled with a Starling ventilator, the stroke output of which was adjusted to maintain a constant arterial pCO_2. Arterial blood samples were obtained from a cannula in the femoral artery, and in one case venous blood samples were obtained from the sagittal sinus. Blood pressure was measured on a damped mercury manometer. The pharyngeal temperature was maintained at 38°C by controlling the environmental temperature.

Arterial pH and pCO_2 values were determined with two micro-Astrup apparatuses. The pCO_2 was also measured directly with a Severinghaus electrode. Arterial and venous pO_2 values were measured with a Radiometer oxygen electrode.

In each animal, blood flow estimations were made first while the animal was breathing air at normal pressure, then during oxygen-breathing at 3 atm, and again during air-breathing at normal pressure. In three of the animals, intermediate measurements were made during oxygen-breathing at 2 atm.

Results

Table 1 shows the values for cerebral cortical blood flow during eight separate experiments. All three animals exposed to oxygen at 2 atm showed a decrease in cerebral cortical blood flow, compared with the air control values. In six of the eight animals exposed to oxygen at 3 atm, the cerebral cortical blood flow rose; the two animals which had no increase had previously been exposed to oxygen-breathing at 2 atm.

Table 1. Cerebral Cortical Blood Flows with Air at 1 atm and Oxygen at 2 and 3 atm [a]

Dog	Cerebral cortical blood flow (ml/gm/min)			
	1 atm air	2 atm O_2	3 atm O_2	1 atm air
1	1.77	—	2.16	—
2	1.34	—	1.39	1.05
3	1.60	—	1.83	1.26
4	1.04	—	1.38	1.02
5	0.83	0.82	0.95	0.76
6	1.20	1.11	1.16	0.94
8	0.98	0.74	0.87	0.79
9	0.80	—	0.82	—

[a] In all but two instances, each value represents the mean of at least three separate blood flow measurements.

Table 2 shows the mean values for cerebral cortical blood flow and arterial pCO_2 in the five animals breathing oxygen at 3 atm, with no intermediate step at 2 atm. With arterial pCO_2 virtually constant, the blood flow increased during oxygen-breathing at 3 atm and fell again with air-breathing at normal pressure. The increase was not statistically significant.

Table 3 shows the mean values for cerebral cortical blood flow and arterial pCO_2 in the three animals exposed to oxygen at 2 and 3 atm. In these animals, there was no increase in cerebral blood flow at 3 atm as compared with the air control values, although there was a reversion of the decrease resulting from the 2-atm exposure.

Table 4 shows the values for arterial blood pressure, pCO_2, and pO_2 in each of the animals in the series; only the arterial pO_2 varied significantly. Alterations in

Table 2. Cerebral Cortical Blood Flows with Air at 1 atm and Oxygen at 3 atm

	1 atm air	3 atm O_2	1 atm air
Mean cerebral cortical blood flow (ml/gm/min)	1.31	1.52	1.11
SD	±0.40	±0.51	±0.13
Mean arterial pCO_2 (mm Hg)	42	43	41
SD	±4	±3	±3

TABLE 3. Cerebral Cortical Blood Flows with Air at 1 atm and Oxygen at 2 and 3 atm

	1 atm air	2 atm O_2	3 atm O_2	1 atm air
Mean cerebral cortical blood flow (ml/gm/min)	1.00	0.89	0.99	0.83
SD	±0.19	±0.20	±0.15	±0.10
Mean arterial pCO_2 (mm Hg)	44	44	43	42
SD	±2	±1	±2	±1

arterial pH and the nonrespiratory components of acid–base balance, in response to the increased arterial pO_2, were similar to alterations found under identical experimental conditions with air-breathing at normal pressure over the same period of time.

Figure 1 shows data obtained from one of the animals in the present series of studies. The mean value for cortical blood flow during air-breathing was 0.83 ml/gm/min. Immediate and rapid increase in pressure to 2 atm over 5 min was followed initially by an increase in blood flow. The first flow at 2 atm was associated with an increase of 5 mm Hg in arterial pCO_2. The remaining pCO_2 values at 2 atm and subsequently at 3 atm did not differ from the air-flow pCO_2 values by more than 2 mm Hg. Only at the end of 1 hour of oxygen-breathing at 2 atm was there an actual reduction in blood flow, in this case amounting to 25%. At this stage, compression to 3 atm of oxygen was followed by a sharp increase in blood flow, which initially rose above the air control values.

The other animals tested at 2 atm showed the same general pattern of blood flow changes, with a decrease in flow only in the latter half of the period of exposure to 2 atm. Figure 2 shows, in the five dogs exposed to oxygen at 3 atm only, that after the initial increase in cortical blood flow during the first 15 min, there was a fall toward but not below air control levels. These blood flow values were recorded in four animals beyond 1.5 hours of exposure to 3 atm and showed no tendency to fall below air control values, in contrast to the blood flow values of animals exposed to 2 atm.

After hyperbaric exposure, the normal response of the cortical blood flow to changes in arterial pCO_2 was tested and found to be within acceptable limits.

Figure 3 demonstrates the levels of pO_2 and pCO_2 found in the sagittal sinus blood during air-breathing at normal pressure and during oxygen-breathing at 3 atm in one of the animals of this series. The venous pO_2 rose from around 44 mm Hg to 110 mm Hg immediately after compression to 3 atm. Thereafter, the venous pO_2 fluctuated between 75 and 95 mm

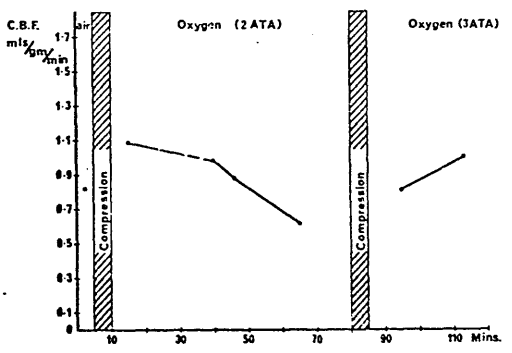

FIGURE 1. Cerebral cortical blood flow related to time and pressure.

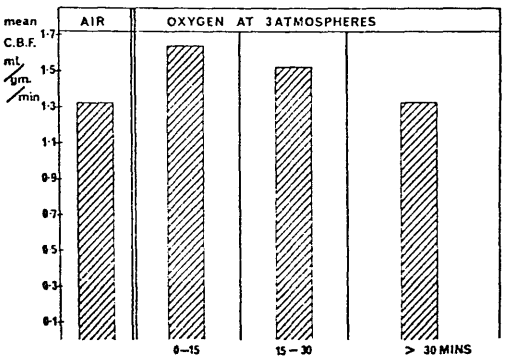

FIGURE 2. Cerebral cortical blood flow related to time at 3 atm of oxygen.

TABLE 4. Blood Pressure and Arterial Blood Gas Values (mm Hg)

Dog	1 atm air			2 atm O_2			3 atm O_2			1 atm air		
	B.P.	pCO_2	pO_2	B.P.	pCO_2	pO_2	B.P.	pCO_2	pO_2	B.P.	pCO_2	pO_2
1	130	41	97	—	—	—	145	45	1973	—	—	—
2	144	44	94	—	—	—	136	46	1730	140	40	—
3	142	37	103	—	—	—	125	39	1845	133	39	121
4	133	47	94	—	—	—	138	42	1845	120	44	84
5	136	46	70	125	44	910	130	43	1480	150	42	64
6	143	43	83	150	43	1032	136	41	1610	145	43	71
8	117	44	80	134	45	1153	135	45	1710	110	41	80
9	121	41	75	—	—	—	105	45	1729	—	—	—
Mean	133	43	87	136	44	1032	131	43	1740	133	42	84
SD	±10	±3	±12	±13	±1	±122	±12	±3	±152	±15	±2	±22

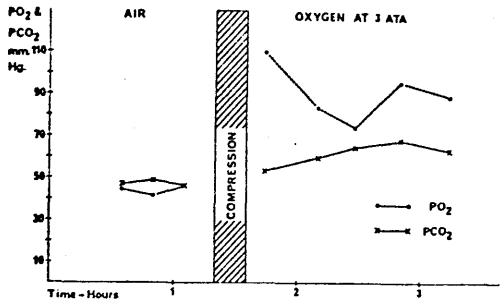

FIGURE 3. Changes in sagittal sinus blood gas values with 3 atm of oxygen.

Hg. The venous pCO_2 rose from 46 mm Hg to 54 mm Hg initially. Then, despite a constant arterial pCO_2 and blood flow by this stage, the venous pCO_2 continued to rise, stabilizing at a level of about 65 mm Hg. The data obtained during the 3-atm exposure showed that there was no alteration in cerebral cortical oxygen uptake compared with the air control values.

DISCUSSION

Although these results are admittedly of a preliminary nature, it seems that oxygen at increased pressure produces changes in cerebral cortical blood flow which vary with the absolute pressure and also with the length of exposure at a particular pressure. Our previous data, compared with the results in the initial air-breathing controls, showed that oxygen at 1 atm resulted in a 12% reduction in flow, and oxygen at 2 atm resulted in a 21% reduction in flow. The present data, however, indicate that the vasoconstriction occurring during oxygen-breathing at 2 atm may be delayed for as long as 30–45 min. In comparison, oxygen at 3 atm appears to stimulate an actual increase in cerebral cortical blood flow initially, with a later fall toward the air control values. At no stage was it possible to demonstrate a vasoconstrictive action with oxygen-breathing at 3 atm.

In the presence of a constant arterial pCO_2, the fact that oxygen at 3 atm is not associated with a reduction in cerebral cortical blood flow would seem to be in agreement with the opinion expressed by Lambertsen *et al.*[2] that the vasoconstriction at 3.5 atm in conscious humans is due to the drop in arterial pCO_2 caused by hyperventilation, rather than to a single direct vasoconstrictive action of increased arterial pO_2. On the other hand, the present studies showed a marked increase in venous pCO_2, presumably a reflection of cortical tissue pCO_2 and presumably based upon the reduced isohydric buffering capacity of venous blood. On the basis of the suggested relationship between local cerebral flow and local metabolic rate,[6] it seems possible that tissue pCO_2 has a regulating influence on flow. In these experiments, there was a marked increase in venous pCO_2 but no statistically significant change in flow. We would tentatively suggest that this points to a balance existing between the increased arterial pO_2 tending to vasoconstrict and the increased tissue pCO_2 tending to vasodilate the cortical blood vessels.

Why the blood flow should decrease only after a certain time of exposure to 2 atm and apparently not at 3 atm over the same period of time is not clear. A sound explanation based upon the available evidence would be difficult, but some connection may exist with the recognized cerebral oxygen toxicity manifestations at 3 atm.

ACKNOWLEDGMENTS

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DISCUSSION

DR. H. WOLLMAN (*Philadelphia, Pa.*): I would like to offer an alternative explanation for these changes in cerebral blood flow with time. At a constant abnormally high or low pCO_2, although the cerebral blood flow changes, it probably tends to return toward a normal value over a period of several hours. Perhaps what we are looking at here is an increase in sagittal sinus or tissue pCO_2, producing an increase in cerebral blood flow. This might be followed by the cerebral vascular compensation which I have suggested, *i.e.*, a type of autoregulatory constriction in response to increased carbon dioxide, resulting in the measured decrease in cerebral blood flow. I admit it occurs a little more quickly here than might be expected. Let me make an additional comment on the pO_2 of venous blood draining the brain, which bears on Dr. Jacobson's earlier remarks. Only those areas with some circulation can contribute blood to the venous drainage. Therefore, a high pO_2 in jugular venous blood means only that those areas of the brain being perfused have a high pO_2. Areas which may have no blood flow at all (*e.g.*, infarcts) do not contribute to jugular blood, and thus jugular pO_2 can be misleading in certain circumstances.

DR. LEDINGHAM: I think your comments pertaining to the blood-flow changes with time are perfectly reasonable. I doubt if they explain altogether the changes that we found with time, but I think that further investigation will elucidate this problem a bit more.

DR. J. W. SEVERINGHAUS (*San Francisco, Calif.*): You made an assumption that a high tissue pCO_2 might be expected to produce cerebral vasodilation, and I wondered what both you and Dr. Lambertsen think is the site at which carbon dioxide acts? I think, on the basis of some transient studies, that it seems to act at the arterial level and probably does not relate to tissue pCO_2. Dr. Lassen and I last year did an experiment in which we suddenly produced a drop of arterial pCO_2 in man from 40 to 25 mm Hg within about 6 seconds, held it there for 2 hours and followed the A-V oxygen difference. The flow, at least as measured by oxygen difference, drops within 30 seconds to its low level, while the jugular venous pCO_2, and therefore presumably the tissue pCO_2, take about 7 or 8 minutes to get down, so that correlation with flow was with the arterial and not with the tissue pCO_2. In that case, the

TOTAL CIRCULATORY ARREST WITH OXYGEN AT 3 ATA

The aim of these experiments was to determine whether the maximum period of safe circulatory arrest at 20 deg C could be extended using oxygen at 3 ATA.

Material and Methods (2/2/66 - 14/9/66)

Seventeen adult mongrel dogs weighing from 9.5 to 24.0 kg were anaesthetised, ventilated and cooled to 20 deg C in the manner previously described for the animals of Group D in chapter 4. The inspired gas was oxygen, delivered at 3 ATA for 30 minutes prior to the period of circulatory arrest and for 30 to 40 minutes after restoration of an adequate blood pressure; otherwise oxygen was delivered at normal atmospheric pressure (apart from the periods of compression and decompression). Bicarbonate was administered prior to arrest of the circulation which was of 40 minutes duration.

The standard cardiorespiratory measurements were performed, and arterial blood samples were withdrawn for assessment of acid-base balance (including lactate and pyruvate) at regular intervals throughout cooling and rewarming. During the period of arrest small samples of arterial and caval venous blood were withdrawn for measurement of PO_2 (eight dogs); prior to withdrawal of the samples gentle mixing of the blood in

the stagnant vascular chambers was carried out using a 10 ml syringe. After rewarming the animals were returned to their cages for long-term neurological assessment. In five of the dogs which recovered for more than a few days, careful post-mortem examination of the brain was performed after perfusion fixation (Prof. J.H. Adams). The details of the latter technique are described in the Appendix.

Results

Eight of the 17 animals died during the procedure, four as a result of irreversible ventricular fibrillation and four owing to respiratory complications during decompression (Table 6.1). Of the remaining nine only two were completely free from neurological disturbances; the others had a variety of sequelae similar to those described in previous chapters.

The changes in acid-base balance during cooling, arrest and rewarming were comparable to the bicarbonate-treated group of dogs at 2 ATA and, in particular, the increase in arterial lactate during arrest was not significantly different from the animals subjected to an equivalent period of arrest at normal atmospheric pressure and 2 ATA (Table 6.2).

Table 6.1

Total Circulatory Arrest at 20°C with 02 at 3ATA (40 min)

Dog date/no.	Cooling time min/kg	Pre arrest BP mmHg	Pre arrest HR beats/ min	Period of arrest (min)	Temp of arrest (°C)	Fate	Comment	Time after arrest (days)
2.2.66 (1)	8.8	85	30	40	20.0	Died	Irreversible VF during arrest	0
8.2.66 (2)	9.0	76	12	40	18.0	Survived	anoxic episodes	1
23.2.66 (3)	6.7	105	40	40	20.8	Survived	Nil neurolog	58 BR
2.3.66 (4)	9.5	86	40	40	21.2	Died	Resp. death during rewarm	0
30.3.66 (5)	7.2	60	38	40	21.8	Died	Irrevers. VF during arr.	0
6.4.66 (6)	11.9	70	38	40	21.0	Survived	Sl.neurolog	48 BR
13.4.66 (7)	12.2	138	38	40	21.0	Died	Haemothorax	0 EEG
18.5.66 (8)	12.5	140	40	40	20.5	Survived	Lung collapse	2 EEG
15.6.66 (9)	8.4	90	20	40	20.0	Survived	Lung collapse	2
13.7.66 (10)	6.0	93	38	40	20.5	Survived	Sl.neurolog	15 BR
18.7.66 (11)	8.4	81	38	40	21.0	Survived	Nil neurolog	16 BR
20.7.66 (12)	-	-	-	-	-	Died	Cooling VF voltage thermocouple	0
21.7.66 (13)	8.7	56	40	40	21.0	Died	no spont. vent.	0
27.7.66 (14)	11.0	83	22	40	20.5	Died	haemothorax	0
17.8.66 (15)	6.1	96	30	40	21.2	Survived	sl.neurolog	27 BR
31.8.66 (16)	8.1	106	40	40	21.2	Died	irrevers. VF during rewarm	0
14.9.66 (17)	5.9	83	32	40	20.8	Survived	Sl.neurolog	3
Mean + SEM	8.8 ± 0.5	90.5 ± 5.8	33.5 ± 2.2		20.7 ± 0.2			

BR = Brain perf.

Table 6.2 Lactate values (mg/100ml) in 3ATA animals

	37°C	25°C	PRE-ARREST	POST-ARREST	REWARMED
2.2.66	13.00	7.90	-	-	-
9.2.66	3.80	7.40	-	39.70	25.90
23.2.66	16.46	-	10.58	46.12	39.40
2.3.66	6.82	7.06	-	39.23	20.39
30.3.66	6.76	2.29	7.87	40.48	-
6.4.66	7.81	8.58	7.75	19.80	21.09
13.4.66	5.65	-	1.29	35.37	18.33
18.5.66	28.79	-	13.39	36.19	29.14
15.6.66	12.17	9.17	19.69	33.49	13.40
13.7.66	-	-	14.57	32.55	30.67
18.7.66	15.40	-	10.87	27.44	29.50
20.7.66	5.29	-	10.17	29.97	32.91
27.7.66	8.64	-	7.23	19.27	32.49
14.9.66	10.93	-	5.47	14.99	23.39
Mean ± SEM	10.89 ± 1.85	7.07 ± 1.01	9.90 ± 1.48	31.89 ± 2.58	26.38 ± 2.12

The mean arterial and caval venous PO_2 measurements (Fig. 6.1) showed a small progressive decrease during arrest but the blood in both chambers remained fully saturated throughout.

Histological examination of the five brains was rather unrewarding and there was little, if any, convincing evidence of ischaemic or hypoxic damage. In dog 3 the only positive finding was a single focus of Purkinje cell loss in the cerebellum and a tiny infarct in the brain stem. In dog 6 there were a few microglial nodules and the possibility of some symmetrical loss of the medially placed cells of the olives. Dogs 10, 11 and 15 showed no neuronal loss (apart from the previously noted changes affecting the olives, in dog 11). In dog 15 there were features suggestive of a subacute meningitis and ventriculitis.

GENERAL DISCUSSION

The cerebral blood flow experiments at normothermia revealed an unexpected difference in cortical vascular response to oxygen at 2 and 3 ATA. The increase in blood flow at 3 ATA was most marked during the 30 minutes following the increase in inspired PO_2 and this determined the pre-arrest duration

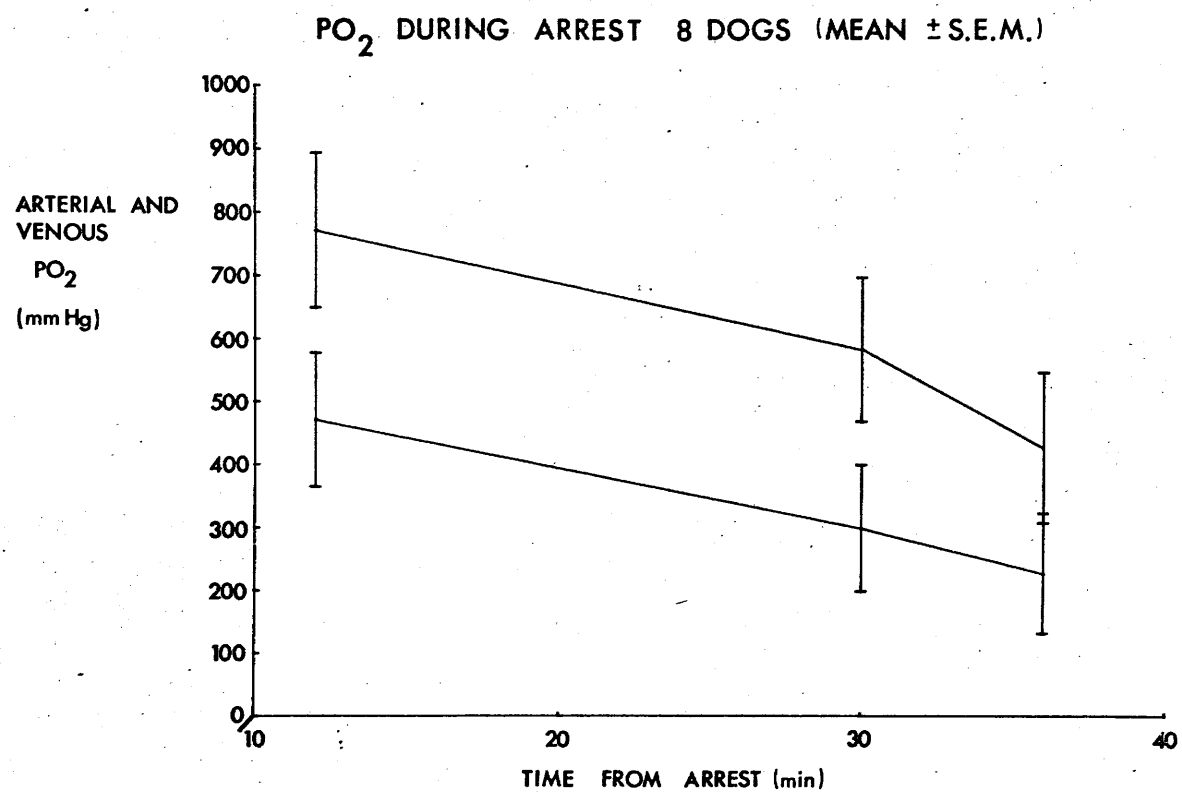

Figure 6.1. Arterial (upper) and venous (lower) PO2 values during a 40 minute period of circulatory arrest (mean ± standard error).

of exposure to oxygen at 3 ATA in the circulatory arrest studies. Whether it was reasonable to assume that the changes in cerebral blood flow which had been observed at normothermia would occur at 20 deg C is uncertain. The most obvious difference was that at 20 deg C the mixed venous (and possibly the cerebral venous) blood was fully saturated with oxygen at 2 ATA (p.128 chapter 5). If, therefore, the explanation advanced for the increase in flow at 3 ATA under normothermic conditions was correct, there would probably have been little difference in flow between 2 and 3 ATA under hypothermic conditions.

Whatever the truth of this enigma the fact was that the duration of safe circulatory arrest at 20 deg C could not be extended by the prior administration of oxygen at 3 ATA. The incidence of deaths attributable to irreversible ventricular fibrillation was unchanged from previous experiments at lower pressures of oxygen, and neurological sequelae were equally common. The increase in lactate during arrest was comparable to that recorded in animals subjected to an equivalent period of circulatory arrest at normal pressure and 2 ATA. Furthermore, the PO_2 measurements made during the period of arrest at both 2 and 3 ATA indicated that the administration of hyperbaric

oxygen undoubtedly increased oxygen storage but this was not reflected in an increase in tissue oxygen availability and consumption. The mixing manoeuvre described in the Methods section failed to influence this pattern in any way and the possibility arises that after a time, large areas of the capillary bed are no longer in communication with the main circulatory system.

Whether or not the reservoir of oxygen becomes useful once the circulation is restored is not clear. There was certainly no evidence from the 3 ATA experiments that acidosis disappeared more readily during rewarming or that neurological recovery was significantly improved.

The lack of major neuronal loss in the long-term survivors was curious since most of these animals showed some residual gait disturbances. None showed lateralizing signs, however, and none was blind. These results would seem to be at variance with the observations of Moor et al (1966) who showed that after circulatory arrest cryptic lesions of the cortex could be demonstrated regularly in animals with no obvious neurological deficit. The implication in the context of the author's experiments is that 40 minutes was a safe duration for total

circulatory arrest using oxygen at 3 ATA under deep hypothermic (20 deg C) conditions. Without further evidence this conclusion is viewed with scepticism.

Chapter 7

The effects of hypoxia on myocardial blood flow and oxygen consumption: negative role of beta adrenoreceptors

This chapter is the first of three in which the effects of hypoxia on the heart are examined in some detail. Hypoxic hypoxia was induced in dogs anaesthetised with trichlorethylene by lowering the inspired oxygen concentration. The details of the study are contained in the following reprint.

Clinical Science (1971) **41**, 257–273.

THE EFFECTS OF HYPOXIA ON MYOCARDIAL BLOOD FLOW AND OXYGEN CONSUMPTION: NEGATIVE ROLE OF BETA ADRENORECEPTORS

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(*Received* 2 *December* 1970)

SUMMARY

1. Myocardial blood flow was measured by using a ^{133}xenon clearance technique in closed-chest dogs anaesthetized with trichlorethylene. A gradual decrease in the inspired oxygen tension resulted in an increase in myocardial blood flow only when the Pa,O_2 fell to between 30 and 35 mmHg.

2. When hypoxia was rapidly induced and sustained for a mean period of 18·3 min, myocardial blood flow markedly increased (from a mean of 118 ± 5 to 162 ± 6 ml 100 g^{-1} min^{-1}). There was a critical mean arterial oxygen tension (35 mmHg) above which increases in myocardial blood flow did not occur. This corresponded to a mean coronary sinus Po_2 of 18 mmHg or an oxygen content of 5·0 ml/100 ml. These flow increases were not dependent on changes in arterial or coronary sinus pH or carbon dioxide tension, nor were they dependent on changes in perfusion pressure or heart rate.

3. Despite the fact that oxygen availability was substantially decreased, myocardial oxygen consumption was maintained throughout the period of hypoxia by means of increased oxygen extraction.

4. Towards the end of the hypoxic period, Pa,CO_2 rose significantly from 40 ± 1 to $48 \pm 1{\cdot}5$ mmHg. There was no significant change in the non-respiratory component of acid–base balance.

5. During prolonged hypoxia (more than 30 min) myocardial blood flow remained consistently elevated, but oxygen consumption tended to fall progressively and this was associated with an increasingly severe metabolic acidosis. The haemodynamic and oxygen consumption changes returned to normal within a short time (15 min) after the resumption of a normal inspired oxygen concentration, as did the frequently observed electrocardiographic disturbances.

6. The responses to hypoxia were unaffected by a combination of atropine and

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propranolol. There was no evidence either that hypoxia-induced coronary vasodilatation was mediated through vascular β-adrenoreceptors or that propranolol interfered with the self-regulating control of myocardial blood flow.

It has been recognized for some time that hypoxia is capable of producing considerable increases in blood flow in the myocardium (Hilton & Eichholtz, 1925; Eckenhoff, Hafkenscheil, Landmesser & Harmel, 1947; Berne, Blackmon & Gardner, 1957; Feinberg, Gerola & Katz, 1958; Aukland, Kiil, Kjekshus & Semb, 1967). Little is known, however, about the exact relationship between arterial oxygen tension and myocardial blood flow. Further, although several factors associated with hypoxia are known to influence myocardial blood flow, the relative importance of each is uncertain; such factors include a direct effect of hypoxia on coronary vascular smooth muscle and indirect effects relating to changes in perfusion pressure, heart rate, extravascular support and associated metabolic disturbances. Likewise, the influence of neurogenic factors on myocardial vascular tone during hypoxia has not been systematically examined.

METHOD

Anaesthesia was induced in twenty-seven healthy adult mongrel dogs with sodium thiopentone (15–20 mg/kg) administered intravenously. After endotracheal intubation anaesthesia was maintained by using a gas mixture containing 0·5–1% trichlorethylene vaporized from a Tritec vaporizer (Cyprane); the carrier gas was a mixture of oxygen and nitrogen, the proportions of which were adjusted to produce for control measurements, an arterial oxygen tension of about 100 mmHg. Ventilation was controlled with a Palmer respiratory pump, the rate and stroke volume of which were adjusted to give an arterial carbon dioxide tension of about 40 mmHg. Reflex movement was prevented by the intramuscular administration of succinylcholine chloride (usually 50 mg at intervals of about 90 min). Catheters were inserted into the descending aorta and into the right atrium via the femoral vessels for pressure recording and blood sampling. During flow measurements arterial and right atrial pressures and the electrocardiogram were recorded on a multi-channel ink jet recorder (Elema-Schönander Mingograph 81), in addition to being continuously visible on an oscilloscope. Temperature was recorded from the rectum and mid-oesophagus by using direct recording copper–constantan thermocouples (Ellab, Copenhagen).

Myocardial blood flow was measured by using a ^{133}Xe clearance technique (Ross, Ueda, Lichtlen & Rees, 1964). A number 7 or 8 Sones catheter was introduced through the left common carotid artery in the neck and manipulated under fluoroscopic control until the tip lay about 5–10 mm within either the circumflex or anterior descending branch of the left coronary artery. In twenty-two of the twenty-seven dogs a wide-lumen catheter was introduced, by way of the left external jugular vein, several centimetres into the coronary sinus. Heparin (2500 i.u.) was administered immediately after coronary artery catheterization and at two-hourly intervals thereafter. For measurement of myocardial blood flow, part of the dead space of the coronary arterial catheter was filled with 0·5–1·0 ml of a solution of ^{133}Xe which was then flushed into the coronary artery with 3 ml of heparinized saline. The xenon was obtained in 10 ml ampoules of 1 mCi/ml from The Radiochemical Centre, Amersham, Bucks. The clearance of xenon from the myocardium (which is a function of capillary blood flow) was measured by means of a narrowly collimated Ekco GP scintillation counter suspended over the

praecordium, an Ekco ratemeter (operating with a 3 s time constant) and a Servoscribe pen recorder (operating at a paper speed of 120 mm/min). Background counts remained at an acceptably low level in all preparations. The major part of the clearance curve was exponential and a straight-line plot of c.p.s. at 5 s intervals was drawn on semi-log paper (see Fig. 1). The half-time ($t_{\frac{1}{2}}$) so obtained was substituted in the formula:

$$\text{myocardial blood flow} = \frac{k\lambda 100}{\rho} \text{ ml 100 g tissue}^{-1} \text{ min}^{-1}$$

where ρ is the density of the myocardium (1·05 g/ml; Herd, Hollenberg, Thorburn, Kopald & Barger, 1962), λ the partition coefficient of xenon between myocardium and blood (0·72; Conn, 1961) and k (the clearance rate constant) = $\log_e 2/t_{\frac{1}{2}}$. The theory of the inert gas clearance technique of measurement of tissue blood flow has been discussed by Conn (1962) and Zierler (1965), and its application to the myocardium has been described in detail by Herd *et al.* (1962) and Ross *et al.* (1964).

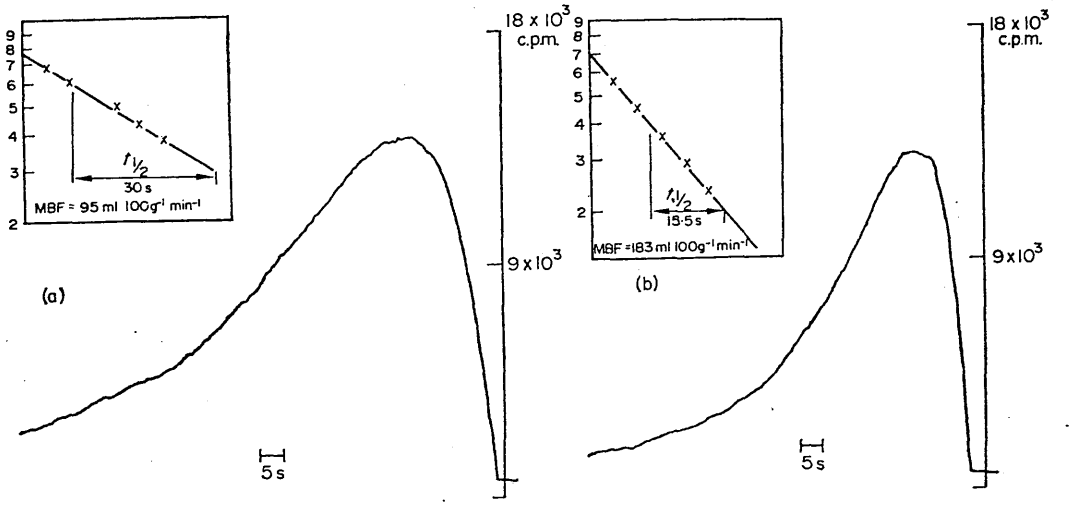

FIG. 1. Radioactive clearance curves from normal myocardium (a) and from the myocardium during systemic hypoxia (b) after the injection of a bolus of ^{133}xenon into the coronary artery. The respective semi-logarithmic plots are shown in the insets. Details are given in text.

Arterial and coronary sinus oxygen and carbon dioxide tensions and pH were measured by using appropriate electrode systems (Radiometer, Copenhagen). The oxygen and carbon dioxide electrodes were calibrated by using known pressures of the appropriate gas and the pH electrode with buffers of known pH. The oxygen and carbon dioxide tensions and pH values were corrected where necessary, for any difference in temperature between the electrode system and the animal's mid-oesophagus, by using the dog cursor on a Radiometer blood gas calculator (984-300). To allow for the difference in measurement of oxygen tension between gas and blood, a blood-gas factor was derived for each experiment (McDowall, Ledingham & Tindal, 1968) with blood tonometered with a known tension of oxygen in a rotating syringe (Torres, 1963). This factor was applied to every measurement of oxygen tension before the calculation of oxygen content which was made as follows: blood oxygen content (ml/100 ml) = Hb(g) (measured by the cyanmethaemoglobin technique) × 1·34 × % saturation/100 +

P_{O_2} (mmHg) × 0·0031 (Bunsen coefficient). There is a good correlation between this method of calculating blood oxygen content and the direct method of measurement of Van Slyke and Neil (Ledingham, McBride, Parratt & Vance, 1970). Lactate and pyruvate concentrations were measured in arterial and coronary sinus blood by using standard spectrophotometric methods (as described by C. F. Boehringer and Soehne, Mannheim, Germany). Blood glucose concentrations were determined by using the standard method of Folin & Wu (1920).

The following data were derived:

1. Myocardial oxygen consumption (ml 100 g^{-1} min^{-1}) = myocardial blood flow (ml 100 g^{-1} min^{-1}) × arterial−coronary sinus oxygen content (ml/100 ml).
2. Coronary vascular resistance (arbitrary units) =

$$\frac{\text{diastolic arterial blood pressure (mmHg)}}{\text{myocardial blood flow (ml 100 g}^{-1}\text{ min}^{-1}\text{)}}$$

3. Myocardial oxygen availability (ml 100 g^{-1} min^{-1}) = arterial oxygen content (ml/100 ml) × myocardial blood flow (ml 100 g^{-1} min^{-1}).
4. Myocardial oxygen extraction (%) =

$$\frac{\text{arterial}-\text{ocronary sinus oxygen content (ml/100 ml)} \times 100}{\text{arterial oxygen content (ml/100 ml)}}$$

Hypoxaemia was induced in two ways. In the first group of five animals, which were those without coronary sinus catheterization, the arterial oxygen tension was gradually decreased by lowering the inspired oxygen concentration (Fin,O_2) in a stepwise manner. This allowed blood flow measurements to be made at progressively lower arterial oxygen tensions. The lowest Pa,O_2 was 20 mmHg (corresponding to a mean Fin,O_2 of 11·1%).

In the second group of twenty-two animals (in which twenty-seven experiments were performed), hypoxaemia was induced by rapidly decreasing Fin,O_2 to 10–11% (mean 10·6%). This was facilitated by measuring the inspired oxygen concentration with a paramagnetic oxygen analyser (Servomex, Crowborough, Sussex). The average time from initial decrease of Fin,O_2 to peak myocardial blood flow was 12·6 min. Hypoxaemia was sustained for an average of 18·3 min (range 10–54 min); in four of the animals hypoxia was sustained for more than 30 min. In seven animals the hypoxic stimulus was repeated after the intravenous administration of atropine (0·04 mg/kg) and propranolol (0·2 mg/kg).

RESULTS

Gradually induced hypoxia

The effects of gradually induced hypoxia on myocardial blood flow, mean arterial pressure and heart rate in five dogs are summarized in Fig. 2. Myocardial blood flow showed no change until Pa,O_2 fell to a value of between 30 and 40 mmHg when a significant increase occurred (see also Fig. 3). Mean blood pressure rose throughout the procedure while heart rate showed little change until Pa,O_2 fell below 50 mmHg when a decrease occurred.

Rapidly induced hypoxia

In these experiments several sets of measurements were made during the hypoxic phase. The

results presented are those that coincided with maximum recorded blood flow in each dog and, unless otherwise indicated, are expressed as the mean ± SEM.

The effects of rapidly induced hypoxia on arterial and coronary sinus oxygen tension, oxygen saturation, oxygen content, carbon dioxide tension and pH are shown in Table 1. The decrease in Fin,O_2 produced a fall in Pa,O_2 from 97 to 29 mmHg while the mean coronary sinus oxygen tension fell from 34 to 18 mmHg. There were corresponding changes in oxygen saturation and content. The lack of significant alteration in arterial and coronary sinus carbon dioxide tensions and pH at the time of the maximum myocardial blood flow is evident. However, when

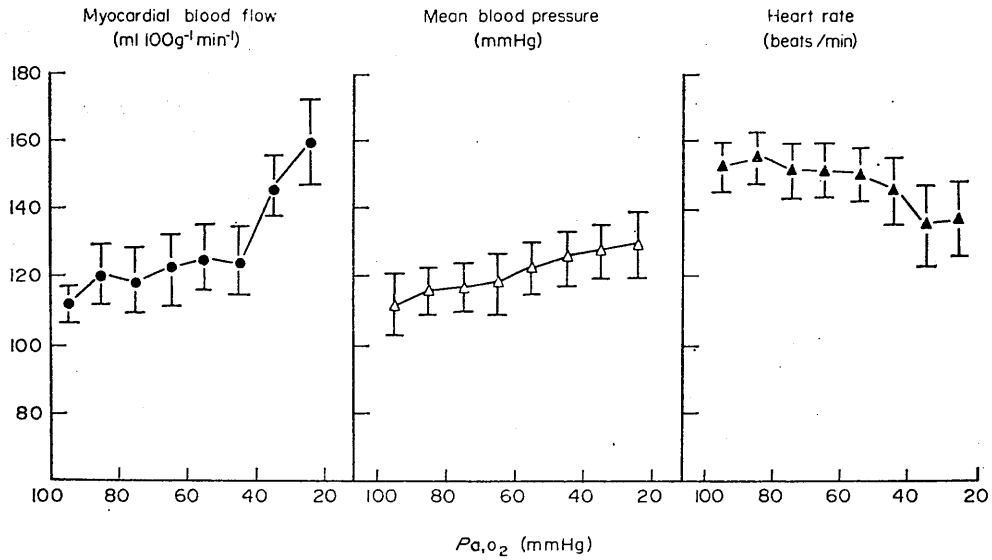

FIG. 2. Changes in myocardial blood flow, mean blood pressure and heart rate during gradually induced hypoxia. Results from five dogs expressed as mean ± SEM.

hypoxaemia was maintained for a further 10–15 min, as it was in twenty-one of the experiments, Pa,CO_2 rose to 48 ± 1·5 mmHg ($P<0·001$). There was no significant change in the non-respiratory component of acid–base balance, base excess, either during or after brief hypoxia.

The myocardial blood flow and haemodynamic changes associated with rapidly induced hypoxia are summarized in Table 2 and illustrated in Fig. 4. Mean arterial pressure, mean right atrial pressure and myocardial blood flow were all significantly increased while myocardial vascular resistance and heart rate were decreased. Although the *mean* heart rate decreased during hypoxia by 20 beats/min, in eleven of the twenty-seven experiments the heart rate increased (Table 3). The main point that emerges from this table and which is also evident in Fig. 4, is that myocardial blood flow was markedly increased during hypoxia whatever the direction of the heart-rate response.

In spite of the considerable increase in myocardial blood flow during hypoxia, myocardial oxygen availability was substantially decreased (from 23·4 ± 1·0 to 17·2 ± 0·9 ml 100 g^{-1} min^{-1}, $P<0·005$) because of the magnitude of the decrease in arterial oxygen content (20·8 to 11·0 ml/100 ml). However, myocardial oxygen extraction (for individual values see Fig. 5) was increased from a mean of 43% to a mean of 55%. These increases in oxygen extraction and flow allowed

TABLE 1. Effect of rapidly induced hypoxia on arterial and coronary sinus O_2 tension, saturation and content, Pco_2 and pH (mean ± SEM, twenty-two dogs, twenty-seven experiments)

	Arterial			Coronary sinus		
	Control		Hypoxia	Control		Hypoxia
Po_2 (mmHg)	97 ± 2	$P < 0{\cdot}001$	29 ± 1	34 ± 1	$P < 0{\cdot}001$	18 ± 1
O_2 saturation (%)	97 ± 0·3	$P < 0{\cdot}001$	48 ± 2	55 ± 3	$P < 0{\cdot}001$	22 ± 2
O_2 content (ml/100 ml)	20·8 ± 0·5	$P < 0{\cdot}001$	11·0 ± 0·5	10·9 ± 0·5	$P < 0{\cdot}001$	4·6 ± 0·3
Pco_2 (mmHg)	40 ± 1	NS	41 ± 1	51 ± 1	NS	50 ± 2
pH	7·330 ± 0·008	NS	7·328 ± 0·014	7·306 ± 0·015	NS	7·312 ± 0·021

NS = not significant.

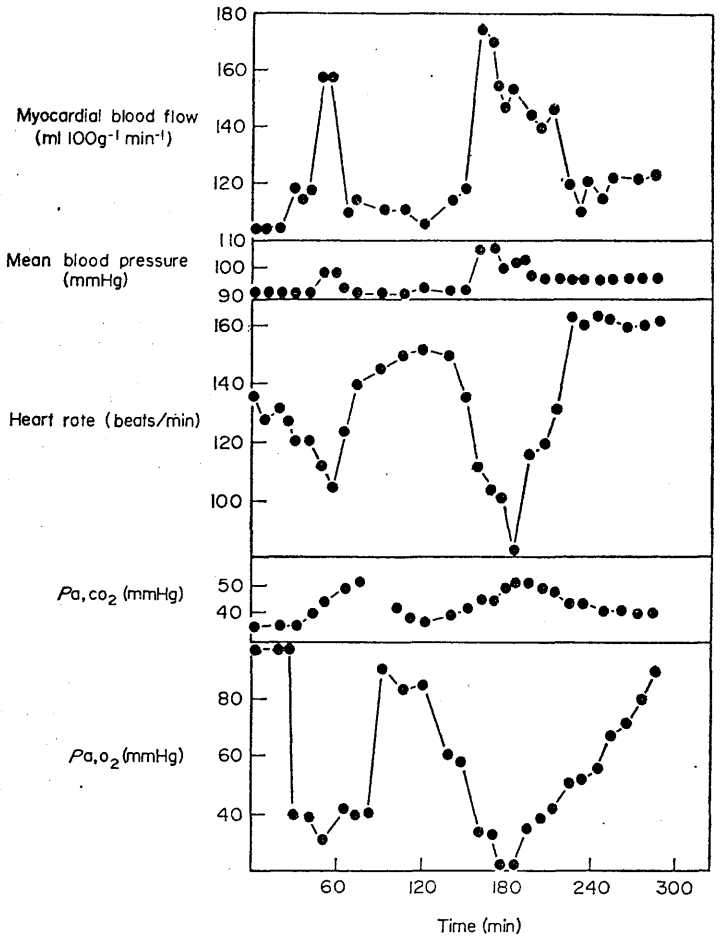

FIG. 3. A comparison of the effects of rapidly and gradually induced hypoxia on myocardial blood flow, systemic arterial pressure, heart rate and Pa,co_2 in a single dog. Myocardial blood flow is only raised when Pa,co_2 falls below about 40 mmHg and the peak flows are similar whether the hypoxia is induced rapidly or gradually.

TABLE 2. Haemodynamic effects of rapidly induced hypoxia (mean ± SEM, twenty-two dogs, twenty-seven experiments)

	Control		Hypoxia		Post hypoxia
Pa,o_2 (mmHg)	97±2	$P<0.001$	29±1	$P<0.001$	96±5
Mean blood pressure (mmHg)	119±3	$P<0.05$	131±5	$P<0.05$	113±3
Heart rate (beats/min)	158±6	$P<0.02$	138±9	$P<0.02$	158±7
Right atrial pressure (mmHg)	+0·6±0·1	$P<0.01$	+2·7±0·1	$P<0.01$	−0·4±0·4
Myocardial blood flow (ml 100 g^{-1} min^{-1})	118±5	$P<0.001$	162±6	$P<0.001$	108±6
Myocardial vascular resistance (units)	1·08±0·05	$P<0.01$	0·84±0·06	$P<0.01$	1·10±0·39

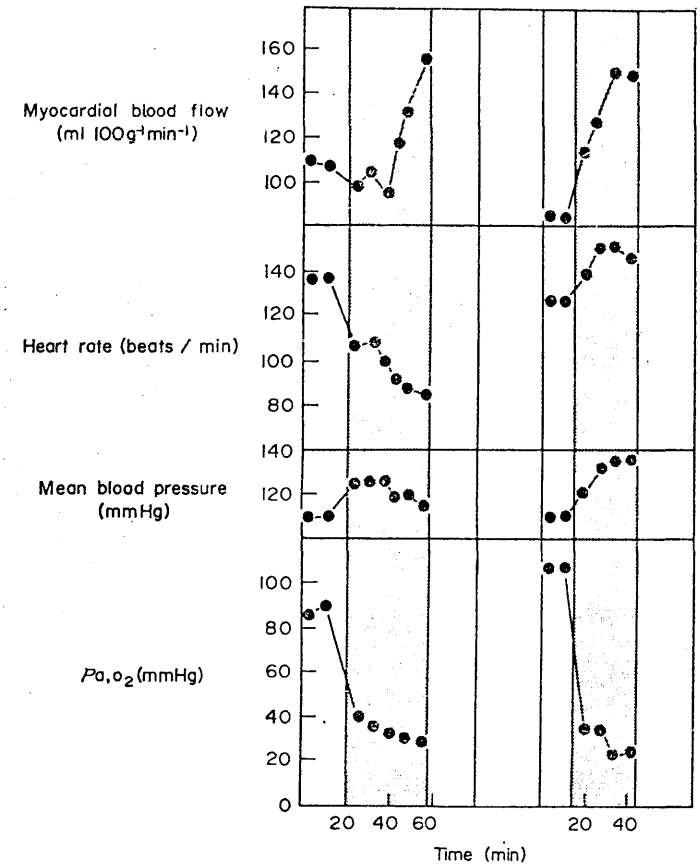

FIG. 4. The cardiovascular effects of rapidly induced hypoxia (shaded areas) in two dogs. Myocardial blood flow was increased when Pa,O_2 fell below 40 mmHg whatever the direction of the heart-rate response.

TABLE 3. Relationships of heart-rate changes to changes in myocardial blood flow, arterial mean pressure and myocardial oxygen consumption in response to rapidly induced hypoxia (mean ± SEM)

	Heart rate decreased (sixteen experiments)			Heart rate increased (eleven experiments)		
	Control		Hypoxia	Control		Hypoxia
Heart rate (beats/min)	160 ± 10		116 ± 6	150 ± 10		177 ± 12
Myocardial blood flow (ml 100 g^{-1} min^{-1})	122 ± 6	$P < 0.001$	161 ± 7	113 ± 10	$P < 0.001$	164 ± 9
Mean systemic blood pressure (mmHg)	121 ± 4	NS	131 ± 7	116 ± 4	$P < 0.005$	137 ± 5
Myocardial oxygen consumption (ml 100 g^{-1} min^{-1})	9·5 ± 0·6	NS	8·9 ± 1·0	9·6 ± 1·9	NS	12·1 ± 1·2

NS = not significant.

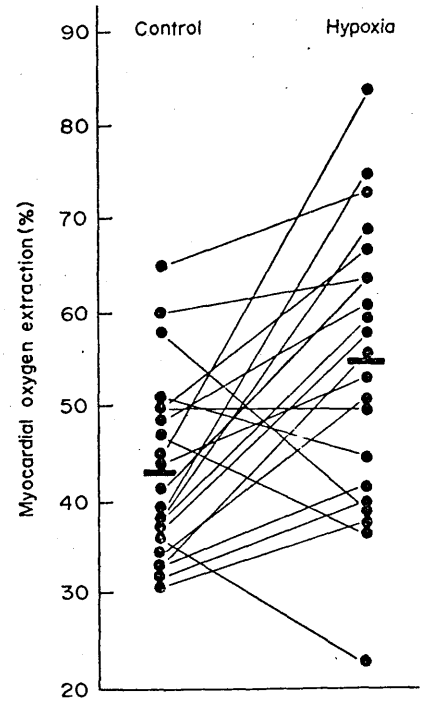

FIG. 5. Changes in myocardial oxygen extraction during rapidly induced hypoxia. Mean extractions for the control and hypoxic periods are shown by the short horizontal bars ($P < 0{\cdot}01$).

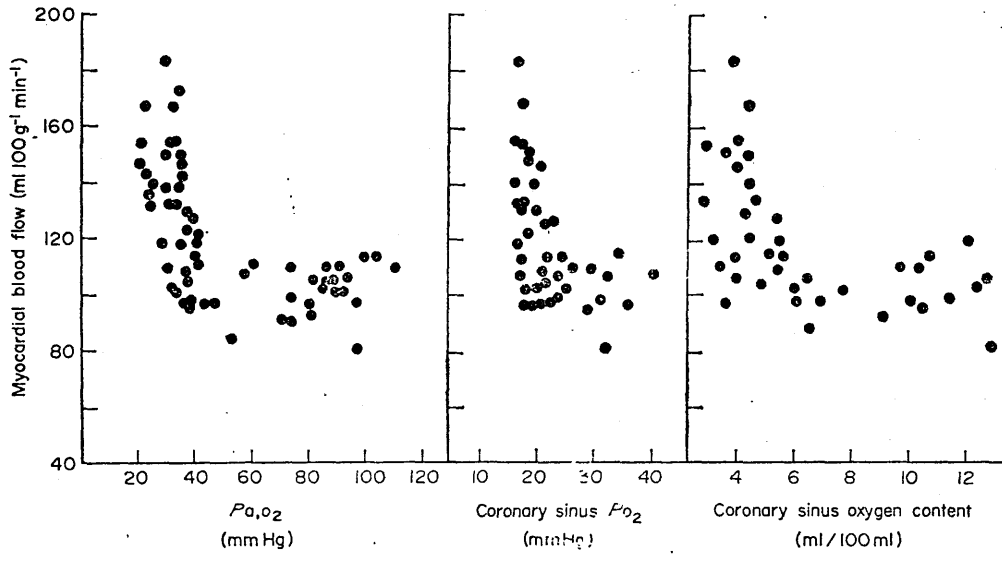

FIG. 6. The relationship between myocardial blood flow and Pa,O_2 coronary sinus Po_2 and coronary sinus oxygen content. Myocardial blood flow was increased when the Pa,O_2 fell below 40 mmHg (equivalent to a coronary sinus Po_2 of 18 mmHg or an oxygen content of 5·0 ml/100 ml coronary sinus blood). The results for Pa,O_2 were obtained from twenty-seven animals and for coronary sinus Po_2 and oxygen content from twenty-two animals.

the myocardium to maintain oxygen consumption at normal levels during hypoxia (10·2±0·6 ml 100 g^{-1} min^{-1} during the control period and 10·6±0·8 ml 100 g^{-1} min^{-1} during hypoxia). Myocardial oxygen consumption was also unchanged in the 15 min period immediately after termination of hypoxia (10·3±1·0 ml 100 g^{-1} min^{-1}).

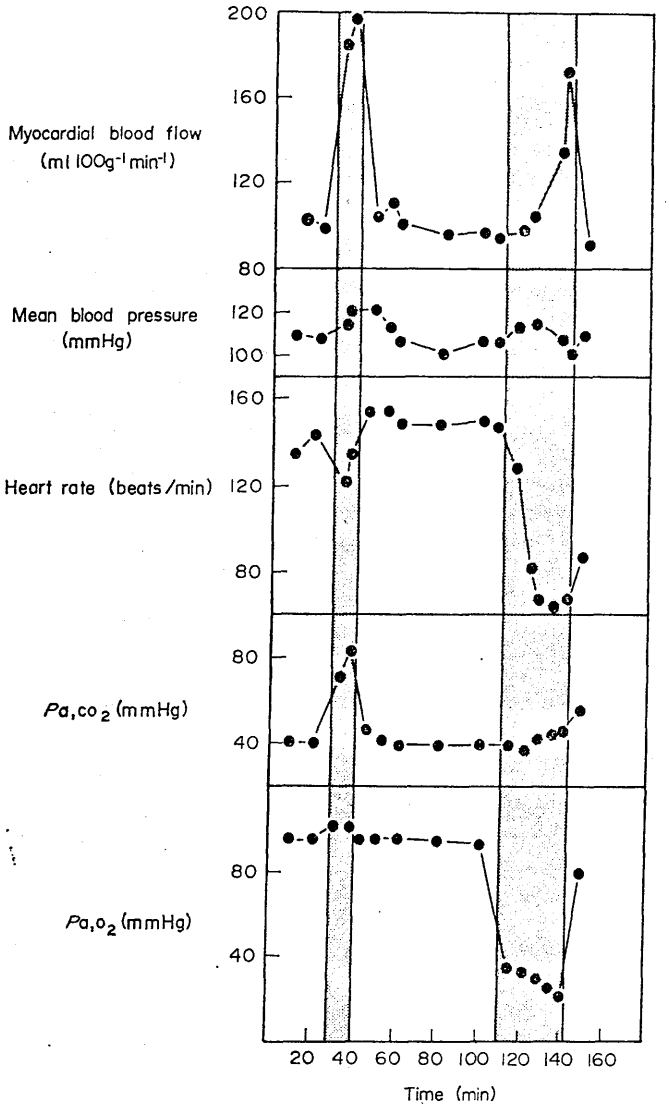

FIG. 7. A comparison of the effects of rapidly induced hypercapnia (to Pa,co_2 84 mmHg) and of hypoxia on myocardial blood flow mean systemic arterial blood pressure and heart rate. Note that maximal coronary vasodilatation was not obtained even at a Pa,o_2 of 20 mmHg.

The relationship between myocardial blood flow and arterial oxygen tension, coronary sinus oxygen tension and coronary sinus oxygen content is shown in Fig. 6. The critical arterial oxygen tension (35 mmHg), above which marked flow increases did not occur, corresponds to a coronary sinus oxygen tension of 18 mmHg (equivalent to an oxygen content of 5·0

ml/100 ml). After the critical level of arterial oxygen tension had been reached further small decrements in $Pa.O_2$ were associated with increments in myocardial blood flow (Figs. 4, 7 and 8). In some of the experiments in spite of a decrease of arterial oxygen tension to 20 mmHg it is probable that maximum coronary vasodilatation was not attained; for example, in the animal illustrated in Fig. 7 myocardial blood flow was 172 ml 100 g^{-1} min^{-1} at an arterial oxygen tension of 20 mmHg whereas a flow of 197 ml 100 g^{-1} min^{-1} was achieved during hypercapnia (Pa,CO_2 84 mmHg).

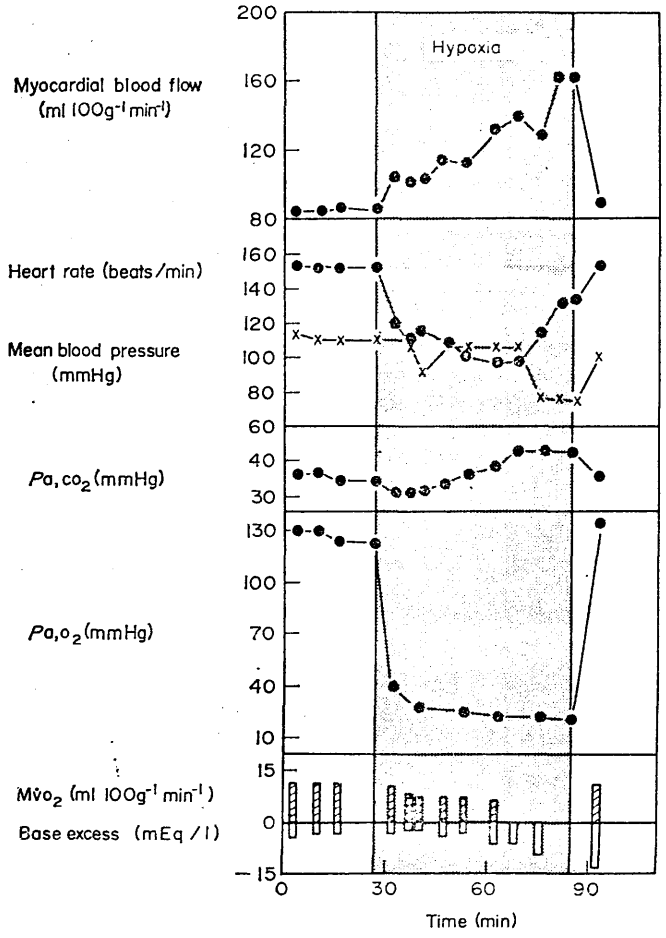

FIG. 8. The effect of prolonged hypoxia on myocardial blood flow, heart rate, mean systemic arterial blood pressure, Pa,CO_2, Pa,O_2, myocardial oxygen consumption (MvO_2) and arterial base excess.

Arterial and coronary sinus concentrations of lactate, pyruvate and glucose were measured in twelve of the animals in the rapidly induced hypoxia series (Table 4). During the control period the myocardium appeared to extract small amounts of lactate and pyruvate but not glucose. During hypoxia mild lactic acidosis and hyperglycaemia occurred but without a significant change either in arterial base excess or in the myocardial extraction of these sub-

strates. It should be noted that the results included under the heading 'hypoxia' in Table 4 did not necessarily coincide with the maximum recorded elevation in myocardial blood flow.

In four of the animals of the series hypoxia was sustained for more than 30 min. Myocardial blood flow remained consistently elevated throughout the period of hypoxia. Myocardial oxygen consumption appeared to fall progressively after the initial 10–15 min and was associated with an increasingly severe metabolic acidosis. The results from one of the animals are illustrated in Fig. 8. Myocardial oxygen consumption fell progressively after the first 10 min in spite of a steadily rising myocardial blood flow and (not shown) a steadily rising myocardial

TABLE 4. Effect of rapidly induced hypoxia on arterial and coronary sinus concentrations of lactate, pyruvate and glucose (mean ± SEM, twelve dogs)

	Arterial			Coronary sinus		
	Control		Hypoxia	Control		Hypoxia
Lactate (mg/100 ml)	19·8 ± 3·0	$P < 0·01$	29·9 ± 5·4	15·1 ± 2·2	$P < 0·02$	26·5 ± 4·8
Pyruvate (mg/100 ml)	1·3 ± 0·1	NS	1·4 ± 0·1	0·9 ± 0·1	$P < 0·005$	1·2 ± 0·1
Glucose (mg/100 ml)	115 ± 6	$P < 0·01$	130 ± 6	113 ± 6	$P < 0·05$	128 ± 7

NS = not significant.

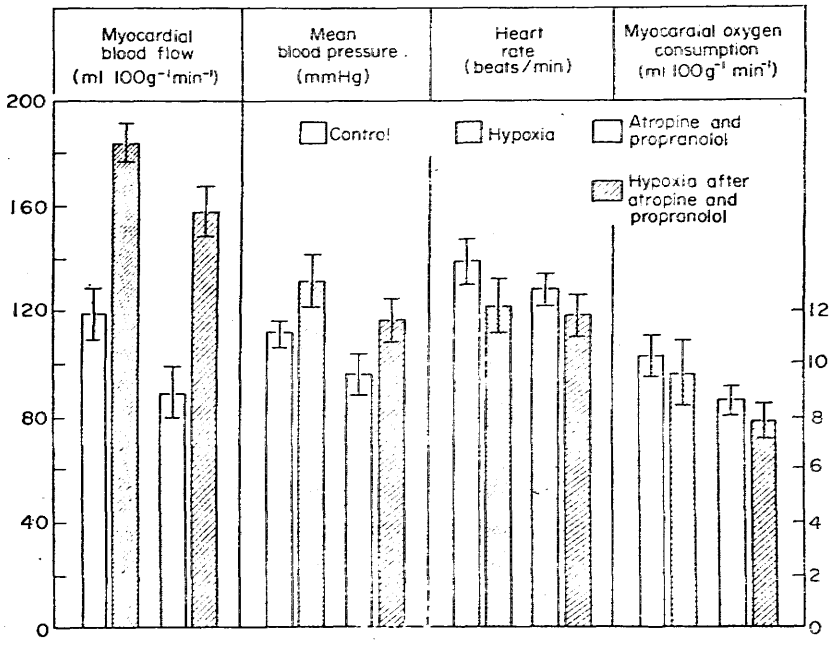

FIG. 9. The effects of rapidly induced hypoxia on myocardial blood flow, mean systemic arterial blood pressure, heart rate and myocardial oxygen consumption, before and after atropine (0·04 mg/kg) and propranolol (0·2 mg/kg). The hypoxia-induced changes in myocardial blood flow and mean blood pressure were significant both before ($P < 0·001$; $P < 0·05$) and after ($P < 0·001$; $P < 0·05$) atropine and propranolol. (Mean ± SEM, seven dogs.)

oxygen extraction such that the coronary sinus oxygen tension at 40 min was 1 mmHg (the corresponding mixed venous oxygen tension was 9 mmHg). Base excess also began to fall after 35 min of hypoxia and reached a value of −10 mEq/l immediately before cessation of the hypoxia. Over the same time, the arterial lactate concentration rose from 13·7 to 68 mg/100 ml

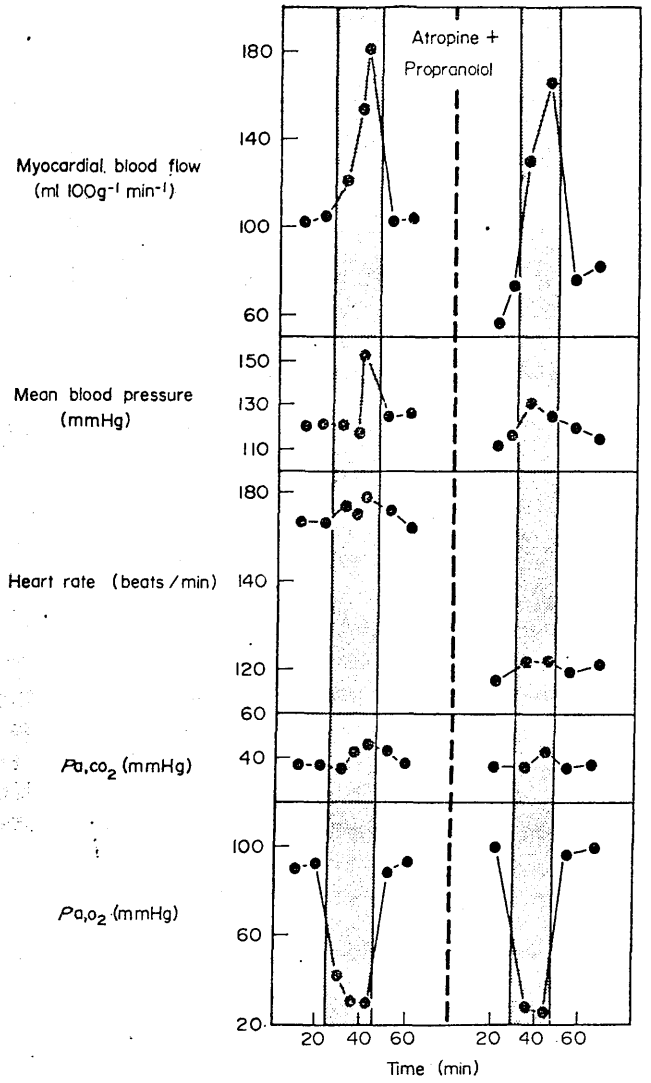

FIG. 10. Cardiovascular and blood-gas responses to rapidly induced hypoxia (shaded areas) before and after atropine (0·04 mg/kg) and propranolol (0·2 mg/kg) in a single dog.

and the arterial glucose concentration from 116 to 139 mg/100 ml. The myocardial consumption of lactate, pyruvate and glucose, however, remained minimal.

Disturbances of electrocardiographic pattern were frequently observed during hypoxia and included nodal rhythm (four animals), multiple ventricular extrasystoles (eleven animals),

complete heart block (two animals) and ST–T wave abnormalities (eight animals). Prolonged hypoxia did not necessarily produce a progressive deterioration in the electrocardiographic pattern and sinus rhythm was promptly restored in all animals after the resumption of a normal inspired oxygen concentration.

The cardiovascular effects of atropine and propranolol in the dosage used in this study have been documented by Ledingham *et al.* (1970). The responses of seven dogs to rapidly induced hypoxia before and after atropine and propranolol are summarized in Fig. 9. Although atropine and propranolol themselves caused a decrease in myocardial blood flow, blood pressure, heart rate and myocardial oxygen consumption, the responses to hypoxia were essentially unaltered by these drugs. The results from a single dog of this series are shown in Fig. 10.

DISCUSSION

It is widely agreed that the myocardium has a very limited capability to function adequately when its oxygen supply is compromised either by anoxia or coronary occlusion (Tennant & Wiggers, 1935; Bing, 1965). The energy requirement of the myocardium cannot be fully met in the absence of oxygen and the heart rapidly fails. When the oxygen content of the blood perfusing the heart is decreased the myocardium must either extract more oxygen or increase the volume flow of blood, or both. Since the myocardial extraction of oxygen is normally high (43% during control measurements in this study), oxygen supply to the myocardium is most readily increased by an elevation of blood flow and this has been an invariable finding in studies of hypoxia. However, myocardial oxygen extraction by no means remains constant since all but five of the dogs in the rapidly induced hypoxia series showed increased oxygen extraction during hypoxia.

The demonstration of a critical level of arterial oxygen tension at which myocardial blood flow began to increase was a consistent finding in this study. The critical level suggested was an arterial oxygen tension of 30–35 mmHg, corresponding to a coronary sinus oxygen tension of about 18 mmHg. Fig. 6 shows that the scatter of coronary sinus oxygen tension values during hypoxia was rather less than the scatter of the arterial oxygen tension values and this would suggest that during hypoxia there is a particularly close relationship between myocardial blood flow and coronary sinus oxygen tension which is itself a reflection of myocardial tissue P_{O_2}. This value of venous oxygen tension may be critical in tissues other than the myocardium since Ernsting (1966) has shown that consciousness is lost when the jugular venous oxygen tension falls to a similar value. Berne *et al.* (1957) suggested, from work on open-chest dogs with an artificially perfused coronary arterial circulation, that coronary blood flow increased when the coronary sinus blood oxygen content fell below 5·5 vol.%, regardless of the arterial oxygen content. The critical coronary sinus oxygen content of 5·0 ml/100 ml in the present study agrees closely with Berne's value.

In the present study hypoxia was associated with a small rise in arterial P_{CO_2} and a relatively larger fall in arterial pH both of which factors increase myocardial blood flow. The maximum increase in myocardial blood flow during hypoxia, however, occurred before significant changes in either Pa,CO_2 or arterial pH. The observation that myocardial blood flow remained elevated during sustained hypoxia also suggests a primary influence of the low arterial oxygen tension since in a previous study (Ledingham *et al.*, 1970) myocardial blood flow returned towards control values in spite of sustained elevation of arterial P_{CO_2} and decrease in arterial pH.

Several authors have suggested that there is normally a close relationship between changes in myocardial blood flow and myocardial oxygen consumption (Braunwald, Sarnoff, Case, Stainsby & Welch, 1958; Feinberg, Katz & Boyd, 1962). In the present study a close relationship between myocardial blood flow and myocardial oxygen consumption was not so obvious. For example, myocardial blood flow rose in all animals irrespective of heart rate changes, while myocardial oxygen consumption fell when heart rate decreased and rose when heart rate increased (Table 3). In other situations where there is a direct coronary vasodilator effect, myocardial blood flow and myocardial oxygen consumption, as one might expect, diverge. This may be observed, for example, during hypercapnia.

It has been suggested that the general circulatory responses to systemic hypoxia will depend largely on whether or not the animal breathes spontaneously or is artificially ventilated (Daly & Scott, 1963; Kontos, Mauck, Richardson & Patterson, 1965). Spontaneously breathing animals will respond to hypoxia by hyperventilation which contributes considerably to the tachycardia, increase in cardiac output and peripheral vasodilatation which are the usual circulatory responses to systemic hypoxia. These circulatory effects are largely the result of reflexes initiated by lung stretching (Daly & Scott, 1963). Although a cardio-accelerator response to hypoxia has also been reported in artificially ventilated animals (Krasney, 1967), the predominant effect in this situation is a reflex bradycardia resulting from the stimulation of carotid chemoreceptors by hypoxic blood (Kontos *et al.*, 1965). It is clear that the circulatory responses to systemic hypoxia depend on a number of opposing influences. These include direct effects of the decreased oxygen tension on vascular smooth muscle, effects on chemoreceptors leading to reflex changes in cardiac rate and contractility and direct effects on cardiac muscle. Some of these result in tachycardia, an increase in cardiac output and peripheral vasodilatation, others in bradycardia, a decrease in cardiac output and peripheral vasoconstriction.

In the present experiments, where the dogs were artificially ventilated and where succinylcholine had been used to produce skeletal-muscle paralysis, there were two quite distinct heart rate responses to systemic hypoxia. In about one-third of the animals the response to hypoxia was a tachycardia. This was probably due to a combination of reflex cardiac sympathetic nerve stimulation, the release of adrenal medullary catecholamines and an inhibition of vagal tone (Krasney, 1967). In most of the animals, however, there was a bradycardia which was often severe and probably resulted from stimulation of carotid and aortic body chemoreceptors together with a direct depressant effect on the myocardium (Kahler, Goldblatt & Braunwald, 1962). The most serious electrocardiographic evidence of myocardial depression in this series was the development of atrioventricular conduction defects. Harris (1951) showed that the commonest terminal electrocardiographic disturbance during hypoxia was the development of either pacemaker or atrioventricular conduction failure. Two of the animals in the present series developed complete heart block and four developed atrioventricular nodal rhythm. No arrhythmia observed in this series persisted after the resumption of a normal inspired oxygen concentration.

The metabolic disturbances associated with a mean arterial oxygen tension of 29 mmHg were minimal in the first 15 min, amounting to a mild systemic lactic acidosis and hyperglycaemia. The increase in myocardial blood flow and oxygen extraction appeared to have prevented significant hypoxia arising in the myocardial cells. On the other hand, when hypoxia was sustained and the arterial P_{O_2} had fallen to nearer 20 mmHg, severe systemic lactic acidosis did occur (Fig. 8). Even under these conditions, however, the myocardial cells did not appear

consistently to demonstrate metabolic embarrassment in that handling of lactate, pyruvate and glucose in the majority of animals studied remained essentially unaltered.

The effects of systemic hypoxia on myocardial blood flow after β-adrenoreceptor blockade are in marked contrast with those reported by Folle & Aviado (1965). These authors measured coronary sinus outflow with a Shipley–Wilson rotameter in open-chest dogs and concluded that the increase in the outflow which occurred during inhalation of 5% oxygen, 95% nitrogen was abolished by the β-adrenoreceptor-blocking drug sotalol (MJ 1999). Folle & Aviado (1965) concluded from their experiments that β-adrenoreceptor-blocking drugs in general might seriously interfere with the self-regulating control of myocardial oxygen supply in patients with coronary artery disease. The present results give no indication that this might occur. Coronary vasodilatation resulting from the hypoxic stimulus was in no way influenced by doses of propranolol sufficient to abolish the cardiac effects of infused catecholamines and of sympathetic nerve stimulation. Further, the present results indicate that coronary vasodilatation, which occurs during hypoxia, is due to an effect of the lowered oxygen tension (or the release of some vasodilator metabolite) on vascular smooth muscle and is not mediated through vascular β-adrenoreceptors. Although β-adrenoreceptor-blocking drugs do not appear to interfere with hypoxia-induced coronary vasodilatation, in some instances myocardial depression resulting from hypoxia might be more pronounced after atropine and propranolol. Thus, in one of the dogs in the series, hypoxia after this drug combination resulted in complete heart block, severe hypotension (40/20 mmHg) and a greatly elevated right atrial pressure. The rapid restoration of the inspired oxygen tension resulted in a return to sinus rhythm and elevation of systemic arterial blood pressure.

The observation of a consistent rise in arterial P_{CO_2} during hypoxia despite constant minute ventilation indicates an increase in pulmonary dead-space ventilation. Hypoxia is known to produce pulmonary vasoconstriction (Duke, 1951; Bergofsky, Haas & Porcelli, 1968) and this will be associated with changes in the pulmonary ventilation/perfusion ratios which probably give rise to areas of inadequate perfusion within the lungs relative to the volume of gas ventilating them. Such disturbances of pulmonary function would also account for the gradual fall in arterial oxygen tension that was observed during hypoxia in spite of a stable inspired oxygen concentration.

ACKNOWLEDGMENT

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Chapter 8

Haemodynamic and myocardial effects of hyperbaric oxygen (2ATA) in dogs subjected to haemorrhage

The second of the three chapters concerns the effects of stagnant hypoxia on the heart and its modification by hyperbaric oxygen (2ATA). The details of the study are contained in the following reprint.

HAEMODYNAMIC AND MYOCARDIAL EFFECTS OF HYPERBARIC OXYGEN IN DOGS SUBJECTED TO HAEMORRHAGE

BY

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Haemodynamic and myocardial effects of hyperbaric oxygen in dogs subjected to haemorrhage

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Authors' synopsis *In closed-chest anaesthetized dogs subjected to moderate and severe haemorrhage (mean blood pressures of 70–75 and 45–50 mm Hg respectively), the administration of oxygen at 2 ATA (OHP) failed to modify the decreases in cardiac output, work, efficiency, and myocardial oxygen consumption that result from blood loss. OHP further decreased myocardial blood flow in these hypotensive dogs and, despite the marked increases in arterial oxygen tension, myocardial oxygen availability was not improved.*

Several years ago, Guyton and Crowell (1961) suggested that the basic mechanism in irreversible shock was related to oxygen debt. During this period of oxygen deficit, the myocardial cells developed structural damage which made it impossible for them to utilize nutrients, even after adequate supplies had been reinstituted. If this supposition is valid, then correction of the myocardial tissue hypoxia before these irreversible changes take place should improve survival. There are two possible theoretical approaches. Firstly, to improve tissue perfusion by increasing coronary driving pressure and decreasing coronary vascular resistance; secondly, by improving myocardial oxygen supply as a result of increasing the amount of oxygen carried by the arterial blood. This second approach to the problem can be achieved by using oxygen at increased ambient pressure. Thus, Cowley and his colleagues (Attar, Esmond, and Cowley, 1962; Cowley, Attar, Blair, Esmond, Ollodart, and Hashimoto, 1965) have claimed increased survival of dogs in shock by the use of hyperbaric oxygen and Ratliff, Hackel, and Mikat (1967) have shown that oxygen at high pressure can prevent subendocardial haemorrhages and necrosis associated with haemorrhagic shock. Recently, a case has been described in which hyperbaric oxygen permanently relieved signs of heart failure and myocardial ischaemia in a patient in haemorrhagic shock who, for religious reasons, had refused blood replacement (Amonic, Cockett, Lorhan, and Thompson, 1969).

The object of the present experiments was to examine the effects of hyperbaric oxygen on cardiac work, myocardial blood flow, and myocardial oxygen consumption in closed-chest dogs subjected to haemorrhage. Two blood pressure levels were chosen, 75 mm Hg and the critical level of 45–50 mm Hg, which is near the terminal portion of the autoregulatory myocardial pressure–flow curve (Berne, 1959; Mosher, Ross, McFate, and Shaw, 1964; Grayson and Parratt, 1966).

Methods

Twenty mongrel dogs, weighing between 16 and 42 kg were used for the study. After induction of anaesthesia with intravenous sodium thiopentone (usually 20 mg/kg) and after endotracheal intubation, anaesthesia was maintained with trichlorethylene (0·5–1%). This was vapourized from a Tritec vapourizer (Cyprane Ltd.). The animals were maintained on intermittent positive pressure ventilation using a Palmer pump: the stroke volume was adjusted to give an arterial carbon dioxide tension of 35–45 mm Hg at the commencement of the experiment. Thereafter respiratory rate and tidal volume were unchanged.

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Reflex movement was prevented by intermittent intramuscular injections of suxamethonium chloride (100 mg).

Catheters were inserted via the left femoral artery into the descending aorta and, via the left femoral vein, into the right atrium, for the measurement of aortic and central venous pressures using capacitance transducers (Elema-Schönander EMT 35 and 33 respectively). These, together with the electrocardiogram (lead II), were recorded on an Elema-Schönander ink-writing recorder (Mingograph 81). Mean pressures were obtained by electronic integration and the heart rate was calculated from the electrocardiogram. Cardiac output was measured by dye-dilution. Indocyanine green (2·5 mg) was injected into the right atrium and blood withdrawn from the descending aorta through a Waters densitometer (XP-302 Waters Company, Rochester, Minnesota).

Myocardial blood flow was measured using a ^{133}xenon clearance technique similar to that outlined by Ross, Ueda, Lichtlen, and Rees (1964). The full details have been outlined elsewhere (Ledingham, McBride, Parratt and Vance, 1970). A Sones No. 7 or 8 catheter was introduced into the right common carotid artery in the neck and, under fluoroscopic control, manipulated until the tip of the catheter lay a distance of 5–10 mm in a major branch (usually the circumflex) of the left coronary artery. Injections of ^{133}xenon (40–100 uc, dissolved in normal saline) were flushed into this catheter with 3 ml. heparinized saline. The myocardial clearance of the isotope (which is a function of blood flow) was measured using an Ekco scintillation counter placed over the praecordium. Details of the calculation of myocardial blood flow from the clearance curve, are given in the paper by Ledingham *et al.* (1970).

For the measurement of myocardial oxygen consumption, a catheter was positioned fluoroscopically in the coronary sinus by way of the right external jugular vein. Anaerobic blood samples (2 ml.) were simultaneously obtained at frequent intervals from the coronary sinus, the right atrium, and the descending aorta. Blood oxygen tension (Po_2), carbon dioxide tension (PCO_2), and pH were measured using appropriately calibrated electrode systems (Radiometer, Copenhagen) and, to allow for the difference in the measurement of oxygen tensions in gas and blood (McDowall, Ledingham, and Tindal, 1968), a blood-gas factor was derived for each experiment using blood tonometered with a known tension of oxygen in a rotating syringe (Torres, 1963). Blood gas tensions and pH were corrected for any temperature difference between the electrode systems and the mid-oesophagus using the Radiometer blood-gas calculator (Severinghaus, 1966). The oxygen content of blood was calculated using the formula:

$$\text{Hb(g)} \times 1{\cdot}34 \times \frac{\%\ \text{saturation}}{100} + \text{Po}_2\text{(mm Hg)} \times 0{\cdot}0031$$

The blood oxygen saturation was calculated using the dog cursor on the blood-gas calculator and the haemoglobin measured by the cyanmethaemoglobin method. There is a good correlation between blood oxygen contents calculated by this indirect method and simultaneous Van Slyke determinations (Ledingham *et al.*, 1970).

Derived calculations were:

1 Total oxygen availability (ml./kg/min) = arterial oxygen content (ml./100 ml.) × cardiac output (ml./kg/min).

2 Total oxygen consumption (ml./kg/min) = arterial minus mixed venous oxygen content (ml./ml.) × cardiac output (ml./kg min).

3 Total peripheral vascular resistance (dynes sec/cm^{-5}) =

$$\frac{\text{mean arterial pressure (mm Hg)} \times 80}{\text{cardiac output (l./min)}}$$

4 External cardiac work (kgm/min) =

$$\frac{13{\cdot}6 \times \text{mean arterial pressure (mm Hg)} \times \text{cardiac output (l./min)}}{1{,}000}$$

5 Myocardial oxygen consumption (ml./100 g/min) = myocardial blood flow (ml./100 g/min) × arterial minus coronary sinus oxygen content (ml./100 ml.).

6 Coronary vascular resistance (arbitrary units) =

$$\frac{\text{diastolic arterial blood pressure (mm Hg)}}{\text{myocardial blood flow (ml./100 g/min)}}$$

7 Myocardial oxygen availability (ml. O_2/100 g/min) = arterial oxygen content (ml./100 ml.) × myocardial blood flow (ml./100 g/min).

8 Myocardial oxygen extraction coefficient =

$$\frac{\text{arterial minus coronary sinus oxygen content (ml./100 ml.)}}{\text{arterial oxygen content (ml./100 ml.)}}$$

(Gorlin, 1960).

9 Mechanical efficiency =

$$\frac{\text{left ventricular work (kgm/min)}}{\text{myocardial oxygen consumption (ml./100 g/min)} \times 2{\cdot}06}$$

(Gorlin, 1960).

After an initial period on pure oxygen, the dogs were ventilated with a mixture of nitrogen and oxygen to give an arterial Po_2 of 99–103 mm Hg. This was facilitated by the use of a paramagnetic oxygen analyser (Servomex Controls, Crowborough, Sussex).

In the first group of nine animals ('moderate haemorrhage' – series 1) the mean arterial pressure was lowered to a level of 70–75 mm Hg. A bleeding bottle was attached to a catheter in the left femoral artery and the animals bled into the bottle at a rate adjusted so that the pressure reached a level of 70–75 mm Hg in 10–20 min. The dogs were maintained at this pressure, while breathing an air-mixture, for about 50 min and were then given 100% oxygen to breathe while the chamber was pressurized (over a 10–15 min. period) to 2 atmospheres absolute (ATA). In some of the experiments this procedure was modified as follows. After the catheters had been placed in position, the chamber was pressurized to 2 ATA with the animals breathing an air-mixture. At pressure the air-mixture was adjusted

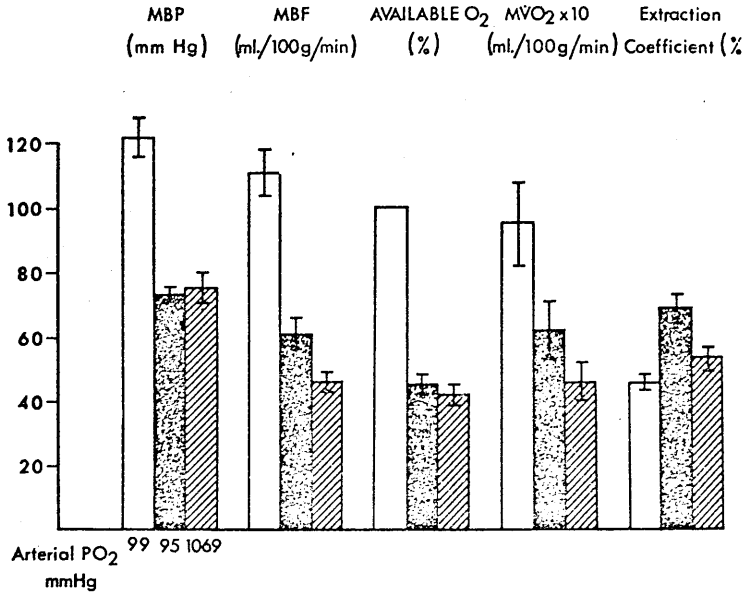

FIG. 1 *Changes in mean blood pressure* (MBP), *myocardial blood flow* (MBF), *myocardial oxygen availability, myocardial oxygen consumption* ($M\dot{V}O_2$), *and myocardial oxygen extraction coefficient in normotensive dogs* (□), *and after moderate haemorrhage breathing AIR* (stipple) *and hyperbaric oxygen* (diagonal). *Values are means ± SE of the mean.*

to give an arterial P_{O_2} of 90–100 mm Hg. The initial haemodynamic measurements were then taken and the animals bled as before. After stabilization at the low mean arterial pressure, 100% oxygen was administered. This latter procedure had the advantage that the arterial P_{O_2} could be increased rapidly and without a concomitant change in total ambient pressure. On five occasions dogs were returned to air-breathing (arterial P_{O_2} 90–100 mm Hg) and finally retransfused.

In the second series of 11 animals ('severe haemorrhage' – series 2) the mean arterial pressure was lowered to 40–45 mm Hg over a period of about 40 min and the dogs were maintained at this pressure, while breathing an air-mixture, for about 60 min. They were then given oxygen to breathe (1 ATA) and allowed to stabilize. The chamber was finally pressurized with the dogs still breathing 100% oxygen.

Results

Effects of 'moderate haemorrhage' (series 1) The mean weight of the dogs in this series was 24 kg (range 16 to 36 kg) and the mean volume of blood withdrawn to obtain a mean arterial blood pressure of 70–75 mm Hg was 43 ml./kg (range 25 to 63 ml./kg). The myocardial and haemodynamic effects of this degree of haemorrhage are summarized in Figs 1 and 2.

Heart rate and total peripheral vascular resistance were significantly increased ($P < 0.01$) and myocardial blood flow, oxygen consumption, cardiac output, work, and efficiency were markedly reduced. Haemorrhage was thus associated with a reduction in myocardial blood flow, an increase in myocardial vascular resistance (from 1.12 ± 0.06 to 1.25 ± 0.12 arbitrary units; mean ± S.E. of the mean) and a marked reduction in myocardial stroke output (from 24.5 ± 3.3 ml./beat to 8.0 ± 1.1 ml./beat, a reduction of 69%). There were also reductions in coronary sinus P_{O_2} and oxygen content (Table 1) and an increase in extraction (Table 1 and Fig. 1). The arterial P_{O_2} was maintained, but because of the reduction in the packed cell volume (from 44 to 38%) and in haemoglobin (from 15.0 ± 0.5 to 13.0 ± 0.5 g/100 ml.), arterial oxygen content was considerably reduced (by 4 ml./100 ml. blood; Table 1). There was a moderate increase in arterial PCO_2 and a reduction in blood pH. This was greater than could be accounted for by the increase in PCO_2 alone and indicates a reduction in arterial base excess of from -1 ± 2 m-equiv/l. (in the normotensive dogs) to -9 ± 2 m-equiv/l. in the haemorrhagic preparations.

The administration to these dogs of oxygen at 2 ATA markedly increased arterial P_{O_2} (from 95 to 1,069 mm Hg, Table 1) and increased arterial oxygen content to the level before haemorrhage. Hyperbaric oxygen had no significant effect, at this blood pressure level, on heart rate, total peripheral vascular resistance, cardiac output or work (Figs 1 and 2) and the most pronounced effects were a further reduction in myocardial blood flow and a further increase in myocardial vascular resistance (from 1.25 ± 0.12 to 1.67 ± 0.17 arbitrary units). Despite the increase in arterial oxygen content therefore the total amount of oxygen made available to the myocardial tissue was unchanged (Fig. 1). Marked increases in coronary sinus P_{O_2} and oxygen content occurred and thus the difference between the arterial and coronary sinus oxygen contents remained the same (Table 1), although the extraction coefficient returned towards the pre-haemorrhage level.

In five of the preparations the effect of returning to air breathing was studied and this was followed by retransfusion. The effects of these procedures on arterial blood pressure, myocardial blood flow, myocardial oxygen availability and consumption, cardiac output and work, and on total peripheral

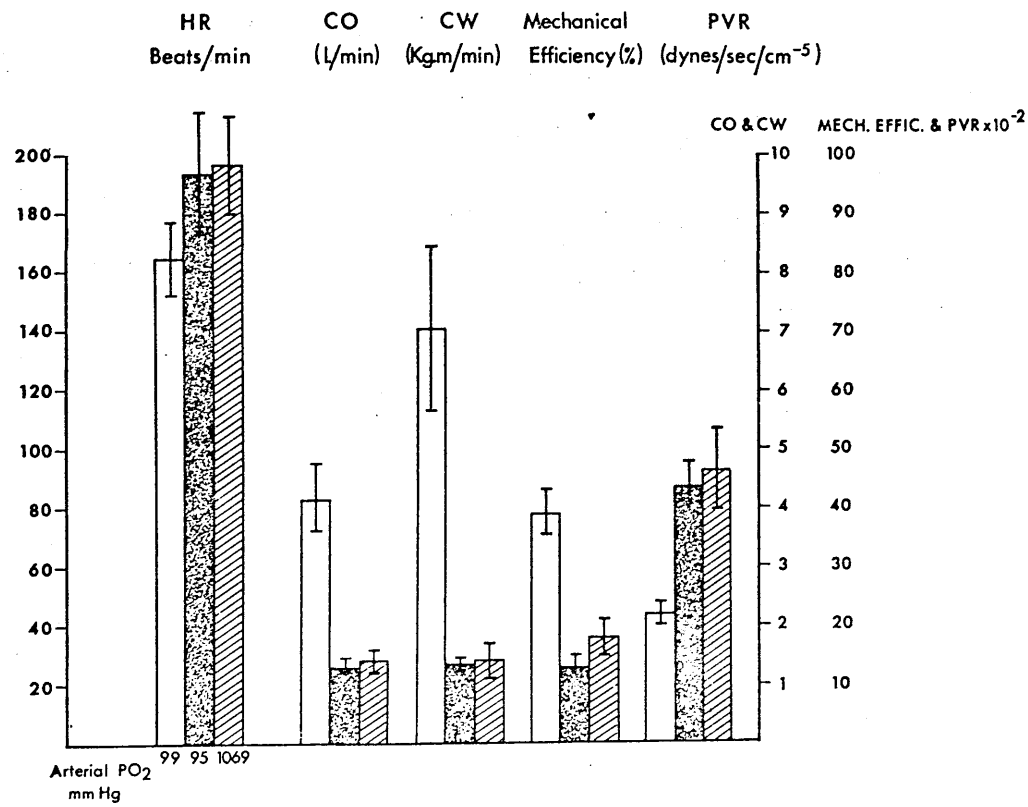

FIG. 2 *Changes in heart rate* (HR), *cardiac output* (CO), *external work* (CW) *and efficiency and in total peripheral vascular resistance* (PVR) *in normotensive dogs* (□), *and after moderate haemorrhage breathing AIR* (stipple) *and hyperbaric oxygen* (diagonal). *Values are means ± SE of the mean.*

vascular resistance are illustrated in Fig. 3. On returning to air-breathing the most pronounced effects were a rise in myocardial blood flow and a reduction in myocardial vascular resistance (from a mean of 1·8 to a mean of 1·1 arbitrary units). In each of the dogs retransfusion of the shed blood was accompanied by increases in myocardial blood flow and myocardial oxygen availability and a partial return of blood pressure (with one exception), cardiac output and work towards pre-haemorrhage levels (Fig. 3).

Effects of 'severe haemorrhage' (series 2)

In this series of dogs (weight 16–42 kg; mean 33 kg) the mean volume of blood with-

TABLE I *Blood-gas changes in dogs subjected to moderate (mean blood pressure 73 mm Hg) and severe (mean blood pressure 49 mm Hg) haemorrhage*

	Moderate haemorrhage			*Severe haemorrhage*			
		Hypotensive			*Hypotensive*		
	Control	*Air*	*OHP*	*Control*	*Air*	*Oxygen*	*OHP*
PaO_2 (mm Hg)	99 ± 3	95 ± 3	1069 ± 25	103 ± 2	97 ± 5	421 ± 60	961 ± 91
$PaCO_2$ (mm Hg)	41 ± 2	48 ± 3	52 ± 4	41 ± 1	57 ± 5	64 ± 6	59 ± 8
PaH (units)	7·386 ± 0·026	7·262 ± 0·048	7·175 ± 0·055	7·369 ± 0·037	7·117 ± 0·051	6·999 ± 0·054	7·024 ± 0·051
Base excess (m-equiv/l.)	−1 ± 2	−9 ± 2	−11 ± 2	−2 ± 1	−15 ± 2	−17 ± 1	−17 ± 1
$P_{CS}O_2$ (mm Hg)	31 ± 2	27 ± 4	43 ± 5	31 ± 2	30 ± 1	40 ± 3	56 ± 7
CaO_2 (ml. %)	20·0 ± 0·8	16·0 ± 0·9	20·0 ± 1·1	20·5 ± 0·5	14·8 ± 1·4	16·4 ± 1·4	15·7 ± 1·4
$C_{CS}O_2$ (ml. %)	11·5 ± 0·7	6·2 ± 1·0	9·9 ± 0·8	9·8 ± 0·5	5·4 ± 0·9	7·1 ± 0·8	9·3 ± 1·2
A-$C_{CS}O_2$ (ml. %)	8·5 ± 0·7	10·4 ± 1·4	10·0 ± 1·2	10·9 ± 1·1	9·4 ± 0·8	9·3 ± 0·9	7·3 ± 1·1

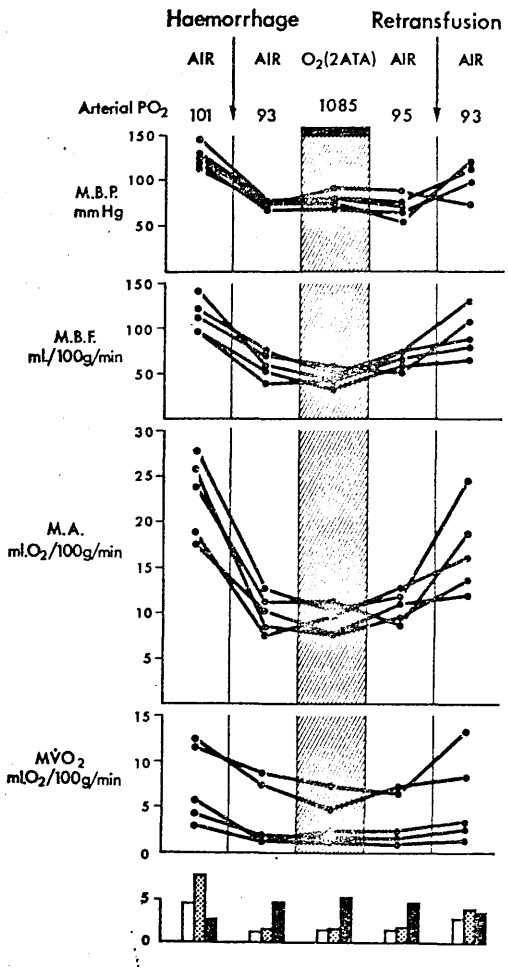

FIG. 3 *Changes in mean blood pressure* (MBP), *myocardial blood flow* (MBF), *myocardial oxygen availability* (MA), *and myocardial oxygen consumption* ($M\dot{V}O_2$) *produced by moderate haemorrhage, hyperbaric oxygen, and retransfusion. Also indicated are cardiac output, cardiac work, and total peripheral vascular resistance. Cardiac output (l./min)* □, *Cardiac work (kg m/min)* (dots), *Peripheral vascular resistance (dynes/sec/cm^{-5})$^{-}$ × 10^{-3}* ■.

drawn to obtain an arterial pressure of 45–50 mm Hg was 51 ml./kg (range 41–66 ml./kg). This degree of haemorrhage lowered the PCV from 46 to 36% and the haemoglobin from 17·1 ± 0·9 to 13·6 ± 1·2 g/100 ml. The response to this degree of haemorrhage was similar to that described above, except that, in general, the changes were more marked. There were substantial reductions in myocardial oxygen consumption and availability, in cardiac output, work, and efficiency (Figs 4 and 5), in stroke volume (from 18·1 ± 2·7 ml./beat to 7·8 ± 1·3 ml./beat) and in right atrial pressure (from a mean of −0·3 to a mean of −2·3 mm Hg). Myocardial blood flow was not very different to that found in the first ('moderate haemorrhage') group. This is presumably because, at this pressure level, flow is just within the autoregulatory range; coronary vascular resistance was certainly substantially reduced (from 1·25 ± 0·07 to 0·96 ± 0·07 arbitrary units). The oxygen extraction coefficient was again raised and there was a slight increase in heart rate. At this blood pressure level there was, however, considerable electrocardiographic evidence of myocardial ischaemia: ST depression, often marked, occurred in all the animals. In three animals there were occasional nodal rhythms and ventricular extrasystoles.

Changes observed in acid-base balance included a marked increase in PCO_2 (Table 1) and a decrease in arterial pH. These were associated with a substantial metabolic acidosis, the arterial base excess falling from −2 ± 1 m-equiv/l. to −15 ± 2 m-equiv/l.

Changing to oxygen at 1 ATA and then at 2 ATA (Figs 4 and 5; Table 1) had little

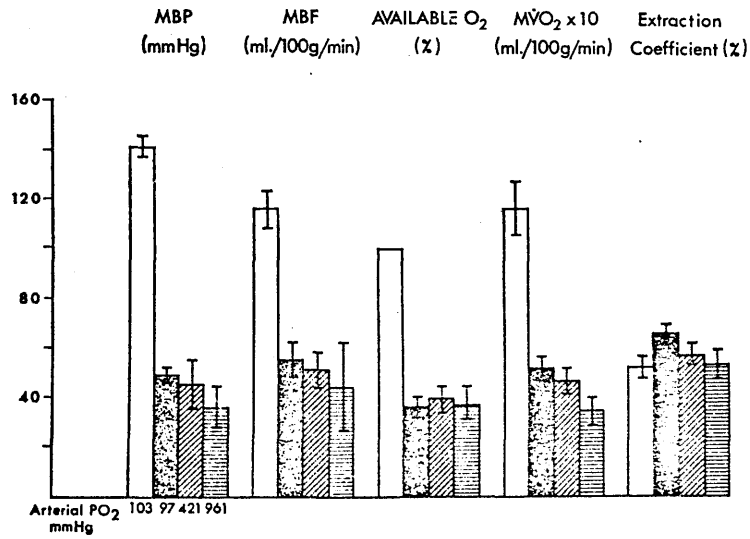

FIG. 4 *Changes in mean blood pressure, myocardial blood flow, oxygen availability and oxygen consumption and in myocardial oxygen extraction coefficient in normotensive dogs* (□), *and after severe haemorrhage breathing AIR* (stipple), *oxygen at normal pressure* (diagonal) *and oxygen at 2 ATA* (≡). *Values are means ± SE of the mean.*

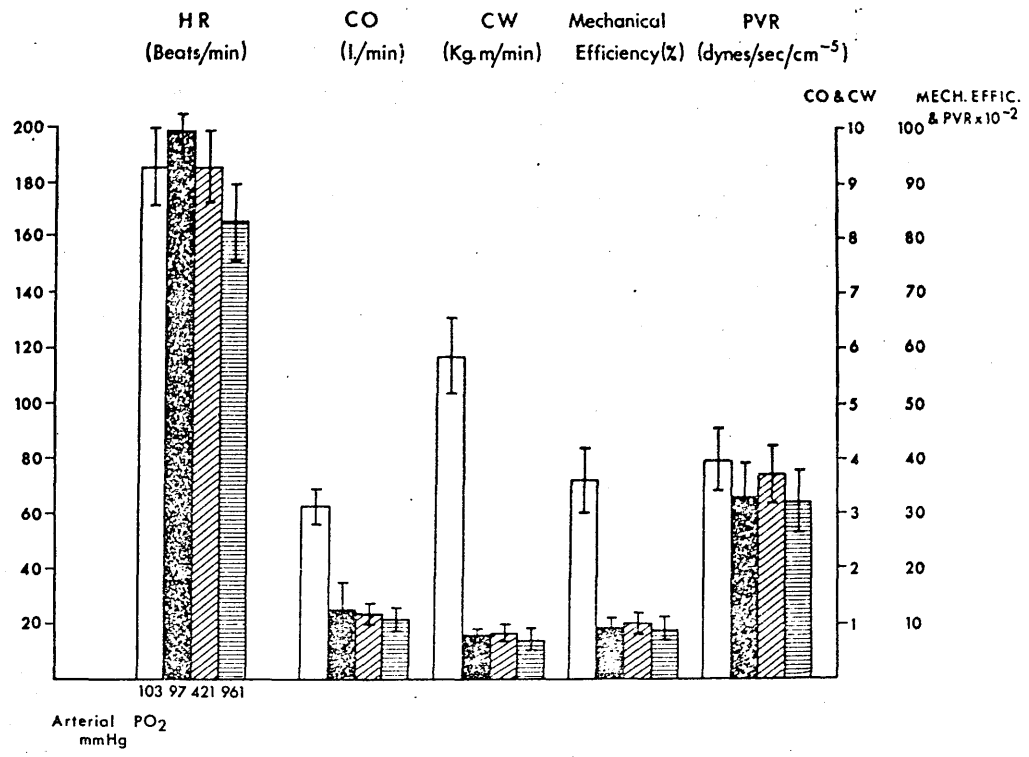

FIG. 5 *Changes in heart rate, cardiac output, external work and efficiency and in total peripheral vascular resistance in normotensive dogs* (□), *and after severe haemorrhage breathing AIR* (stipple), *oxygen at normal pressure* (diagonal) *and oxygen at 2 ATA* (▭). *Values are means ± SE of the mean.*

TABLE 2 *Cardiac output, total oxygen availability and consumption in moderate haemorrhage (mean ± SE of mean)*

	Cardiac output (ml./kg./min)	*Available oxygen (ml./kg/min)*	*Oxygen consumption (ml./kg/min)*
Control	145 ± 14	28·9 ± 3·7	5·0 ± 0·9
Haemorrhage (air)	48 ± 4	8·1 ± 1·1	4·0 ± 0·3
Haemorrhage (OHP)	48 ± 3	9·5 ± 1·0	3·2 ± 0·4
Haemorrhage (air)	54 ± 2	9·2 ± 0·7	4·6 ± 0·3
Retransfusion	89 ± 20	16·6 ± 3·7	4·8 ± 0·2

TABLE 3 *Cardiac output, total oxygen availability and consumption in severe haemorrhage (mean ± SE of mean)*

	Cardiac output (ml./kg/min)	*Available oxygen (ml./kg/min)*	*Oxygen consumption (ml./kg/min)*
Control	64 ± 4	12·8 ± 0·4	2·1 ± 0·2
Haemorrhage (air)	31 ± 3	4·7 ± 0·8	3·2 ± 0·2
Haemorrhage (oxygen)	31 ± 4	4·4 ± 0·6	3·1 ± 0·3
Haemorrhage (OHP)	29 ± 3	5·1 ± 0·6	2·9 ± 0·5

effect on blood pressure, myocardial flow, or cardiac function; the most marked effect was a substantial increase in coronary sinus P_{O_2} and oxygen content (Table 1) and, as in the 'moderate haemorrhage' group, a return of the extraction coefficient towards pre-haemorrhage levels. In a few of the animals there was a marked electrocardiographic improvement with OHP.

In an earlier study from this laboratory on dogs subjected to haemorrhagic shock, Clark (1966) had demonstrated that there was an increase in total oxygen consumption with hyperbaric oxygen. In view of this fact and our own finding that hyperbaric oxygen was associated with a reduction in myocardial oxygen consumption, total oxygen consumption was calculated. The changes in cardiac output, total oxygen availability, and total oxygen consumption produced by moderate and severe haemorrhage and by the subsequent administration of hyperbaric oxygen are indicated in Tables 2 and 3. In the moderate haemorrhage group, bleeding was associated with a 72% and 20% reduction in total oxygen availability and consumption.

Oxygen at 2 atmospheres produced a mean increase of 17% (8·1 to 9·5 ml./kg/min) in total oxygen availability during hypotension but total oxygen consumption fell by a further 20% (4·0 to 3·2 ml./kg/min). In the severe haemorrhage group, the same pattern of results was noted, except that total oxygen consumption after haemorrhage rose above the control values. This unexpected finding probably related to the low initial cardiac output in these animals.

Discussion

Because of the combination of decreased myocardial blood flow and decreased arterial oxygen content during severe haemorrhagic shock, the heart rapidly becomes hypoxic, suffers characteristic lesions (sub-endocardial haemorrhages and necrosis) and ultimately fails. Although one cannot of course ignore the deterioration of the peripheral circulation in shock, there is evidence (reviewed by Guyton and Crowell, 1961) that the heart itself is the primary and lethal deteriorative structure in the circulation. If this deterioration were due to hypoxia alone it is conceivable that simply raising the arterial oxygen content would act as a protective. It has, in fact, been demonstrated (Ratcliff *et al.*, 1967) that hyperbaric oxygen does decrease the incidence of subendocardial haemorrhage in dogs subjected to haemorrhagic shock. In the present experiments, haemorrhage was associated with substantial decrease in cardiac stroke and minute output, work, oxygen consumption, and mechanical efficiency. Administration of oxygen at 1 and 2 ATA did not substantially modify the function of the heart or of the peripheral circulation. There was no improvement in cardiac output or work and, in fact, a decrease occurred in myocardial oxygen consumption. This appeared to reflect changes occurring in other parts of the body. In the dogs subjected to moderate haemorrhage, hyperbaric oxygen increased the arterial oxygen content but this was not associated with an increase in myocardial oxygen availability (since myocardial blood flow fell) or with an increased myocardial extraction of oxygen. The coronary sinus P_{O_2} and oxygen content were substantially increased and one can only conclude that the heart was for some reason incapable of utilizing more oxygen. Although in high concentrations oxygen itself depresses cardiac function (Daniell and Bagwell, 1968), the most likely reason would appear to be severe metabolic acidosis which accompanied haemorrhage. This depresses myocardial contractility (Thrower, Darby, and Aldinger, 1961; Opie, 1965; Ng, Levy, and Zieske, 1967) and reduces the inotropic response to catecholamines (Thrower *et al.*, 1961; Ford, Cline, and Fleming, 1968). A different response to hyperbaric oxygen in haemorrhagic shock may well be seen if this metabolic acidosis were corrected.

A characteristic effect of hyperbaric oxygen, especially in the 'moderate haemorrhage' group, was a decrease in myocardial blood flow. Since systemic blood pressure was unaltered (Fig. 1), this means an increase in myocardial vascular resistance and, since the various indices of contractility and output were not substantially changed, this can be interpreted as resulting from myocardial vasoconstriction. It is well documented that 100% oxygen at 1 and at 2 ATA reduces coronary blood flow in normotensive open-chest dogs (Sobol, Wanlass, Joseph, and Azarshahy, 1962; Weglicki, Rubenstein, Entman, and McIntosh, 1966), in closed-chest dogs previously subjected to thoracotomy (Ratliff, Hackel, and Mikat, 1969) and in dogs without thoracotomy (Lammarant, De Schryver, Becsei and Mertens-Strijthagen, 1968; McBride and Ledingham, 1968; McBride, 1969). The present experiments demonstrate that, even when the perfusion pressure is low and the vessels dilated, hyperbaric oxygen is still capable of causing vasoconstriction and that further, this is readily reversed on returning to air breathing (Fig. 3). The surprising thing perhaps is the fact that hyperbaric oxygen was not, in these experiments, capable of improving myocardial oxygen availability. Any increase in arterial blood oxygen content was counteracted by a decrease in myocardial blood flow. Nevertheless, the oxygen was delivered to the heart at a higher than normal oxygen tension. Some myocardial cells, therefore, would be exposed to the high oxygen tension even although the mean tissue oxygen tension had not significantly altered. Moreover it would not be valid from these experiments alone to draw the conclusion that hyperbaric oxygen could not increase oxygen availability to the heart in other circumstances. For example, in the case reported by Amonic *et al.* (1969), the haemoglobin was so low (2·2 g/100 ml.) that the increase in dissolved oxygen obtained with hyperbaric oxygen could not fail but to have increased tissue oxygen availability. It could be, however, that the failure to demonstrate conclusively the value of hyperbaric oxygen in acute myocardial infarction (Cameron, Gibb, Ledingham, and

McGuinness, 1965), could be due to a failure to improve myocardial oxygen availability. If the vasoconstriction induced by oxygen could be counteracted – for example, by the use of coronary vasodilator drugs – it might indeed be possible substantially to increase tissue oxygen content in the developing infarct and therefore perhaps reduce infarct size.

Summary

Subjecting closed-chest dogs, anaesthetized with trichlorethylene, to both moderate and severe acute blood loss (to mean pressures of 70–75 and 45–50 mm Hg respectively) increased heart rate, total peripheral vascular resistance (in the 'moderate haemorrhage' group only) arterial PCO_2, and the myocardial oxygen extraction coefficient and decreased arterial base excess, cardiac output, work, efficiency and myocardial blood flow, oxygen consumption and availability. The administration of oxygen at 2 ATA (OHP) such that the arterial oxygen tension was raised from 95–97 mm Hg to 961–1069 mm Hg, failed significantly to alter the output, work, or efficiency of the heart. There was a further decrease in myocardial blood flow and an increase in myocardial vascular resistance such that myocardial oxygen availability, despite the enormous increase in arterial oxygen tension, was unaltered. Any increase in arterial blood oxygen content was thus counteracted by a decrease in blood flow, due, presumably, to a direct effect of oxygen on myocardial vascular smooth muscle. These effects on the myocardial circulation were reversed when the dogs were returned to air-breathing.

We wish to thank the Medical Research Council for generous financial support.

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Chapter 9

Myocardial vascular and metabolic responses to hypoxia and hypercapnia during hypothermia (26°C)

In the third of the three chapters dealing with the heart, the myocardial vascular and metabolic responses to hypoxia and hypercapnia at normal body temperature and in the cooled state were compared.

Previous studies (Chapter 7 and Ledingham et al, 1970) showed that both hypoxia and hypercapnia produced marked increases in myocardial blood flow in the normothermic dog. Similar responses have been described at reduced temperature (Berne, 1954; Cross, Rieben and Salisbury, 1962) but the precise relationship between arterial PO_2 and PCO_2, and myocardial blood flow has not been established. This information together with related metabolic data may have clinical relevance in resuscitation of the hypothermic patient who shows evidence of cardiorespiratory insufficiency. The opportunity was taken to examine the effect of hypothermia on pulmonary oxygen transport.

Material and Methods (3/4/68 - 30/5/68; 10/1/72, 17/1/72, 20/1/72)

Anaesthesia was induced in a total of 13 adult mongrel dogs (weight - 19.5 $\pm$ 2.8 kg: mean $\pm$ standard error of the mean)

with a 2.5% solution of thiopentone sodium administered intravenously (usually 20 mg/kg). After endotracheal intubation, intermittent positive pressure ventilation (IPPV) was established using a Palmer respiratory pump, the stroke volume of which was adjusted to maintain arterial carbon dioxide tension between 35 and 45 mm Hg under control conditions at normothermia; the ventilation rate was kept constant. Reflex movement was prevented by the intramuscular administration of intermittent (100 mg) doses of suxamethonium. Anaesthesia was maintained with trichlorethylene (0.5 - 1.0% vaporized from a Tritec vaporizer (Cyprane Ltd.) in a mixture of nitrogen and oxygen, the proportions of which were adjusted so that under control conditions at normothermia the arterial oxygen tension was between 85 and 105 mm Hg. This was facilitated by monitoring the inspired oxygen concentration with a paramagnetic oxygen analyser (Servomex OA101 Mk II, Servomex Controls, Crowborough, Sussex). The animal's temperature was recorded routinely from the midoesophagus and occasionally also from the rectum using direct recording thermocouples.

Catheters were inserted into the descending aorta and into the right atrium via the femoral vessels for pressure recording and blood sampling. Arterial and right atrial pressures, central aortic dp/dt and lead two of the electrocardiogram (ECG) were

recorded on a multi-channel ink jet recorder (Elema-Schönander Mingograph 81), in addition to being continuously visible on an oscilloscope.

Myocardial blood flow was measured using the ^{133}Xenon clearance technique described in detail in chapter 7. Arterial, coronary sinus and mixed venous oxygen and carbon dioxide tensions and pH were measured using appropriate electrode systems, calibrated as previously described; all blood gas values were corrected to normal body temperature. Lactate, pyruvate and glucose concentrations were measured using standard techniques.

The following data were dervied:

1. Myocardial oxygen availability (ml/100g/min) = arterial oxygen content (ml/100ml) x myocardial blood flow (ml/100g/min).

2. Myocardial oxygen extraction (%) =

$$\frac{\text{arterial-coronary sinus oxygen content (ml/100ml)} \times 100}{\text{arterial oxygen content (ml/100ml)}}$$

3. Myocardial oxygen consumption (ml/100g/min) = myocardial blood flow (ml/100g/min) x arterial-coronary sinus oxygen content (ml/100ml).

4. Coronary vascular resistance (arbitrary units) =

$$\frac{\text{diastolic arterial blood pressure (mm Hg)}}{\text{myocardial blood flow (ml/100g/min)}}$$

5. Myocardial lactate and pyruvate extraction were measured as for 2. with lactate and pyruvate substituted for oxygen.
6. Myocardial lactate and pyruvate consumption were measured as for 3. with lactate and pyruvate substituted for oxygen.
7. Total oxygen extraction (%) = arterial oxygen content (ml/100ml) minus mixed venous oxygen content (ml/100ml)/ arterial oxygen content (ml/100ml).
8. Alveolar-arterial oxygen tension difference (using the alveolar air equation to calculate alveolar oxygen pressure and assuming r = 0.8).

After completion of the appropriate series of measurements at normothermia (mean duration - 3.9 hours, range 3 - 5 hours), hypothermia was induced by immersing the animal in a bath of iced water at 4 deg C. Anaesthesia was discontinued soon after the animal entered the iced water. Cooling lasted 59 minutes (range 30 - 90 minutes), after which the animal was removed from the bath (mean mid-oesophageal temperature - 29.2 deg C, range 26.3 - 30.9 deg C). The mid-oesophageal temperature fell further to a mean of 26.4 deg C (range 24.7 - 28.4 deg C). Rectal temperature was as much as 2 deg C higher than mid-oesophageal during cooling although rarely more than 0.5 deg C higher when hypothermia became stable. The position of the intravascular

catheters was checked by fluoroscopy after cooling and a further series of measurements made.

Hypoxaemia was induced by rapidly decreasing the inspired oxygen fraction (F_IO_2) to a mean of 0.095 at normothermia (six animals) and a mean of 0.076 at hypothermia (seven animals). Hypoxaemia was sustained for an average of 21 minutes (range 12 - 35 minutes) at normothermia and an average of 32 minutes (range 15 - 54 minutes) at hypothermia. Hypercapnia was induced both at normothermia (seven animals) and at hypothermia (11 animals) by rapidly adding carbon dioxide to the inspired gas mixture, the actual concentration (varying between 10 and 15%) being monitored on an infra-red carbon dioxide analyser (URAS4, Hartmann and Braun). Throughout the period of hypercapnia, which was sustained for 15 minutes (range 9 - 35 minutes) at normothermia and for 34 minutes (range 16 - 105 minutes) at hypothermia, the inspired oxygen concentration was adjusted so that the arterial oxygen tension remained between 80 and 110 mm Hg. The shorter period of hypercapnia at normothermia was determined by data obtained in an earlier study (Ledingham et al, 1970) showing that myocardial blood flow returned towards control values even when arterial carbon dioxide tension remained elevated. The upper and lower limits of hypoxaemia and hypercapnia were determined by myocardial blood flow responses described in

previous studies (chapter 7 and Ledingham et al, 1970).

In three additional animals the haemodynamic and metabolic effects of hypothermia without prior hypoxia and hypercapnia were determined. Measurements were also made of cardiac output by dye dilution (indocyanine green) with a Waters densitometer (XP-302) and left ventricular pressure via a number 8 Sones catheter inserted through the carotid artery. The rate of change of left ventricular pressure with time (dp/dt) was obtained by means of an Elema Schönander differentiator circuit. Blood volume was measured using I125 serum albumen (Amersham, England) with samples taken at five, 10 and 20 minutes post-injection and counted in a "blood volume computer" (D.A. Pitman, Weybridge, Surrey, England). Arterial and coronary sinus free fatty acids were measured using the Boehringer combination set.

Physiological dead space was calculated using the equation:

$$V_D = (PaCO_2)\ VE/PaCO_2$$

Expired gas was collected over a 20 minute period in a Douglas bag and the volume measured with a dry gas meter (Parkinson Cowan). Prolonged hypoxaemia (70 min) was induced in one of the animals and prolonged hypercapnia (34 and 70 minutes) in the other two during the later stages of hypothermia. The data from these animals were not included in the statistical analyses

of data of the main series although changes similar to those observed in the main series occurred.

RESULTS

The Effect of Hypothermia

The effect of surface cooling to a mean mid-oesophageal temperature of 26.4 deg C on systemic and coronary haemodynamic values is illustrated in Fig. 9.1. The normothermic data were taken immediately before cooling commenced and therefore followed an episode of either hypoxaemia or hypercapnia although time was given for the animal to make a complete haemodynamic recovery from these procedures. The 'initial cooled' set of hypothermic data were taken within 30 minutes of cessation of active cooling with the exception of three animals in which the recordings were made within 60 minutes. The 'subsequent cooled' data refer to measurements made from 20 to 90 minutes after the first series. There were significant falls in heart rate (30% - $p < 0.001$), mean arterial pressure (11% - $p < 0.05$) and aortic dp/dt (41% - $p < 0.05$). Myocardial blood flow fell from 103 $\pm$ 6 ml/100g/min to 60 $\pm$ 6 ml/100g/min (by 41% - $p < 0.001$) and coronary vascular resistance rose by 62% ($p < 0.001$). Right atrial pressure was not significantly altered by cooling.

In the three additional animals (Table 9.1), cardiac output fell

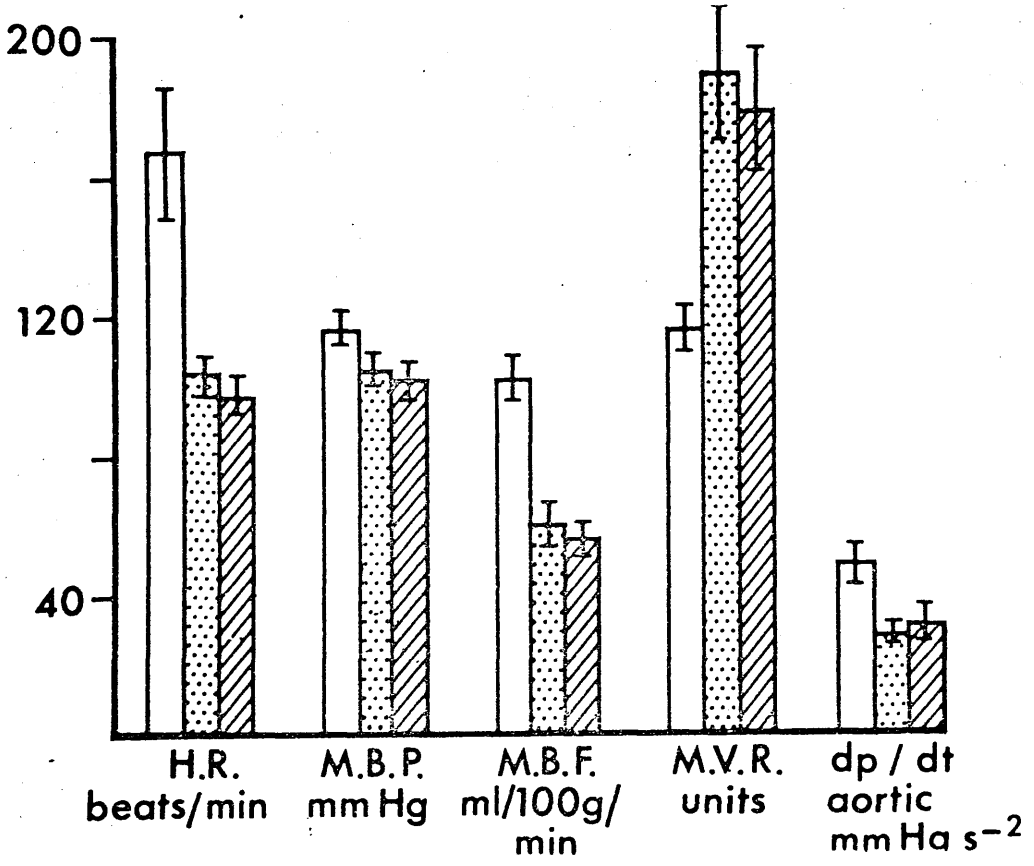


Figure 9.1. Effect of hypothermia on systemic and coronary haemodynamic values (mean ± S.E.); open columns - normothermic data, dotted columns - 'initial cooled' data; diagonal columns - 'subsequent cooled' data.

Table 9.1 Systemic and coronary haemodynamic values in the three additional animals

Additional dogs	Temp °C	HR beats/ min	MBP mmHg	CO L/min	SV ml	Cardiac work kgm/min	Cardiac Efficiency ml/100g/min	PVR dynes/ sec/ cm^{-5}	LV dp/dt mmHg/ sec	Aortic dp/dt mmHg/ sec^{-2}	LVP mmHg	BV l
1	37.0	200	145	2.0	10.1	4.0	15	5,800	3,400	1,500	175/ 0.0	2.0
	25.5	100	60	0.6	6.3	0.5	9	8,000	1,300	250	70/ 0.0	1.6
2	37.2	165	145	1.4	8.6	2.8	12	8,285	-	-	-	1.8
	26.0	95	100	0.7	7.2	0.9	16	11,429	-	-	-	1.5
3	37.0	150	115	2.5	16.6	3.9	18	3,680	2,500	1,000	150/ 2.5	2.1
	25.7	96	99	0.6	6.0	0.8	7	13,200	1,700	500	124/ 2.5	1.7

HR heart rate
MBP mean blood pressure
CO cardiac output
PVR peripheral vascular resistance
LVP left ventricular pressure
BV blood volume

by between 50 and 75% with a consistent fall in heart rate and a variable fall in stroke volume. The increase in total peripheral resistance was moderate to marked. Left ventricular dp/dt fell from 3,400 and 2,500 to 1,300 and 1,700 mm Hg/second respectively in two of the additional animals with no change in left ventricular end-diastolic pressure; (these together indicate a reduction in left ventricular contractility). Cardiac work fell substantially in all three animals and cardiac efficiency in two.

Arterial and coronary sinus blood gas and pH values at normothermia and hypothermia are indicated in table 9.2. Because of an anticipated fall in arterial oxygen tension (independent of in vitro temperature changes), the inspired oxygen fraction (F_IO_2) was increased from 0.23 $\pm$ 0.02 at normothermia to 0.34 $\pm$ 0.04 at hypothermia. Thus although there was no significant change in arterial oxygen tension with hypothermia the alveolar-arterial oxygen tension difference rose from 26 $\pm$ 7 mm Hg at normothermia to 77 $\pm$ 18 mm Hg at hypothermia ($p < 0.001$). The fall in arterial carbon dioxide tension accounted entirely for the change in arterial pH, the non-respiratory component of acid-base balance remaining unaltered. The coronary sinus PO_2 fell from 32 $\pm$ 1 to 15 $\pm$ 1 mm Hg but this represented a decrease in oxygen content

Table 9.2 Arterial and coronary sinus blood gas and pH values

a. NORMOTHERMIA (FIO_2 - 0.23)

	Arterial	Coronary sinus
oxygen tension (mmHg)	105 ± 5	32 ± 1
Oxygen content (ml/100ml)	21.4 ± 1.0	11.2 ± 1.0
carbon dioxide tension (mmHg)	39 ± 1	53 ± 1
pH (units)	7.35 ± 0.01	7.32 ± 0.01
base excess (meq/L)	-4 ± 1	-

b. HYPOTHERMIA (FIO_2 - 0.34)

	Arterial	Coronary sinus
oxygen tension (mmHg)	113 ± 10	15 ± 1
oxygen content (ml/100ml)	21.9 ± 1.0	10.3 ± 1.2
carbon dioxide tension (mmHg)	24 ± 1	35 ± 2
pH (units)	7.48 ± 0.02	7.40 ± 0.03
base excess (meq/L)	-4 ± 1	-

of only 0.9 ml/100ml. Dead space ventilation was increased from 16 to 34% in the three additional animals. Hypothermia per se did not produce a significant alteration in haemoglobin or packed cell volume. Blood volume estimations revealed decreases of from 17 to 20% (Table 9.1).

Myocardial oxygen availability fell from 21.9 ± 1.1 ml/100g/min to 12.5 ± 1.3 ml/100g/min (by 43% - $p < 0.001$) after cooling, myocardial oxygen extraction did not change significantly from the control value of 48% and myocardial oxygen consumption fell from 10.3 ± 0.7 ml/100g/min to 7.1 ± 0.8 ml/100g/min (by 31% - $p < 0.01$). Whole body oxygen extraction did not change significantly; in the three animals in which cardiac output measurements were made, whole body oxygen consumption fell by 73% in each case.

Both arterial and coronary sinus lactate and pyruvate values fell with hypothermia (Table 9.3) but only the fall in arterial pyruvate was statistically significant ($p < 0.001$). The rise in arterial blood glucose was small but significant ($p < 0.05$); the high value of glucose in arterial blood at normothermia immediately prior to cooling was consequent on the earlier episodes of either hypoxaemia or hypercapnia (the first control value for arterial

Table 9.3 Arterial and coronary sinus lactate, pyruvate and glucose

Normothermia	Arterial	Coronary sinus
lactate (mg/100ml)	20.5 ± 3.7	15.9 ± 3.3
pyruvate (mg/100ml)	1.5 ± 0.2	0.9 ± 0.1
glucose (mg/100ml)	129 ± 14	123 ± 14
Hypothermia		
lactate (mg/100ml)	17.3 ± 2.9 NS	15.7 ± 2.6 NS
pyruvate (mg/100ml)	0.8 ± 0.2 $P < 0.001$	0.8 ± 0.2 NS
glucose (mg/100ml)	154 ± 12 $P < 0.05$	151 ± 12 NS

blood glucose was 105 ± 5 ml/100ml). Extraction and consumption of lactate and pyruvate by the myocardium fell but again only the pyruvate changes were significant (Fig. 9.2). No consistent consumption of glucose by the myocardium was demonstrable either at normothermia or at hypothermia. In the three additional animals, hypothermia of between one and two hours duration had no effect either on the absolute values of arterial glucose or on myocardial glucose consumption. Arterial free fatty acids showed no change in one and rose slightly in the other two of the three animals while fatty acid consumption fell from 36 and 47 millimicromoles/100g/min to 10 and 20 millimicromoles 100g/min respectively at hypothermia with no change in the remaining animal.

In nine animals, the repeat series of haemodynamic (Fig. 9.1) and metabolic measurements made after the first series at hypothermia showed no consistent alteration in any of the variables.

ECG Effects of Hypothermia

The mean change which occurred in the various components of the ECG are illustrated in Fig. 9.3. Myocardial conductivity was uniformly and progressively depressed during hypothermia and the PR, QRS and QT_c (QT interval corrected for heart rate)

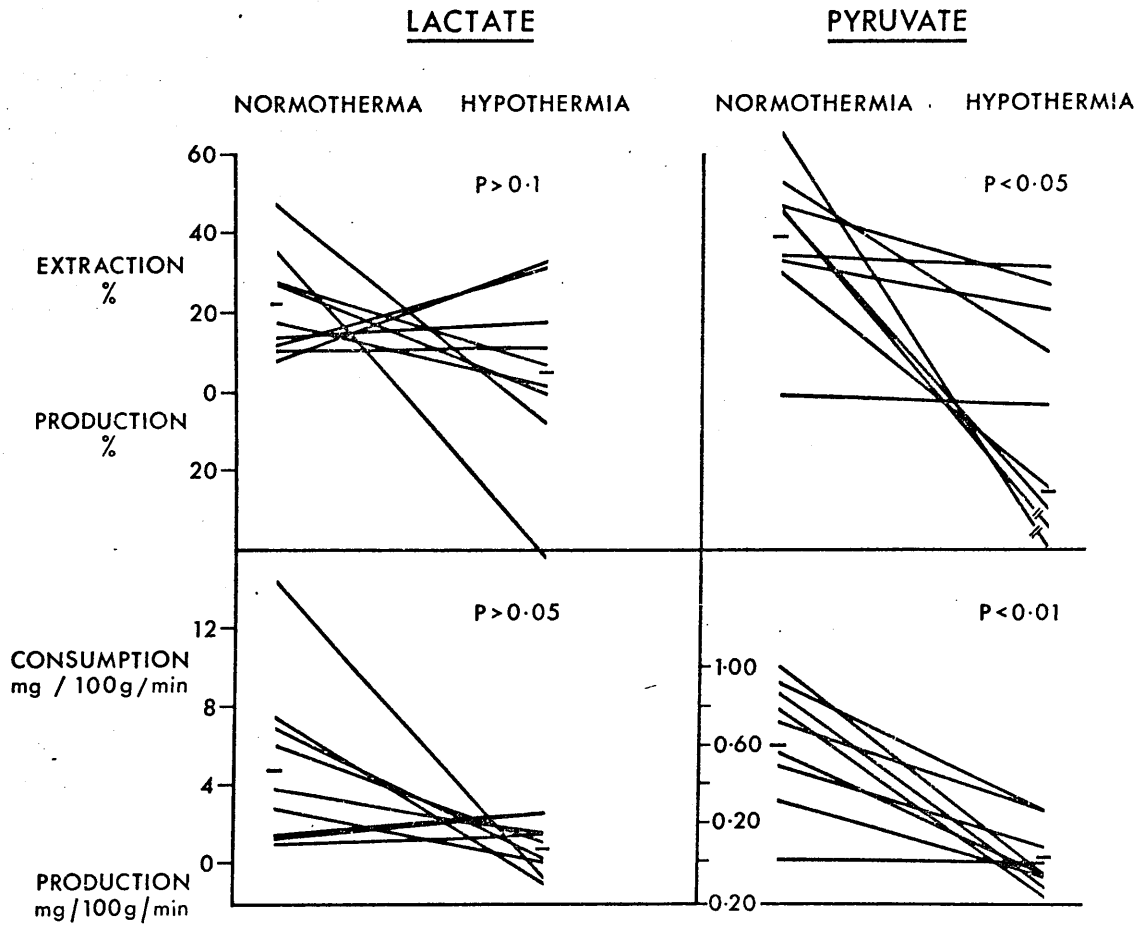


Figure 9.2. Extraction, consumption and production of lactate and pyruvate at normothermia and hypothermia; bars represent means.

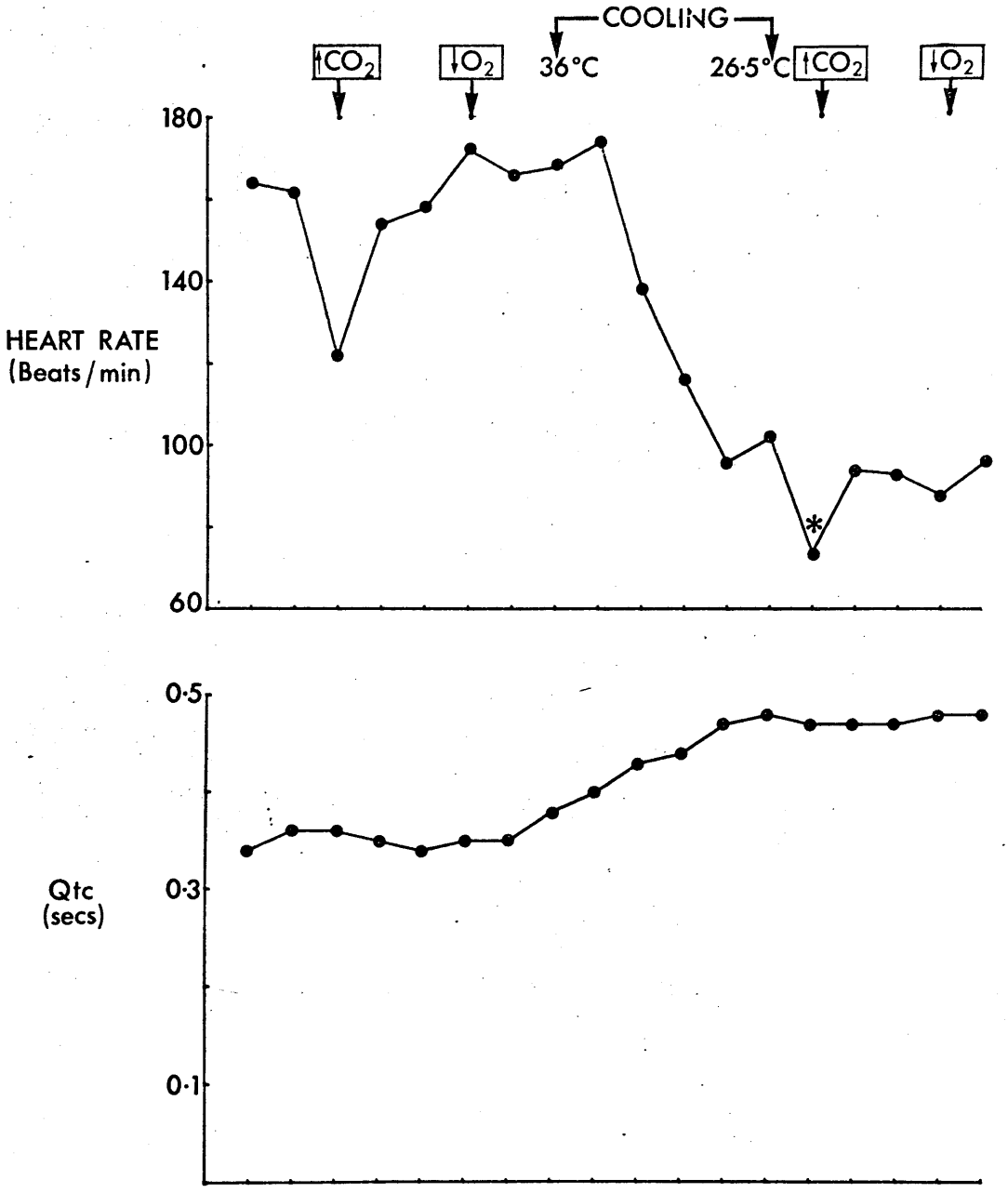


Figure 9.3a. Changes in components of ECG during cooling and in response to hypoxia and hypercapnia at normothermia and hypothermia; asterisks indicate significant differences from preceding or subsequent value.

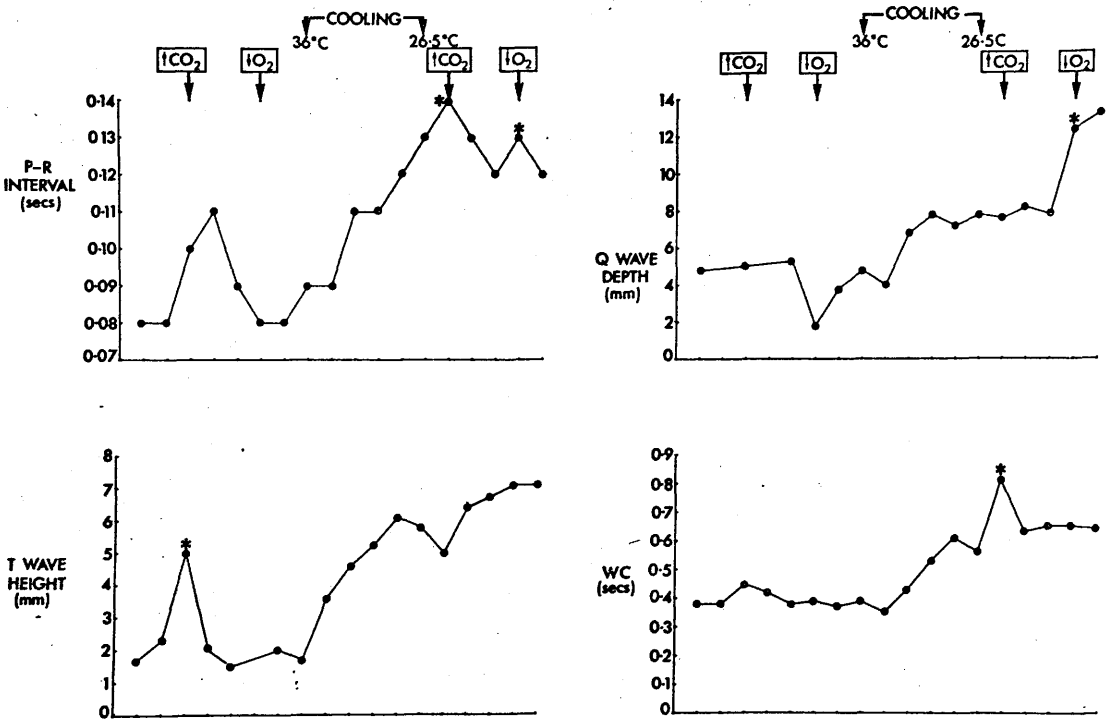


Figure 9.3b. Changes in components of ECG during cooling and in response to hypoxia and hypercapnia at normothermia and hypothermia; asterisks indicate significant differences from preceding or subsequent value.

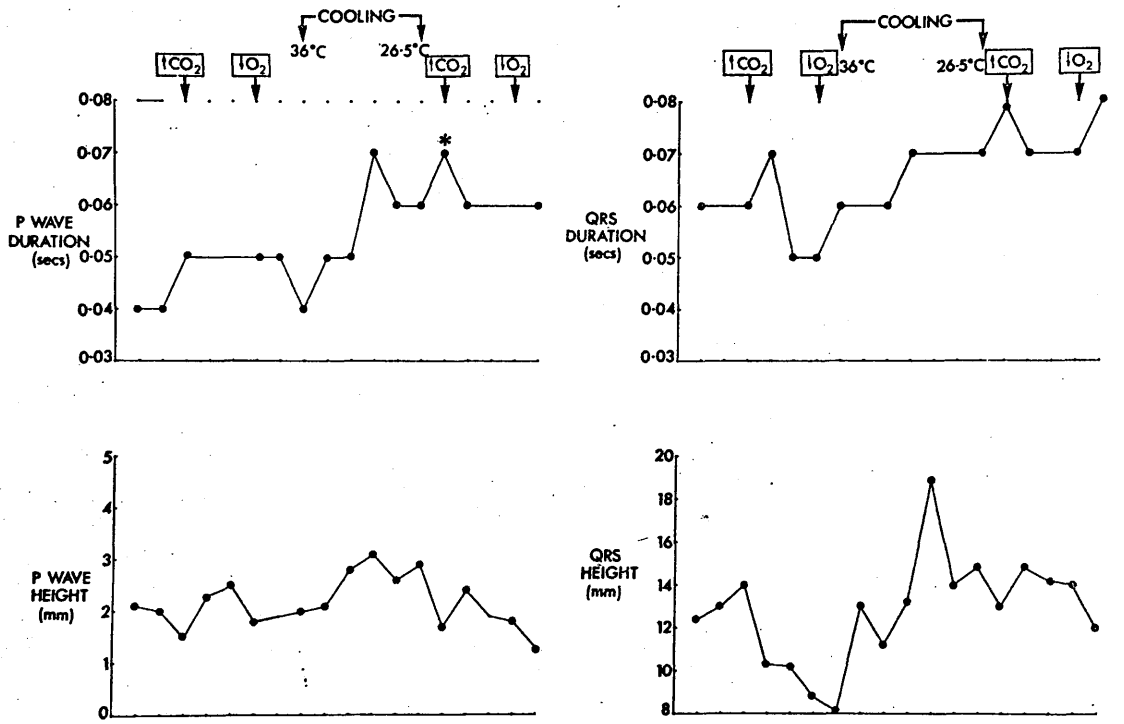


Figure 9.3c. Changes in components of ECG during cooling and in response to hypoxia and hypercapnia at normothermia and hypothermia; asterisks indicate significant differences from preceding or subsequent value.

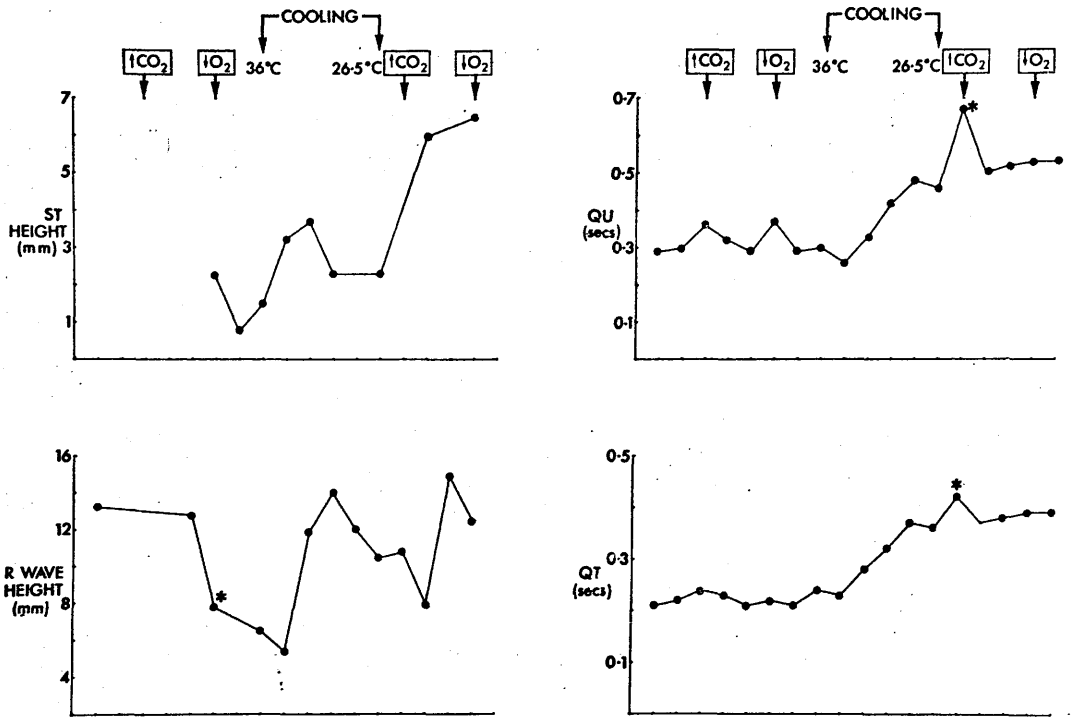


Figure 9.3d. Changes in components of ECG during cooling and in response to hypoxia and hypercapnia at normothermia and hypothermia; asterisks indicate significant differences from preceding or subsequent value.

intervals were all prolonged. The amplitudes of the atrial and ventricular action potentials, on the other hand, were little altered. A definite junctional ("J") wave was seen on only three occasions. Dysrhythmias attributable to hypothermia were noted on seven occasions (regularly occurring ventricular extrasystoles - four animals; junctional rhythm - three animals).

The Effect of Hypoxia at Normothermia and Hypothermia

Arterial oxygen tension fell from 108 $\pm$ 2 to 30 $\pm$ 2 mm Hg during hypoxia at normothermia (Fig. 9.4a). There was an associated maximal increase in myocardial blood flow of 24% ($p < 0.001$) and decrease in coronary vascular resistance of 14% (N.S.). The corresponding heart rate, aortic dp/dt, right atrial pressure and mean arterial blood pressure did not change significantly. At hypothermia (Fig. 9.4b) arterial oxygen tension fell from 113 $\pm$ 8 mm Hg to 21 $\pm$ 4 mm Hg during hypoxia. There was an associated maximal increase in myocardial blood flow of 53% ($p < 0.02$) and decrease in coronary vascular resistance of 37% ($p < 0.05$). The decrease in heart rate of 20 beats/min and arterial blood pressure of 12 mm Hg were not significant. Restoration of arterial oxygen tension to normal at hypothermia was associated with return to control haemodynamic values but at normothermia myocardial blood flow, mean arterial blood

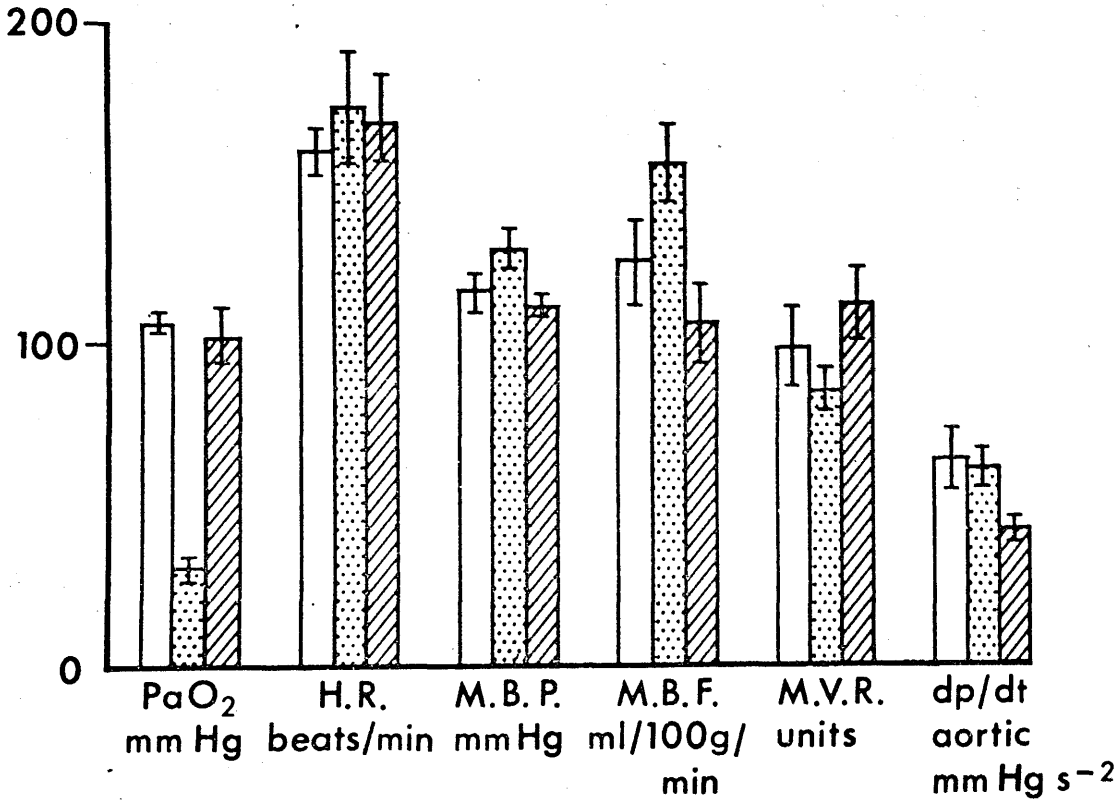


Figure 9.4a. Changes in systemic and coronary haemodynamic values in response to hypoxia at normothermia; open columns - prehypoxia, dotted columns - hypoxia, diagonal columns - posthypoxia.

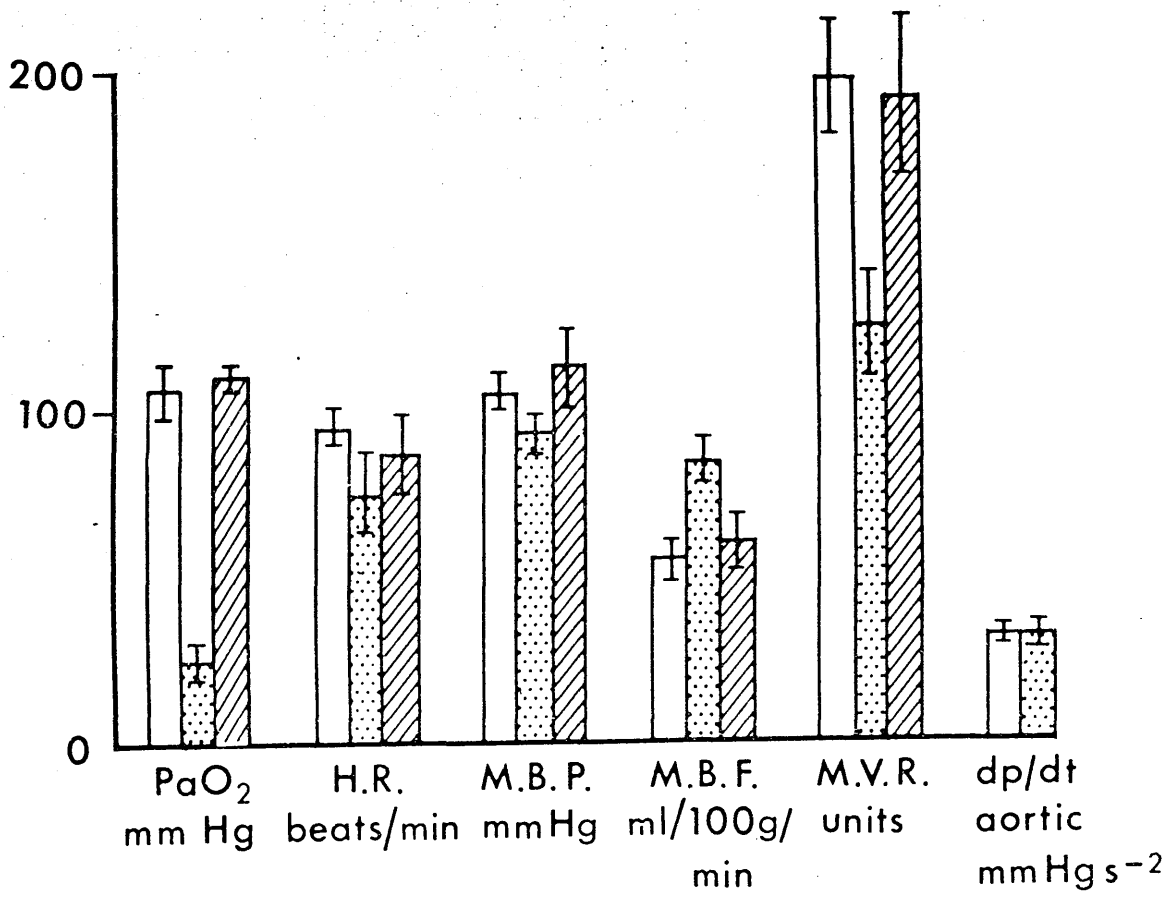


Figure 9.4b. Changes in systemic and coronary haemodynamic values in response to hypoxia at hypothermia; key as for 9.4a.

pressure and aortic dp/dt tended to be below control values. Two differences in the pattern of myocardial blood flow response to hypoxia at the two temperatures were noted (Fig. 9.5).

1) The interval between the onset of hypoxia and the occurrence of peak flow was a mean of 11 minutes (range 5 - 20 minutes) at normothermia and 18 minutes (range 7 - 39 minutes) at hypothermia.

2) The absolute arterial oxygen tension producing peak flow response was 30 $\pm$ 2 mm Hg at normothermia and 21 $\pm$ 4 mm Hg at hypothermia (corresponding to inspired oxygen fractions of 0.095 and 0.076 respectively).

At both temperatures myocardial blood flow remained elevated throughout hypoxia. Two of the hypothermic series showed an early transient fall in flow in response to hypoxia.

Myocardial oxygen availability fell by 31% ($p < 0.01$) and extraction rose from 39 $\pm$ 2 to 63 $\pm$ 5% ($p < 0.01$) during hypoxia at normothermia; myocardial oxygen consumption did not change significantly. Myocardial oxygen availability, extraction and consumption were not significantly altered during hypoxia at hypothermia. Coronary sinus oxygen tension and content fell markedly at normothermia and less so at hypothermia

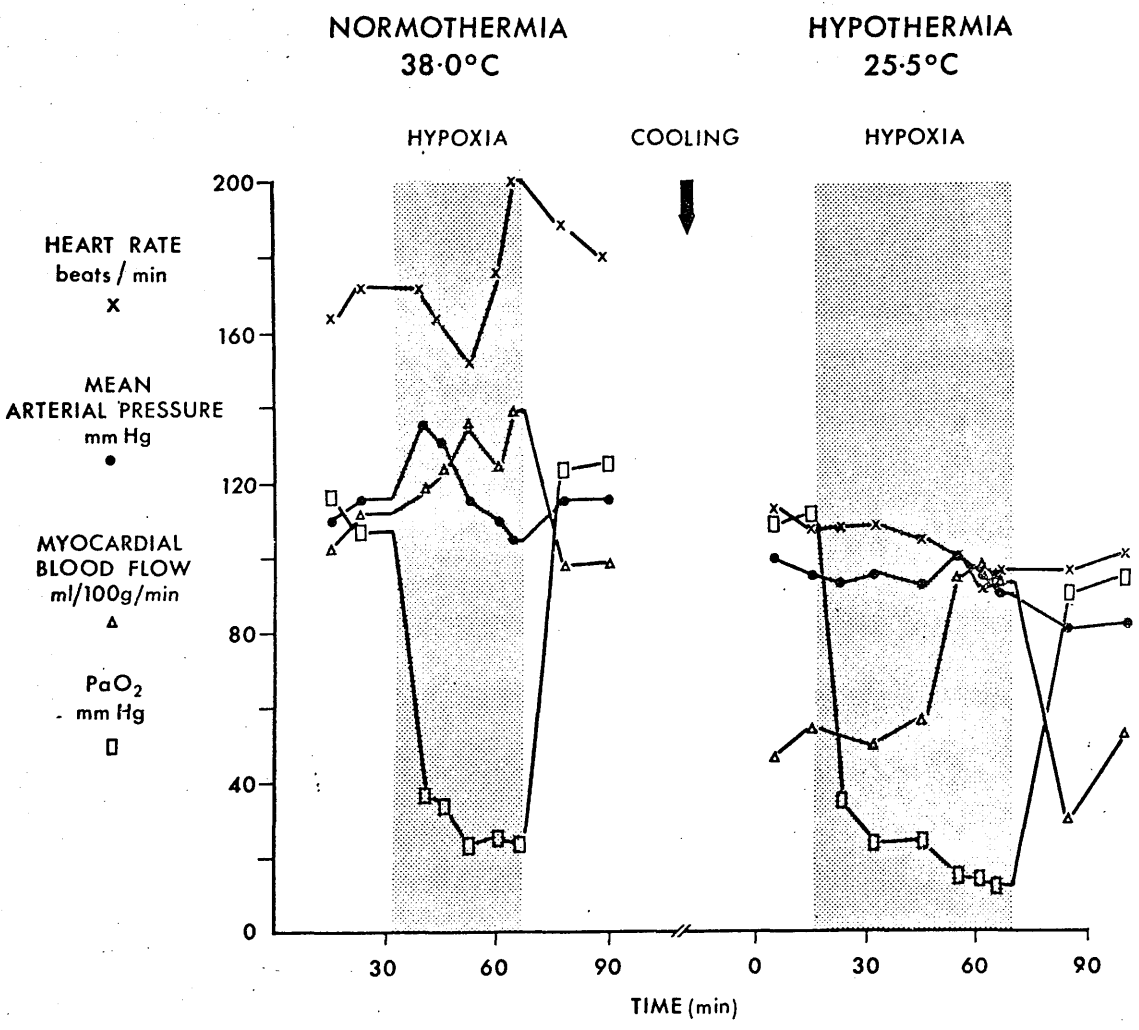


Figure 9.5. Heart rate, mean arterial pressure and myocardial blood flow changes in response to hypoxia at normothermia and hypothermia in a single animal.

(Fig. 9.6). During hypoxia there were no significant changes in arterial pH, PCO_2 or base excess either at normothermia or hypothermia.

Arterial lactate rose by 5 and 6 mg/100ml during hypoxia at normothermia and hypothermia respectively but only the former was a significant rise ($p < 0.05$). Arterial pyruvate and glucose also rose but not significantly. Myocardial lactate extraction fell significantly ($p < 0.01$) during hypoxia at normothermia but lactate consumption did not change. No significant change occurred in myocardial consumption of any of the substrates measured during hypoxia at hypothermia even when the hypoxia was sustained for over one hour.

ECG Effect on Hypoxia

Disturbances of the ECG pattern at normothermia included junctional rhythm (three animals), ventricular extrasystoles (four animals) and ST-T wave abnormalities (three animals). At hypothermia junctional rhythm was not observed in response to hypoxia but ventricular extrasystoles were common (six animals) and ST-T wave abnormalities were also noted (three animals).

Effect of Hypercapnia at Normothermia and Hypothermia

Arterial carbon dioxide tension rose from 40 $\pm$ 1 mm Hg to

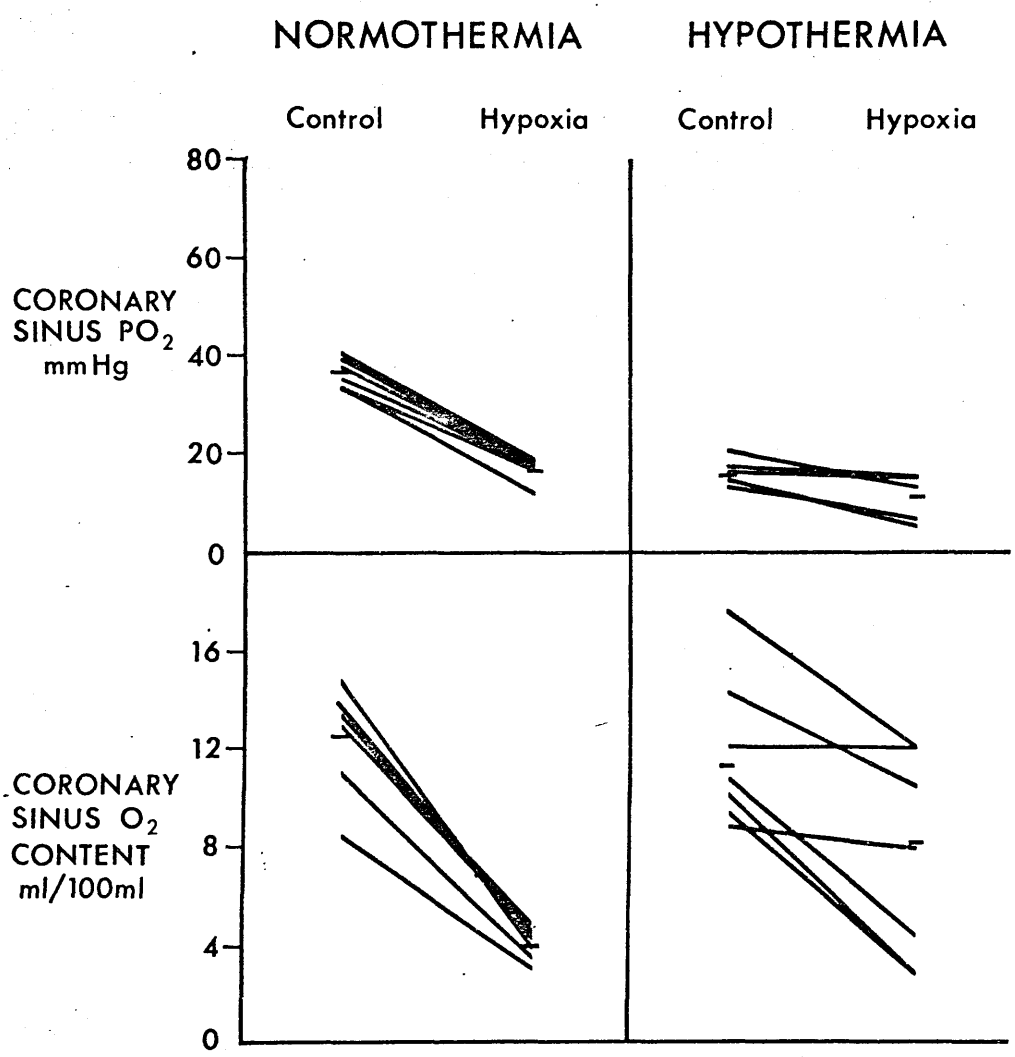


Figure 9.6. Coronary sinus PO2 and oxygen content changes in response to hypoxia at normothermia and hypothermia; bars indicate means.

95 ± 5 mm Hg during hypercapnia at normal body temperature (Fig. 9.7a). There was an associated maximal increase in myocardial blood flow of 32% ($p < 0.02$) and decrease in coronary vascular resistance of 25% ($p < 0.01$). Heart rate, arterial blood pressure and aortic dp/dt did not change significantly but right atrial pressure rose from -1.6 ± 0.7 mm Hg to +0.4 ± 1.1 mm Hg ($p < 0.01$). At hypothermia (Fig. 9.7b) arterial carbon dioxide tension rose from 25 ± 1 mm Hg to 77 ± 4 mm Hg during hypercapnia. There was an associated maximal increase in myocardial blood flow of 69% ($p < 0.001$) and fall in coronary vascular resistance of 37% ($p < 0.001$). Heart rate fell by a mean of 16 beats/min ($p < 0.01$). Arterial blood pressure, aortic dp/dt and right atrial pressure were not significantly affected. Within 20 to 30 minutes of withdrawal of the added carbon dioxide the haemodynamic values had returned to normal.

Four differences in the pattern of myocardial response to hypercapnia at the two temperatures were noted:

1) The interval between the onset of hypercapnia and peak flow was a mean of six minutes (range 3 - 10 minutes) at normothermia and 14 minutes (range 3 - 25 minutes) at hypothermia.

2) The response to sustained elevation of PCO_2 varied in

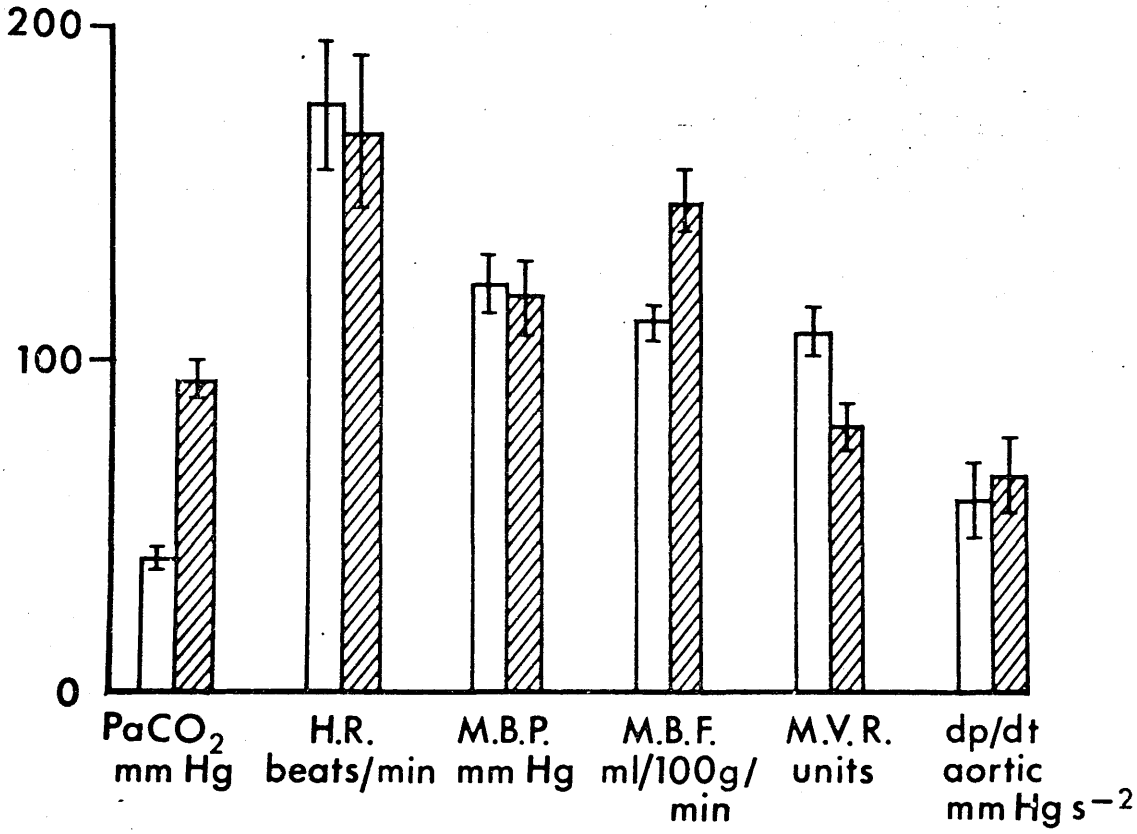


Figure 9.7a. Changes in systemic and coronary haemodynamic values in response to hypercapnia at normothermia; open columns - prehypercapnia, diagonal columns - hypercapnia

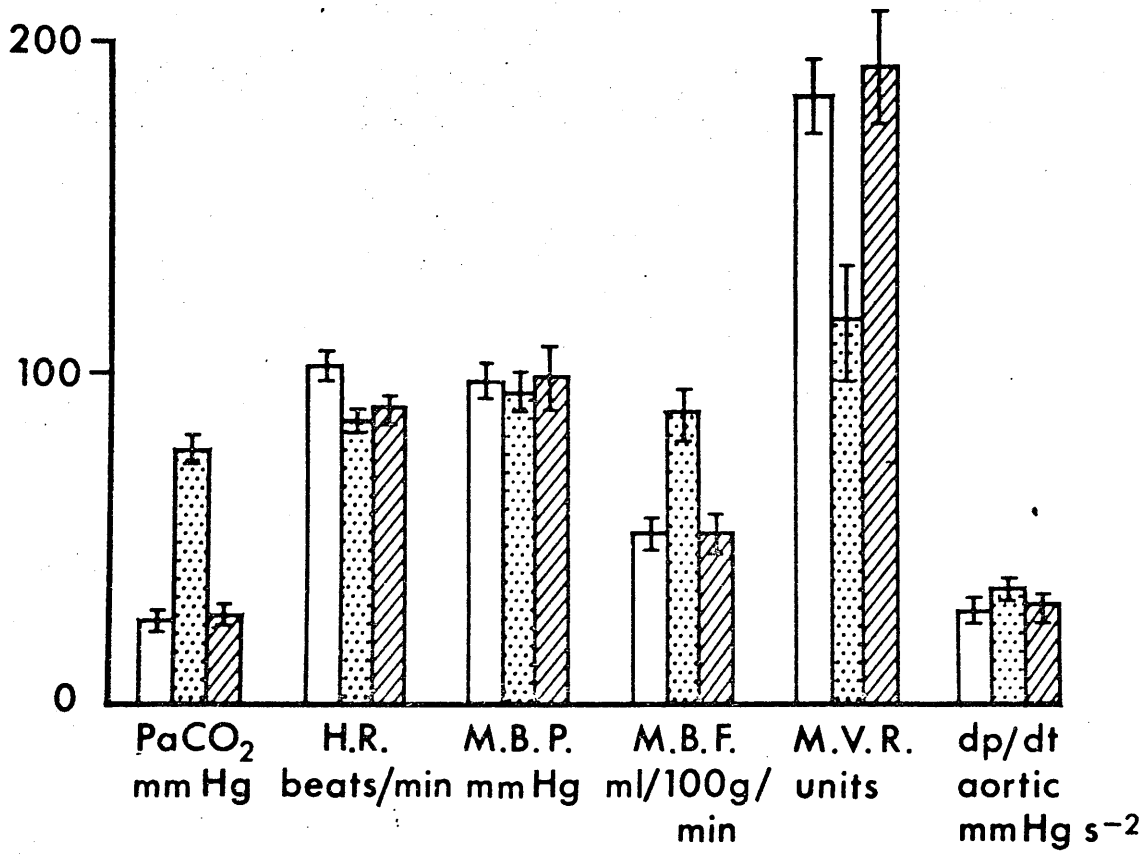


Figure 9.7b. Changes in systemic and coronary haemodynamic values in response to hypercapnia at hypothermia; open columns - prehypercapnia, dotted columns - hypercapnia, diagonal columns - posthypercapnia.

that at normothermia myocardial blood flow fell rapidly towards control values after peak flow, while at hypothermia myocardial blood flow remained high for prolonged periods after peak flow (Fig. 9.8).

3) The absolute $PaCO_2$ level related to peak flow at normothermia was 95 ± 5 mm Hg and at hypothermia was 77 ± 25 mm Hg. The control $PaCO_2$ levels in each situation of course differed significantly. In four animals, increases in $PaCO_2$ at hypothermia above that producing peak flow response resulted in a fall of myocardial blood flow. In two, the falls were severe and associated with supraventricular bradycardia and hypotension; in one of these sudden ventricular fibrillation occurred.

4) In four of the animals at hypothermia a transient fall in myocardial blood flow was observed in the first few minutes after elevation of $PaCO_2$ (Fig. 9.9). This effect was not seen in any of the animals at normothermia.

Myocardial oxygen availability increased during hypercapnia at both temperature levels although proportionately more at hypothermia (70% - $p < 0.001$ and 35% - $p < 0.02$) because of the greater increase in myocardial blood flow. Myocardial oxygen extraction fell significantly at both temperatures ($p < 0.05$ (n) $p < 0.01$ (h); oxygen consumption was not significantly altered

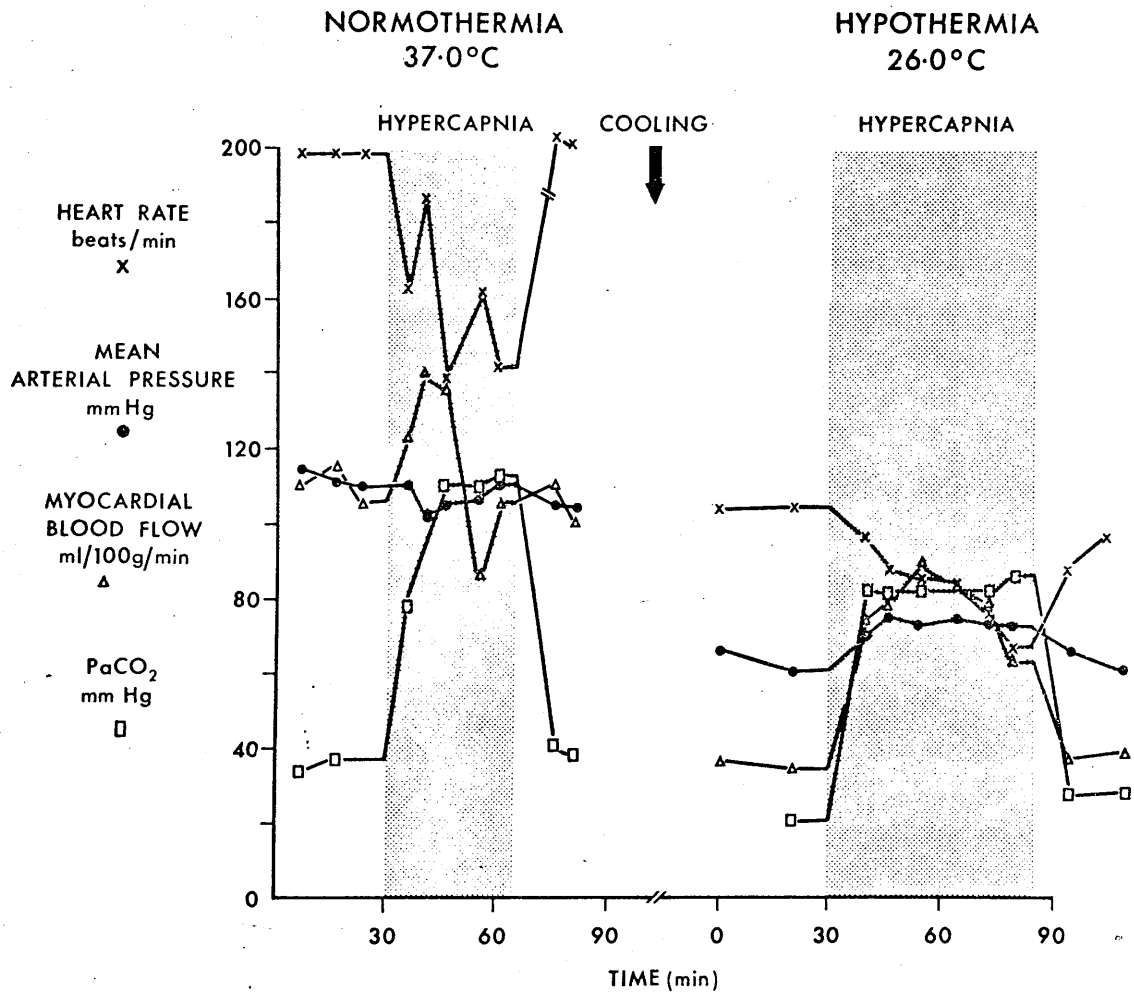


Figure 9.8. Heart rate, mean arterial pressure and myocardial blood flow changes in response to hypercapnia at normothermia and hypothermia in a single animal.

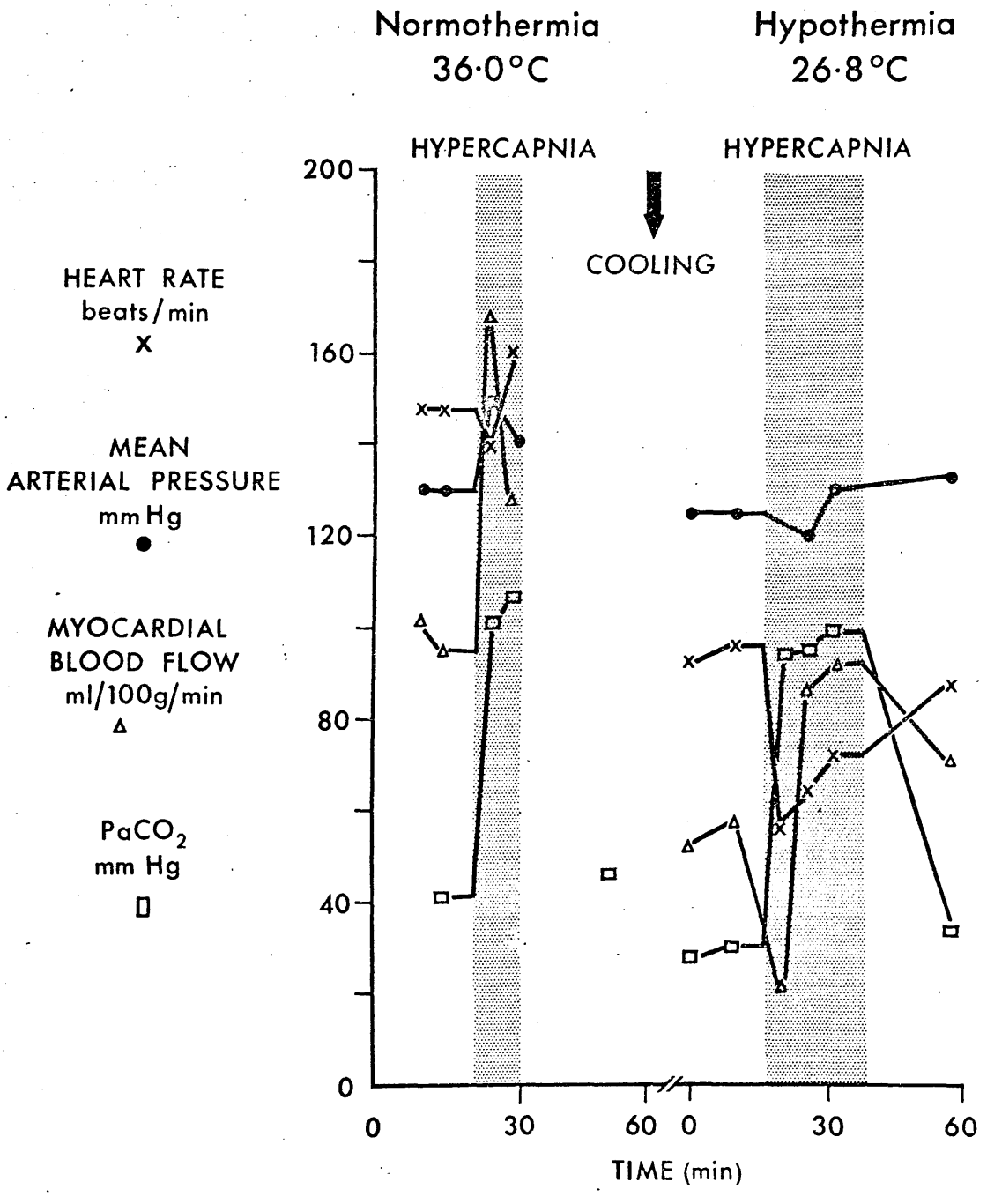


Figure 9.9. Heart rate, mean arterial pressure and myocardial blood flow changes in response to hypercapnia at normothermia and hypothermia in another single animal.

at normothermia but fell significantly at hypothermia ($p < 0.01$). Coronary sinus oxygen tension and content rose markedly at both temperatures (Fig. 9.10).

Hypercapnia produced an expected fall in the pH of arterial blood at normothermia from 7.36 $\pm$ 0.01 units to 7.09 $\pm$ 0.02 units with a minor shift in base excess from -3 $\pm$ 1 mEq/l to -6 $\pm$ 2 mEq/l; at hypothermia the equivalent changes in pH were 7.47 $\pm$ 0.02 units to 7.09 $\pm$ 0.03 units with a more marked increase in base excess from -4 $\pm$ 1 mEq/l to -10 $\pm$ 1 mEq/l.

Arterial lactate fell during hypercapnia at normothermia ($p < 0.05$) with no significant changes in coronary sinus lactate or arterial and coronary sinus pyruvate; arterial glucose rose by 17 mg/100ml (N.S.). At hypothermia no significant changes occurred in lactate or pyruvate values during hypercapnia although there were significant increases ($p < 0.05$ and < 0.01 respectively) in the arterial and coronary sinus glucose values (by 45 mg/100ml and 51 mg/100 ml respectively). Lactate extraction and consumption were unchanged during hypercapnia at normothermia but fell significantly at hypothermia ($p < 0.01$ and < 0.05 respectively); myocardial handling of pyruvate at hypothermia was unchanged. In spite of the increase in arterial glucose with hypercapnia

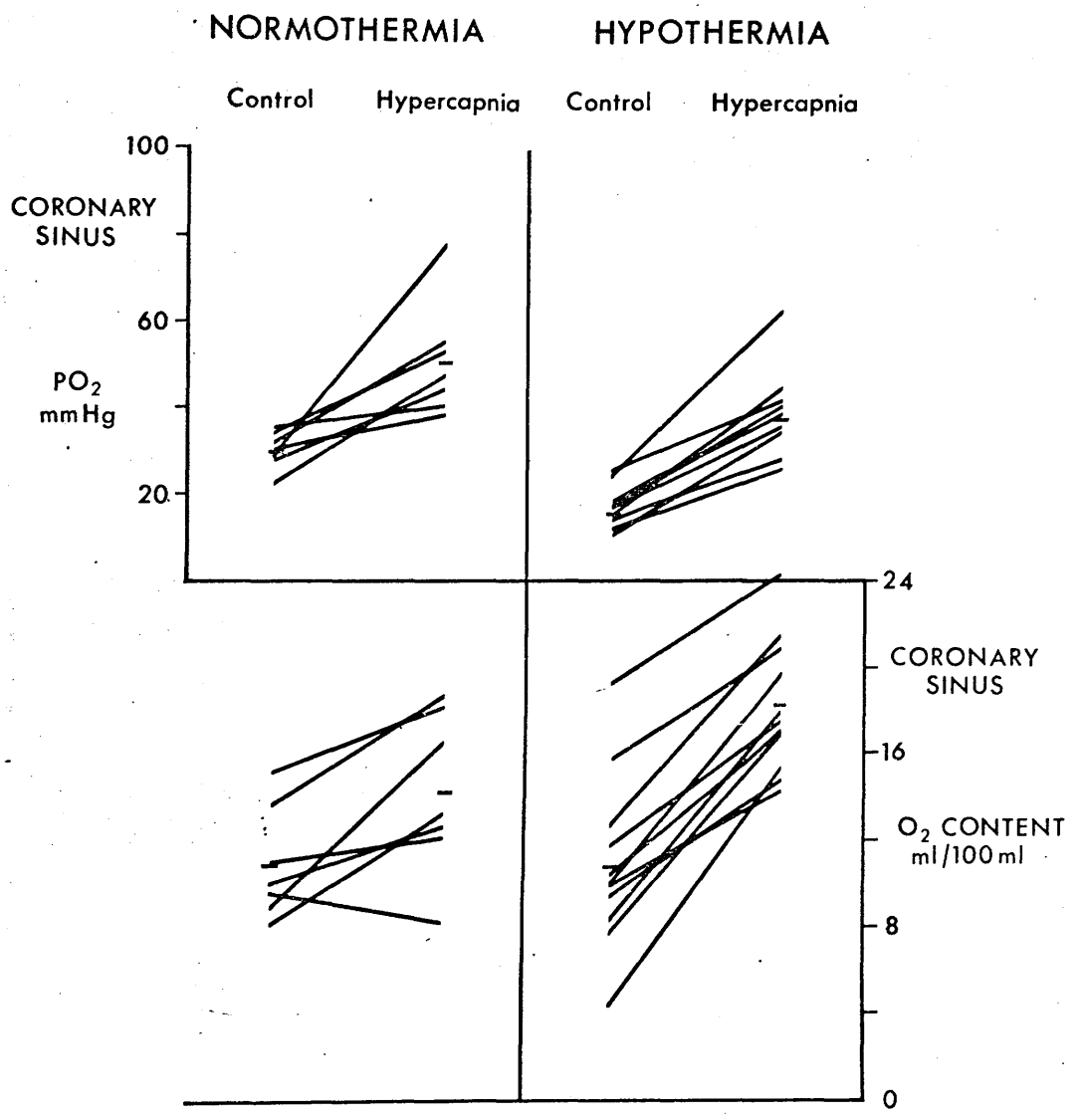


Figure 9.10. Coronary sinus P02 and oxygen content changes in response to hypercapnia at normothermia and hypothermia; bars represent means.

no utilisation of this substrate was consistently demonstrable at either temperature. Neither the arterial level nor the consumption by the heart of free fatty acids was influenced by hypercapnia at hypothermia in two animals.

ECG Effects of Hypercapnia

Raised arterial PCO_2 had no statistically significant effects on the measured components of the ECG at normothermia (Fig. 9.3) but at hypothermia the PR interval was prolonged ($p < 0.05$) and heart rate was reduced ($p < 0.02$). The incidence of junctional rhythm, ventricular extrasystoles and ST-T wave abnormalities was comparable to hypoxia at normal body temperature. At hypothermia, however, multiple extrasystoles were more common and ventricular fibrillation occurred on one occasion.

Discussion

Effect of Hypothermia

The cardiovascular effects of surface-cooling hypothermia observed in this study are similar to those previously reported. The fall in cardiac output is attributed mainly to a decrease in heart rate (Bigelow, Lindsay and Greenwood, 1950; Kuhn and Turner, 1959); changes in stroke volume appear to relate more to depth of associated anaesthesia or reduced venous return (Prec et al, 1949). Since hypothermia

per se appears to improve myocardial contractility at least to 27 deg C (Berne, 1959; Schmidt and Chang, 1960; Badeer, 1962; Badeer, 1967) the fall in left ventricular dp/dt during cooling may also be explained in part by the continuing effect of anaesthesia (Rittenhouse et al, 1971). Cardiac work and myocardial oxygen consumption decrease progressively with temperature but in the intact organism the relative magnitude of these changes varies such that cardiac efficiency may fall (Edwards et al, 1954; Jude, Haroutunian and Folse, 1957), rise (McMillan et al, 1957) or remain unchanged (Hansen et al, 1956). It has been suggested that this difference depends on work load and that comparisons of efficiency at normal temperature and high work loads with efficiency at low temperature and low work loads may be misleading (Reissmann and Van Citters, 1956; Berne, 1959).

Myocardial blood flow is reduced in response to a reduction in body temperature. Since coronary blood flow in the normothermic dog is intrinsically adjusted to cardiac metabolic needs (Gregg, 1950), it seemed reasonable to explain the reduced blood flow during hypothermia on the basis of decreased cardiac work and oxygen consumption (Berne, 1954). There is disagreement about the precise effect of cold on the coronary vessels. Vasodilatation

has been observed in some studies (Markwalder and Starling, 1913; Cruickshank and Subba Rau, 1927; Anrep, Blalock and Hammonda, 1929; Sabiston, Theilen and Gregg, 1955; Berne, 1956; Mangiardi et al, 1965) while other studies have indicated no change or vasoconstriction (Gerola, Feinberg and Katz, 1959; Jude, Haroutounian and Folse, 1957; Gollan, 1959). Cross, Rieben and Salisbury (1962) sought to explain these discrepancies and concluded that in the non-failing heart the coronary vessels only dilated during cooling if oxygen tension fell; in the failing heart, however, neither reduced temperature nor low oxygen tension altered coronary vasomotor tonus. In most in vivo hypothermia experiments, at least at moderate temperature levels, myocardial vascular resistance is increased. To what extent this is due to coronary vasoconstriction or to increased viscosity remains unclear.

Sympathetic stimulation and high catecholamine levels (Warner et al, 1970) would tend to dilate coronary blood vessels; on the other hand blood angiotensin levels are also elevated in hypothermia (Mundy and Noble, 1970), which would have the effect of reducing myocardial perfusion (Morton et al, 1977). The increase in blood viscosity with reduced temperature has been attributed to haemoconcentration (Hegnauer, Shriber and

Haterius, 1950) and to changes in the rheological properties of plasma (Merrill et al, 1963). More recent work by Fukusumi and Adolph (1970) and Marty and his colleagues (1970) has highlighted the adverse flow effects in hypothermia of blood with a haematocrit in excess of 40%. Both vasoconstriction and increased viscosity could have accounted for the raised myocardial vascular resistance observed in the present experiments.

In spite of the reduction in myocardial blood flow it has been generally accepted that oxygen availability to the cooled heart is adequate for its requirements. The older concept that hypoxia was a major factor in producing the cardiac responses to hypothermia (Lang, Weiner and Gold, 1949; Osborn, 1953) has been discounted. Bigelow and his colleagues (1950) concluded that tissue hypoxia did not exist during hypothermia because (a) there were no residual effects in warmed dogs, (b) oxygen consumption was not increased after rewarming and (c) oxygen consumption did not change in dogs maintained at 19 deg C for periods up to four hours; Penrod (1951) reported that the coronary arteriovenous difference for oxygen was unchanged at hypothermia and was not affected by the administration of 100% oxygen; Berne (1954) observed that myocardial function was not significantly altered at temperatures above 20 deg C;

and Edwards et al (1954) found no change in myocardial lactate metabolism.

The data in the present study are in accord with these latter observations. Nevertheless, the author is wary of accepting unconditionally the conclusion that the myocardium is unharmed by hypothermia, particularly if prolonged. Histological studies in the dog (Sarajas, 1964) and in man (Keen and Dowlatshaki, 1970) show evidence of damage to the fine structure of the myocardium. Furthermore, the physiological findings do not necessarily imply that the myocardium is free from focal ischaemic areas, the existence of which would not be detected by sampling coronary sinus outflow (see chapter 1, p.45). In this respect the similarity of the cooled heart to the heart in shock states is of note (Heimbach et al, 1973). The possibility of foci of microvascular stasis in the myocardium led Fukusumi and Adolph (1970) to examine the effect of the administration ofdextran, apparently to good effect.

The ECG changes during hypothermia were unremarkable and confirmed previous observations (Hook and Stormant, 1941; Osborn, 1953). Emslie-Smith, Sladden and Stirling (1959) have pointed out that the "J" wave can be detected in all cooled animals if sought carefully, and is of no sinister significance.

The fasted myocardium dervies its energy mainly from lipid metabolism although carbohydrate sources are also utilized (Hackel, 1960). Fatty acid, lactate and pyruvate consumption all fell in response to hypothermia but there was no obvious change in the proportion of each substrate utilized.

The only change in lung function directly attributable to hypothermia is an increase in physiological dead space due to bronchodilatation (Severinghaus, 1959; Prakash et al, 1978). In the present study physiological dead space increased, and since respiratory minute volume was constant, alveolar ventilation fell. The alveolar/arterial oxygen tension difference rose, with the result that an increase in F_IO_2 was required to maintain a constant arterial PO_2. In a few animals the increase in F_IO_2 was delayed until reduced temperature had been attained; the degree of hypoxaemia in some was quite marked (for further discussion of this topic see chapter 13, p317).

Effect of Hypoxia

The coronary blood vessels dilated in response to hypoxic hypoxaemia much to the same extent during hypothermia as at normal body temperature. The apparently greater decrease in myocardial vascular resistance at reduced temperature may be explained by the lower arterial PO_2. At the point of maximum increase in flow at normothermia the mean coronary sinus PO_2 was 17 mm Hg, corresponding to an oxygen content of 4.0 ml/100ml

blood (similar to that observed in the animals reported in chapter 7, p150). At hypothermia the equivalent coronary sinus PO_2 was 12 mm Hg, corresponding to an oxygen content of 8.2 ml/100ml blood (illustrating the alteration in oxygen dissociation). Coronary sinus PO_2 would appear to be an important factor in the control of coronary blood flow at low temperature and is independent of coronary sinus PCO_2 and pH which were, on average, 13 mm Hg and 0.19 units lower and higher respectively than the equivalent values during hypoxia at normothermia.

The observation that myocardial oxygen consumption remained unchanged during hypoxia at hypothermia indicates that the normal heart is able to protect itself satisfactorily under these circumstances. Penrod (1951) came to a similar conclusion when he reported that coronary arteriovenous oxygen differences remained quite large even when coronary sinus PO_2 was as low as 4 mm Hg. These observations were not substantiated, however, in the failing heart which was shown to be unresponsive to diminishing PO_2 (Cross, Rieben and Salisbury, 1962).

Effect of Hypercapnia

A coronary vasodilator response to hypercapnia during hypothermia

was observed. The decrease in myocardial vascular resistance, however, was greater at hypothermia than at normal body temperature and was sustained throughout the period of hypercapnia. Why the coronary blood vessels at reduced temperature should not become refractory to the vasodilating effect of raised CO_2 as they appeared to do at normothermia is uncertain. As had been noted in earlier studies (chapter 4, p115), hypercapnia was associated with a number of undesirable side effects; although hypotension did not occur consistently, bradycardia and metabolic acidosis were common findings and if arterial PCO_2 was further raised, nyocardial blood flow fell and dangerous arrhythmias ensued.

It was concluded that coronary vascular reactivity in the normal heart remains unaltered in character although not necessarily in degree under hypothermic conditions (26 deg C).

CLINICAL SECTION

Chapter 10

Treatment of patients suffering from generalised hypoxia (or its consequences) involving hyperbaric oxygen, hypothermia and correction of acidosis; a miscellaneous group of clinical histories relevant to the Experimental Section

In this chapter data are presented from a series of patients in whom the common pathophysiological feature was generalised hypoxia although of widely varying aetiology.

COAL GAS POISONING

It is appropriate to give priority to coal gas poisoning since historically this hypoxic condition was amongst the first to be treated with hyperbaric oxygen. The details of treatment and outcome have been extensively reviewed elsewhere (Norman and Ledingham, 1967; Ledingham, 1972) and only the main points will be cited here.

Carbon monoxide has an affinity for haemoglobin approximately 250 times greater than that of oxygen and also affects the dissociation of the remaining oxyhaemoglobin. Tissue death occurs as an indirect result of hypoxia rather than of any direct toxic action of the gas. Apart from its lethal

effects, carbon monoxide poisoning is associated with prolonged, if not permanent, damage to several tissues of the body including the brain (Garland and Pearce, 1967), the peripheral nerves and the heart (Jaffe, 1965). The muscle and skin changes which have been described may be attributed, in many instances, to a combination of hypoxia and local pressure ischaemia.

Two factors are of particular importance in the treatment of carbon monoxide poisoning - the partial pressure of oxygen in the pulmonary capillaries and alveolar ventilation. The lungs offer the only pathway for excretion of the gas, and oxygen at 2 to 2.5 ATA is the optimum gas for treatment in that the maximum rate of excretion of carbon monoxide is combined with freedom from acute cerebral oxygen toxicity.

Although experimental evidence of the effectiveness of hyperbaric oxygen in carbon monoxide poisoning is abundant (Norman and Ledingham, 1967), clinical experience has not been so clearcut (Ledingham, 1967). There appear to be two facets to the problem and these can best be presented with reference to a recent study (Smith and Brandon, 1970) in a

defined population within the United Kingdom. The overall mortality from coal gas poisoning in this region was 40%. As is common, the great majority (96%) died before reaching hospital and the only method of improving this figure in the future would be to provide mobile hyperbaric oxygen facilities. (Limited experience with such facilities in the Glasgow area was discouraging). Of the patients who were admitted to hospital only a very small number died (2%) and this confirmed the finding in another centre (Ledingham, 1967). In spite of its undoubted clinical efficacy, therefore (Fig. 10.1), hyperbaric oxygen has little or no part to play in increasing survival rate following carbon monoxide poisoning. On the other hand, hyperbaric oxygen may lower the morbidity associated with this condition. Prolonged delirium complicated 20% of patients recovering from carbon monoxide poisoning in the study of Smith and Brandon (1970) and only 50% received any form of oxygen therapy. Clearly carbon monoxide receives less energetic treatment in some centres than the condition justifies and results from the Glasgow group (Smith et al, 1962) suggested that hyperbaric oxygen is capable of eliminating much of the long-term neurological sequelae.

One of the reasons advanced for the protracted delay in

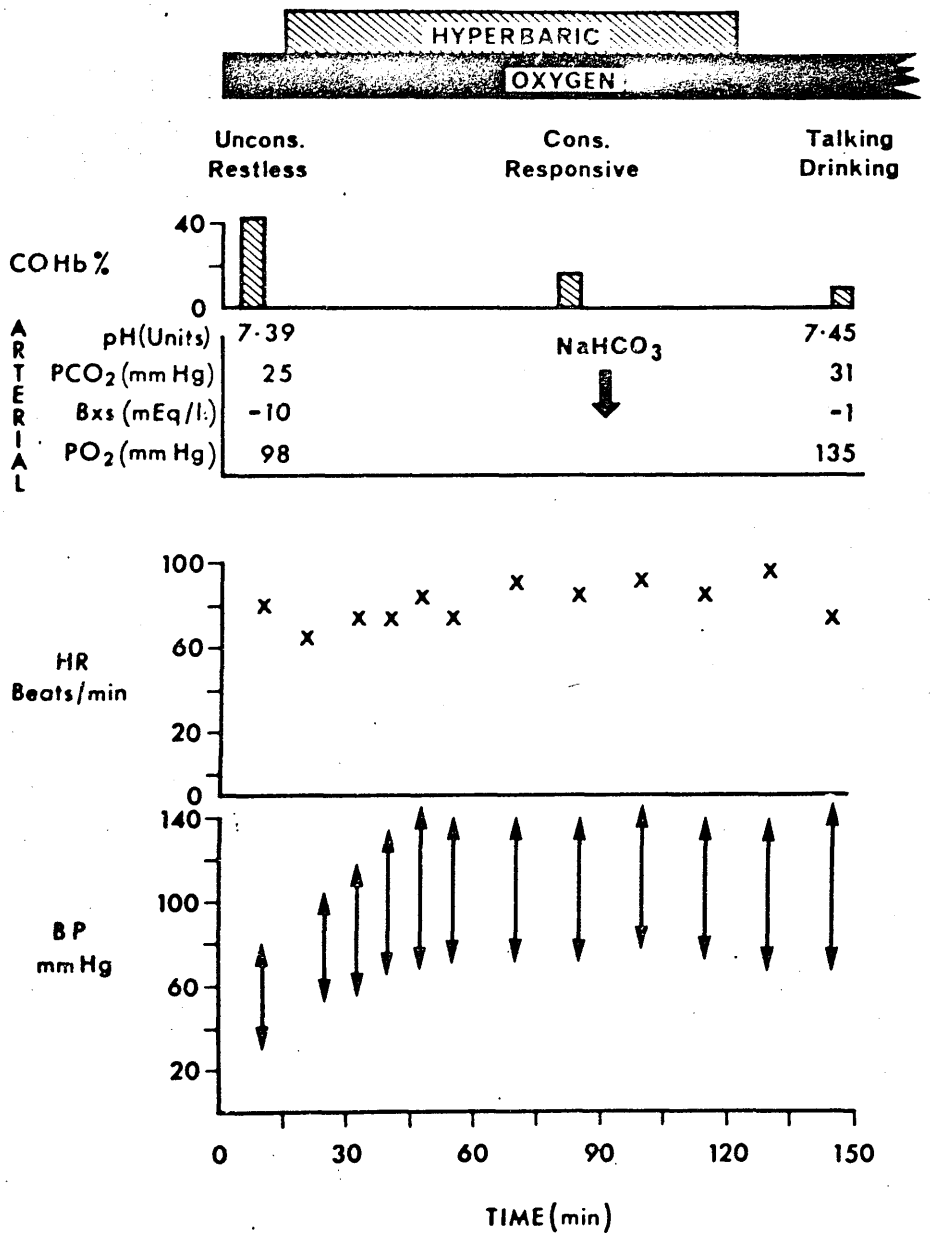


Figure 10.1. Hyperbaric oxygen treatment of a patient with carbon monoxide poisoning.

recovery of consciousness in patients with severe carbon monoxide poisoning has been the development of cerebral oedema. Hyperbaric oxygen can reduce raised intracranial pressure resulting from cerebral oedema (Miller, Ledingham and Jennett, 1970) but clinical evidence of the value of hyperbaric oxygen at this stage of carbon monoxide poisoning is lacking. Sluijter (1967), in an experimental study, was unable to demonstrate any beneficial influence of hyperbaric oxygen in delayed recovery of consciousness following severe poisoning although the protective influence of hypothermia was readily demonstrable.

It is fortunate that in the United Kingdom the change from coal gas to natural gas as a fuel source has reduced the incidence of carbon monoxide poisoning (Fig.10.2).

PULMONARY GAS EXCHANGE DISTURBANCES

A number of assorted conditions have been grouped under this heading including severe pulmonary oedema, for which hyperbaric oxygen has been used, and paraquat poisoning and acute exacerbations of chronic respiratory failure, for which hyperbaric air has been used.

Pulmonary Oedema

Severe pulmonary oedema may result from acute left ventricular failure, from the irritant effects of certain gases and liquids, from infection, or as a sequel to trauma and shock. An increase in the inspired oxygen concentration usually relieves the hypoxaemia until such time as recovery of the primary disturbance occurs. Occasionally high concentrations of oxygen together with intermittent positive pressure ventilation become necessary to maintain an adequate arterial PO_2. The value of membrane oxygenators, which reduce dependency on the lungs, is currently being assessed.

Very few reports are available of treatment using hyperbaric oxygen (Horatz, 1966; Patrick et al, 1970; Jacobson et al, 1970) but there is no doubt that a low arterial PO_2 can be corrected in this way. Figure 10.3 shows data from a patient with severe hypoxaemia in whom oxygen at 2 ATA prevented a potentially lethal fall in arterial PO_2 on three occasions.

Another example concerns a patient of 28 years of age who was suffering from coliform septicaemia secondary to septic abortion. On admission the patient was in severe shock,

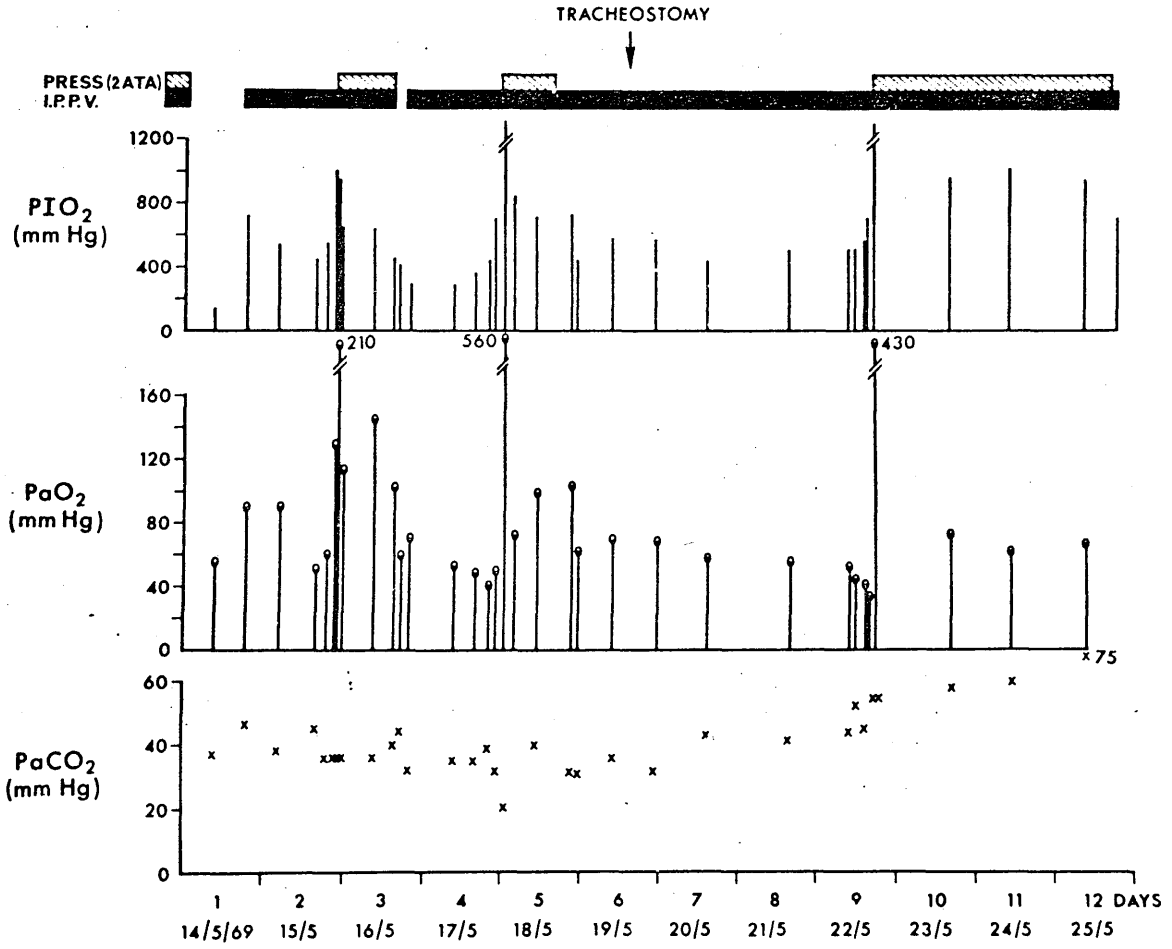


Figure 10.3. A patient (aged 44 years) with recurrent episodes of pulmonary oedema of uncertain aetiology. On three occasions the arterial PO2 fell below 40 mm Hg in spite of IPPV and an inspired oxygen concentration of 100%. Oxygen at 2 ATA produced a prompt and sustained improvement in oxygenation on each occasion. The terminal elevation of arterial PCO2 was related to overwhelming respiratory infection.

hypotensive, cyanosed, toxic, and anaemic. The arterial blood gas values were: pH 7.49 units; PCO_2 18 mm Hg; base excess 7 mEq per litre; PO_2 not measured. Treatment with rapid intravenous infusion of blood, plasma, hydrocortisone, and antibiotics (the latter two in large doses), and 100% oxygen was instituted. Three hours after the commencement of this therapy, the arterial blood gas values were: pH 7.41 units; PCO_2 32 mm Hg; base excess 4 mEq per litre; PO_2 260 mm Hg. The PO_2 of mixed venous blood, withdrawn from the pulmonary artery, was 37 mm Hg. At the end of nine hours of continuous intensive therapy along these lines, the patient's clinical condition had deteriorated; shock was more marked, and oliguria was present. Chest x-ray revealed severe pulmonary congestion probably aggravated by somewhat enthusiastic intravenous fluid infusion.

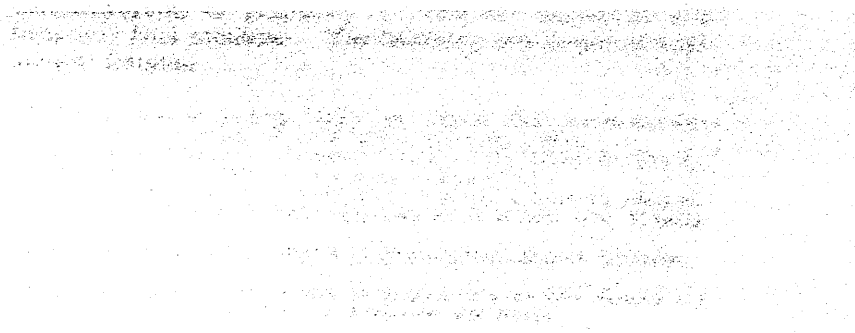
Within two to two and a half hours of compression to 2 ATA the patient's clinical condition improved. The blood pressure was 115/60 and the arterial PO_2 had risen to 560 mm Hg. Later arterial blood gas analysis revealed the following values: pH 7.40 units; PCO_2 40 mm Hg;

base excess 0 mEq per litre; PO_2 820 mm Hg. Mixed venous blood had an oxygen tension of 60 mm Hg. Exposure to 100% oxygen at 2 ATA was continued for 13 hours, by which time the patient was much improved clinically, her tachycardia had lessened, and she was passing reasonable quantities of urine. Decompression to normal pressure was completed 24 hours after admission to the hospital.

During the initial phase of treatment, when the patient was breathing 100% oxygen at normal pressure, the calculated intrapulmonary true shunt was 25% of the cardiac output compared with the normal value of around 1%. With oxygen at twice atmospheric pressure, after an initial rise, the true shunt apparently fell to 18%. A reasonable explanation of these data would be that pulmonary oedema had been partially cleared during the exposure to oxygen at 2 ATA. Largely because of the haemolytic anaemia which was present in this patient during the shock state, the mixed venous oxygen content was only 4.2 ml/100 ml blood. Oxygen administration at normal pressure raised the mixed venous oxygen content to 8.3 ml/100ml, while oxygen at 2 ATA increased the value to 11.8 ml/100ml. Complete restoration of the mixed venous value to the normal of about 14 ml oxygen per 100 ml blood

could have been achieved by increasing the ambient pressure to 3 ATA. Hyperbaric oxygen in this instance appeared to break the vicious circle of infection, hypotension and vasoconstriction.

The final example of the benefit accruing from the use of hyperbaric oxygen in selected cases of severe pulmonary oedema is described in detail in the following reprint.



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Fatal Brain Damage Associated with Cardiomyopathy of Pregnancy, with Notes on Caesarean Section in a Hyperbaric Chamber

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Summary: Three weeks after admission to a maternity hospital for observation following minor antepartum haemorrhage, a primiparous patient aged 22 suffered a sudden left hemiplegia and became comatose. Congestive cardiac failure ensued and because of the subsequent severe hypoxaemia she was transferred to the hyperbaric oxygen unit at the Western Infirmary, Glasgow, where it was found possible to improve her condition by means of oxygen at increased pressure. A caesarean section was successfully performed in the hyperbaric chamber, and a normal live female infant was delivered. Though the patient's general condition improved she never regained consciousness and died almost three months later. Necropsy confirmed the clinical diagnosis of cardiomyopathy of pregnancy with severe ischaemic changes in the brain.

Introduction

Cardiomyopathy of pregnancy is a relatively uncommon and frequently fatal condition. The following case presented some unusual features.

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Case Report

On 26 December 1966 a 22-year-old primipara in the 37th week of pregnancy was admitted to a maternity hospital for observation because of minor antepartum haemorrhage. There was no record of any illness before her pregnancy, and until the time of her admission she had been in good health. On admission clinical examination was negative, her pulse rate being 84 per minute and blood pressure 110/70 mm. Hg.

She was kept under observation for three weeks, during which no alteration occurred in her condition, until suddenly, while in bed at 6.50 p.m. on 16 January 1967, she complained of tingling and pins-and-needles in her left limb and abruptly became unconscious and cyanosed with stertorous respiration. Within minutes the pulse rate was 140 and the blood pressure 150/100. Neurological examination revealed an unconscious patient with left-sided hemiplegia, the right pupil being larger than the left.

To eliminate the possibility of intracranial haemorrhage or occlusion of a major artery which might be amenable to surgery, emergency transfer was arranged to the Institute of Neurological Sciences (Killearn Hospital). A right carotid angiogram showed no abnormality. The lumbar cerebrospinal fluid was clear though the protein level was 240 mg./100 ml. The diagnosis therefore remained in serious doubt.

By the following morning (17 January) the patient's general condition had deteriorated, the most claimant features being hyperventilation and gross cyanosis. There was a persistent tachycardia (120 per minute), and the blood pressure was 135/100. The arterial blood gas values while the patient breathed air were: *p*H 7.330 units; P_{CO_2} 32 mm. Hg; base excess −8 mEq/l.; P_{O_2} 48 mm. Hg. After the administration of 100 mEq of sodium bicarbonate a slight improvement in her condition was noted, and spontaneous movements of the left side were observed. Oxygenation of the patient, however, continued to be a source of anxiety, and during the subsequent administration of 100% oxygen the arterial oxygen tension was found to be only 50 mm. Hg. A chest radiograph showed a severe degree of pulmonary oedema with enlargement of the heart. On the afternoon of 17 January—that is, 24 hours after the initial collapse—the patient was transferred to the hyperbaric oxygen unit of the Western Infirmary for further assessment and therapy.

On her admission the blood pressure, which had been 100/80 before she left the neurosurgical centre, had fallen to 95/60, and the pulse rate was 144. The heart was clinically enlarged, and there was triple rhythm. No murmurs were noted. Clinical examination of the lungs showed widespread crepitations, and the jugular venous pressure was raised. An initial electrocardiogram (lead II only) showed sinus tachycardia. Blood gas values while the patient breathed 100% oxygen are shown in Table I.

Among other possible manœuvres to relieve the patient's hypoxia, the question of early caesarean section was raised at this stage. There was, however, little evidence of foetal distress, nor were there any acute obstetrical indications for the procedure. Obstetrical

TABLE I.—*Arterial Blood Gas Values during Period of Acute Resuscitation*

Hours after Admission to Western Infirmary, Glasgow	pH (Units)	P_{CO_2} (mm. Hg)	Base Excess (mEq/l.)	P_{O_2} (mm. Hg)	Ventilation	Inspired Oxygen (%)	Comments
0	7·255	43	−9	75	Spontaneous	100	On admission
2	7·405	45	+3	61	Spontaneous	100	After bicarbonate
4	7·160	65	−8	69	Spontaneous	100	After convulsions
				Compression			
6	7·455	47	+8	310	I.P.P.V.	100	At 2 atmospheres absolute
7	7·500	43	+9	490	I.P.P.V.	100	Immediately after section
				Decompression			
9	7·550	35	+8	121	I.P.P.V.	100	Normal pressure

I.P.P.V. = Intermittent positive-pressure ventilation.

opinion favoured at least some delay in the hope that continued oxygenation at normal pressure with relief of metabolic acidosis might improve the patient's condition without the necessity for operative intervention. The blood gas values two hours later with the patient breathing oxygen spontaneously are given in Table I. An electrocardiogram showed changes consistent with widespread anterolateral ischaemia (Fig. 2). Because of the marginal nature of the improvement which had taken place in the patient's condition with 100% oxygen at normal pressure, and because of the onset now of foetal distress (the foetal heart rate had risen to approximately 200 per minute and was irregular), it was decided to assess the effect of oxygen administration at 2 atmospheres absolute.

Before compression started, however, the patient began to have generalized convulsions, which became continuous within minutes, and her general condition deteriorated until death was thought to be imminent. Curare was administered intravenously and positive-pressure ventilation begun, which brought the convulsions under control. The blood gas values after this episode, at four hours, are given in Table I. Ventilation with 100% oxygen and administration of bicarbonate promptly corrected the respiratory and metabolic acidoses, but the arterial oxygen tension remained unchanged at 70 mm. Hg. Over the next 20 minutes the blood pressure rose to

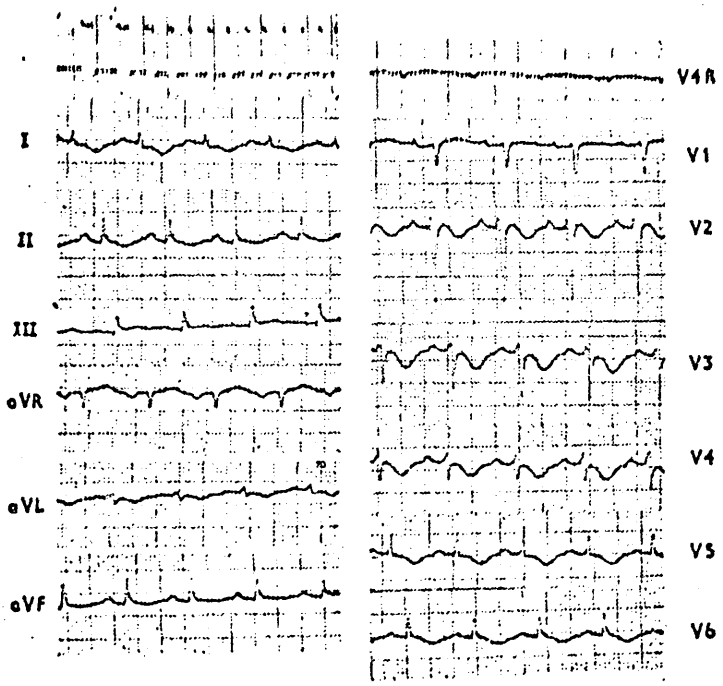

FIG. 1.—Electrocardiogram taken during period of hypoxaemia, showing evidence of widespread anterolateral ischaemia.

90/60, though gross peripheral vasoconstriction was present and the pulse rate was 166.

Following compression to 2 atmospheres absolute there was a marked improvement in the patient's condition: the blood pressure rose to 100/70 mm. Hg and the periphery became warm and pink. The blood gas values shortly after reaching the increased pressure are given in Table I. The foetal heart rate, which had been 220 and irregular immediately before compression, fell to 165 and became regular. Caesarean section was now performed (Professor I. Donald, University Department of Obstetrics and Gynaecology), and proceeded remarkably smoothly, though it was noted that the uterus remained slight cyanosed in spite of the high maternal arterial oxygen tension. A normal live female child was born with an Apgar score of 9 (Apgar *et al.*, 1958).

After two hours at 2 atmospheres absolute the chamber was decompressed to normal pressure, ventilation of the patient being continued by means of an East Radcliffe ventilator with 100% oxygen. The maximum arterial oxygen tension at increased pressure was 490 (Table I): a few minutes after reaching normal pressure it was 121 mm. Hg (Table I). Phenytoin sodium and phenobarbitone were given as anticonvulsants; hydrocortisone and digoxin as non-specific therapy for cardiomyopathy. Mannitol was administered as prophylaxis against cerebral oedema.

Over the next few days the patient's general condition improved until, breathing air without added oxygen, she was able to remain well oxygenated. He conscious level rose until she could grip to command with her right hand, but the left hemiplegia persisted. No further clinical improvement occurred, though serial electroencephalography showed resolution of the profound abnormalities seen in the early stages. She remained in this state of unconsciousness until her death two and a half months after admission.

During the period which succeeded the caesarean section attempts were made to clarify the primary diagnosis. Biparietal burr-holes revealed normal intracranial pressure; a brain biopsy specimen was taken, the appearances being suggestive of recent ischaemic neuronal necrosis: viral studies on the biopsy fragments were negative. Enzyme studies on the blood were carried out (Table II). Evidence of continuing destruction of cells was present, the myocardium being especially incriminated in view of the continued raised levels of the heart-specific fraction of lactic dehydrogenase.

Necropsy Report

Significant abnormalities were restricted to the cardiovascular and central nervous systems.

Cardiovascular System.—The heart (415 g.) was increased in its transverse diameter owing mainly to enlargement of the right ventricle. The valve cusps and the endocardium appeared normal, and there was no intramural thrombus. The coronary arteries, the aorta, and the major neck arteries were of entirely normal appearance. On section the myocardium was uniformly pale and

TABLE II.—*Blood Enzyme Values Throughout Postpartum Period*

Enzyme:	L.D.H. (mu./ml.)	L.D.H. (H.S.) (mu./ml.)	S.AsT. (Frankel Units)	S.AlT. (Frankel Units)	Aldolase (mu./ml.)	C.P.K. (mu./ml.)
Normal upper limits	195	70	40	40	6	1·0
Day:						
1			365	90		
3	474	195	185	22		
6	444	202	90	88	4·1	
8	390	181	80	85	4·8	
9	477	200	130	180	3·6	0·64
12	328	166	105	125	3·1	0·53
13	328	155	90	100	2·5	0·42
14	312	141	105	125	2·7	0·64
16	220	135	80	125	2·9	0·32
19	314	121	125	260	4·3	0·53
22	264	—	96	188	2·3	
26	248		49	108	2·1	
29	218		50	93	1·8	
37	394		85	136	2·2	
47	306		115	63	2·2	
55	194		120	112		
75	162		10	8	1·5	

L.D.H. = Lactic dehydrogenase. L.D.H. (H.S.) = Lactic dehydrogenase (heart specific fraction). S.AsT. = Serum aspartate aminotransferase. S.AlT. = Serum alanine aminotransferase. C.P.K. = Creatine phosphokinase.

rather waxy in appearance. Microscopical examination disclosed many lightly collagenized foci devoid of muscle fibres throughout the myocardium, but particularly in the subendocardial portion of the left ventricle. At the margins of these foci there were histiocytes and empty sarcolemmal envelopes. There was no diffuse inflammatory process, but there were very occasional small discrete foci of lymphocytes and eosinophil leucocytes.

Central Nervous System.—In the brain (1,320 g.) the only external abnormalities were small rather ill-defined bilateral depressions in the cortex of the frontal, parietal, and occipital lobes about 1–2 cm. lateral to the interhemispheric fissure. Coronal sections of the cerebrum after fixation showed that these depressions were due to bilateral essentially symmetrical bands in the boundary zone ("watershed") between the anterior and middle cerebral arterial territories where the cortex was shrunken, soft, and rather granular. In all of the many large sections examined microscopically the central part of each lesion had the appearance of old total infarction. These foci of total necrosis were continuous on either side, with a narrow zone of subtotal and often pseudolaminar neuronal loss beyond which the cortex was normal. The entire lesion was rarely more than about 1.5 cm. wide and affected the cortex on the gyral crests as well as within sulci (Fig. 2). Where infarction of the cortex was complete there was a narrow subcortical band of myelin loss.

No other naked-eye abnormalities were observed in the brain or spinal cord, but a full neurohistological study showed more widespread morbidity. On the inferior aspect of the left occipital lobe, in the boundary zone between the middle and posterior cerebral arterial territories, there were two large foci of subtotal neuronal loss in the cortex. In each insula and in the temporal gyri there

was a mild laminar thinning of neurones. In Ammon's horns there was subtotal neuronal loss and gliosis in each endfolium and mild focal neuronal loss in the Sommer sectors. In the thalamus there was a profound bilateral loss of neurones in the dorsomedial nuclei and in the anterior and lateral complexes. There was also a moderate neuronal loss in the corticomedial and central segments of the amygdaloid nuclei. In the cerebellum there was a considerable loss of Purkinje cells.

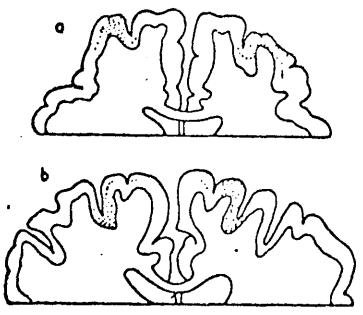

FIG. 2.—Diagrams of (a) posterior part of frontal lobes and (b) parietal lobes based on tracings made from large celloidin sections. The distribution of neuronal loss in the cortex is shown by the dotted areas. These lie in the boundary zones ("watersheds") between the anterior and middle cerebral arterial territories. Neuronal loss affects the full thickness of the cortex in the central part of each abnormal area but becomes subtotal on each side. The reduction in thickness of the cortex secondary to the ischaemic damage is not shown.

There was no naked-eye or microscopical evidence of vascular occlusion or of intrinsic arterial disease.

Discussion

This patient presented problems both in diagnosis and in management. There was clear evidence of abnormality in the brain and in the heart.

A diagnosis of cardiomyopathy of pregnancy was supported by the presence of an enlarged heart, triple rhythm, sinus tachycardia, and electrocardiographic abnormalities (Meadows, 1960); the blood enzyme disturbances were also consistent with this diagnosis. There was no clinical or electrocardiographic support for the diagnosis of myocardial infarction, and at no time was there evidence of a valvular lesion. The presence of cardiomyopathy was confirmed after death because of the presence of many discrete collagenized foci devoid of muscle fibres in the myocardium in the absence of any arterial abnormalities.

The search for a specific aetiological factor in this condition, or group of conditions, has failed in the past, and exhaustive investigations in the present case were also unsuccessful. The only tenuous connecting factor was that promethazine hydrochloride, a phenothiazine drug, had been administered in the antenatal period, and such drugs have been implicated in

cardiomyopathies. Whether there is a cardiomyopathy specific to pregnancy is still an open question, but in a recent review Brown *et al.* (1967) reported three cases in which this diagnosis was entertained.

It had been suggested in the past that embolism is the usual cause of strokes in patients with cardiomyopathy of pregnancy (Rosen, 1959), but there was no evidence of embolism in this case nor was there any mural thrombus in the heart. Connor and Adams (1966) have, however, emphasized that profound and fatal ischaemic cerebral damage apparently caused by an acute episode of cerebral perfusion failure may occur in cases of pregnancy cardiomyopathy. The bilateral essentially symmetrical watershed cortical infarcts in the present case associated with profound neuronal loss in the thalamus, moderately severe loss of Purkinje cells, and only focal abnormalities in the Ammon's horns with relative sparing of the "vulnerable" Sommer sectors, are in keeping with a severe though short-lived episode of cerebral perfusion failure. Adams *et al.* (1966) have argued that neuropathological abnormalities of this type are due to systemic hypotension, and it would appear that in the present case, a young woman with no occlusive arterial disease, the acute cerebral perfusion failure must be attributed to an episode of severe hypotension possibly associated with a transient dysrhythmia, a known complication of cardiomyopathy of pregnancy. Another speculation is that in pregnancy there may be some disturbance of vascular reflexes predisposing to perfusion failure.

Management of such patients is limited to the standard therapy of congestive cardiac failure. Bed rest, digoxin, and diuretics remain the main pillars of treatment. The position of steroids in cardiomyopathies is debatable. Some success with this therapy has been reported, but there is no convincing evidence that these drugs are of definite value.

The management of the acute episode of hypoxaemia was of interest in relation to the administration of hyperbaric oxygen. An arterial oxygen tension of 70 mm. Hg would not by itself be a cause of serious anxiety even if, as in this case, it were achieved when using positive-pressure ventilation and 100% oxygen. The improved clinical condition of the patient, however, following the increase of the arterial oxygen tension to over 300 mm. Hg at 2 atmospheres absolute was striking, as was the relief of the signs of foetal distress. The finding of an increase in arterial oxygen tension from 70 mm. Hg with oxygen at normal barometric pressure to about 300 mm. Hg as a result of oxygen administration at 2 atmospheres absolute would be expected, assuming that there was no change in the amount of venous admixture (shunting) or in cardiac output. The later rise in arterial oxygen tension at increased pressure

to nearly 500 mm. Hg is consistent with an increase in cardiac output in the immediate postpartum period (Adams, 1954). Sustained improvement in oxygenation probably resulted from the effects of the increase in cardiac output combined with the disappearance of the acute pulmonary oedema for which intermittent positive-pressure ventilation was most likely to have been responsible.

Cardiomyopathy does not usually present in such a dramatic fashion, and there may even be unsuspected cases among pregnant women, some of whom develop cardiac failure for no obvious reason. Screening of the antenatal population with 12-lead electrocardiography may bring the problem to light. It would seem logical to keep under close observation any patients who show unexplained electrocardiographic abnormalities in order that immediate hospital admission might be arranged if early signs of cardiac decompensation occur. On the other hand, when catastrophic cerebral events develop within minutes, as in this patient, it would be impossible to suggest any specifically effective prophylactic or therapeutic measure.

We gratefully acknowledge the help and co-operation of Professor I. Donald and staff of the University Department of Obstetrics and Gynaecology, and of Dr. J. G. Mone and Dr. J. P. Vance, of the Department of Anaesthetics, in the management of this patient.

We are further grateful to Dr. I. Haliburton, of the Department of Biochemistry, for the detailed serum enzyme studies, and to Dr. Constance A. C. Ross for virological studies.

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Paraquat Poisoning

In the case of the pulmonary complications of paraquat poisoning the high pressure environment has been used for rather different reasons. When more than 60% oxygen at normal pressure is required to maintain an adequate arterial PO_2, particularly if this concentration has to be administered over a prolonged period, the danger of oxygen toxicity has to be considered. There is evidence that oxygen in concentrations of this order at normal pressure can eventually lead to progressive thickening of the alveolar membrane with variable effects on the ephithelial lining of the alveoli and the endothelium of the pulmonary capillaries (Mullinax and Beischer, 1958; Michel, Langevin and Gell, 1960). No alternative to increasingly high concentrations of inspired oxygen is available at normal pressure in the presence of a steadily falling arterial PO_2. On the other hand, use of a compressed air environment permits the maintenance of a normal arterial PO_2 without the administration of unduly high concentrations of oxygen although the partial pressure of oxygen in the alveoli will, of course, be elevated. In a patient with severe paraquat poisoning the inspired and arterial blood gas data were as follows (gas tensions in mm Hg):

Ambient pressure	PIO_2	FIO_2	PaO_2	$PaCO_2$	paH
normal	600	0.84	63	44	7.43

These figures were achieved while the patient was mechanically ventilated. Later at 2 ATA the corresponding data were:

Ambient pressure	PIO_2	FIO_2	PaO_2	$PaCO_2$	paH
normal	600	0.41	64	45	7.51

There is some experimental evidence that the presence of an inert gas such as nitrogen will delay the onset of oxygen toxicity by a mechanism similar to that of certain anaesthetic agents. It has been demonstrated, for example, that animals survive significantly longer at a pressure of 3 ATA when the inspired oxygen concentration is 66%, than at 2 ATA when the inspired oxygen concentration is 100%, in spite of identical alveolar and arterial oxygen tensions at both pressures (Clarke et al, 1973).

Acute Respiratory Failure

During acute exacerbations of their illness, some patients with chronic pulmonary disease require oxygen to alleviate serious hypoxaemia. An elevation of the arterial PO_2 of as

little as 20 mm Hg may result in considerable improvement and this is normally achieved by raising the inspired oxygen concentration to 28-35%. Amongst the various problems associated with the administration of these concentrations is the distinctly practical one that masks are not universally acceptable to patients over a prolonged period; the dangers of intermittent oxygenation in these patients have been described by several authors (Campbell, 1964).

An awareness of these difficulties led to the investigation of an alternative method of producing modest elevations of the inspired oxygen pressure - namely, increased pressure of air. It will be readily appreciated that, in terms of the inspired oxygen pressure, 30% oxygen at normal pressure (30/100 x 760 - 47) mm Hg is equivalent to 21% oxygen (air) at 5 p.s.i.g. (21/100 x 1061 - 47) mm Hg.

A group of 10 patients in acute respiratory failures were exposed first to an inspired gas mixture containing around 30% oxygen at normal pressure (the exact concentration for each patient depending on individual requirement); subsequently they were exposed to increased air pressure with an equivalent

partial pressure of oxygen. The mean increases in arterial PO_2 and PCO_2 in response to the two forms of oxygen administration were measured (Fig. 10.4). In each case (circa 30% oxygen at normal pressure and air at increased pressure) there was a satisfactory and similar increment in arterial PO_2. The increases in arterial PCO_2 were undramatic and equal in both situations. This manoeuvre was repeated using 40% oxygen at normal pressure (and its equivalent at increased pressure) in 11 patients with acute respiratory failure. There was the expected greater increase in arterial PO_2 in both groups (Fig. 10.5) but at the cost of a considerable elevation of PCO_2 which was significantly greater ($p < 0.05$) at normal atmospheric pressure.

From these results it was accepted that, in general, there was little difference in the blood gas response to either form of oxygenation. The advantages of the method involving the administration of air at increased pressure were that no form of mask need be worn, thus avoiding anxiety about dangerous fluctuations in arterial PO_2: ancillary procedures e.g., physiotherapy, were facilitated by the more co-operative attitude of the patient and humidification was a function of

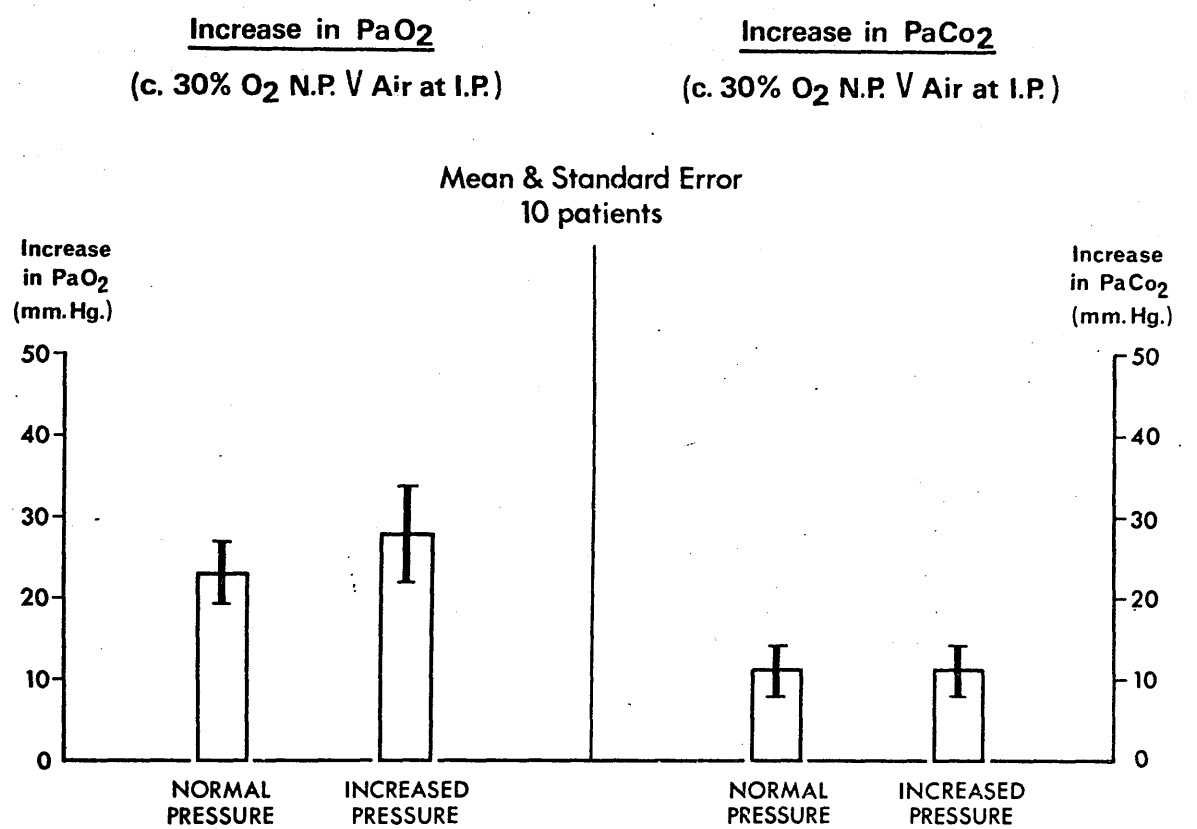

Figure 10.4. Increases in arterial PO2 and PCO2 in 10 patients with respiratory failure exposed to 30% oxygen at normal pressure and air at slightly increased pressure.

the overall chamber humidity which could be controlled at will. Fears that the denser air might precipitate further respiratory deterioration (Saltzman, Sieker and Duffy, 1964) were not substantiated; expiratory reserve volume may, in fact, have increased (Yanda, Motley and Smart, 1964; Spence et al, 1970).

Experience of longer term management in some of these patients was gained (Fig. 10.6 and 10.7) from which it was concluded that air at increased pressure was advantageous in the treatment of a patient who was difficult to control by means of conventional oxygenation and in whom tracheostomy and positive pressure ventilation was not a readily acceptable alternative solution.

CARDIAC ARREST AND NEUROLOGICAL SEQUELAE

The metabolic acidosis produced by total circulatory arrest has been described in some detail in the Experimental Section. Identical metabolic disturbances may follow cardiac arrest e.g., after myocardial infarction, and the inserted reprint outlines the successful treatment of ventricular fibrillation in one such patient using intravenous sodium bicarbonate as the sole pharmacological agent.

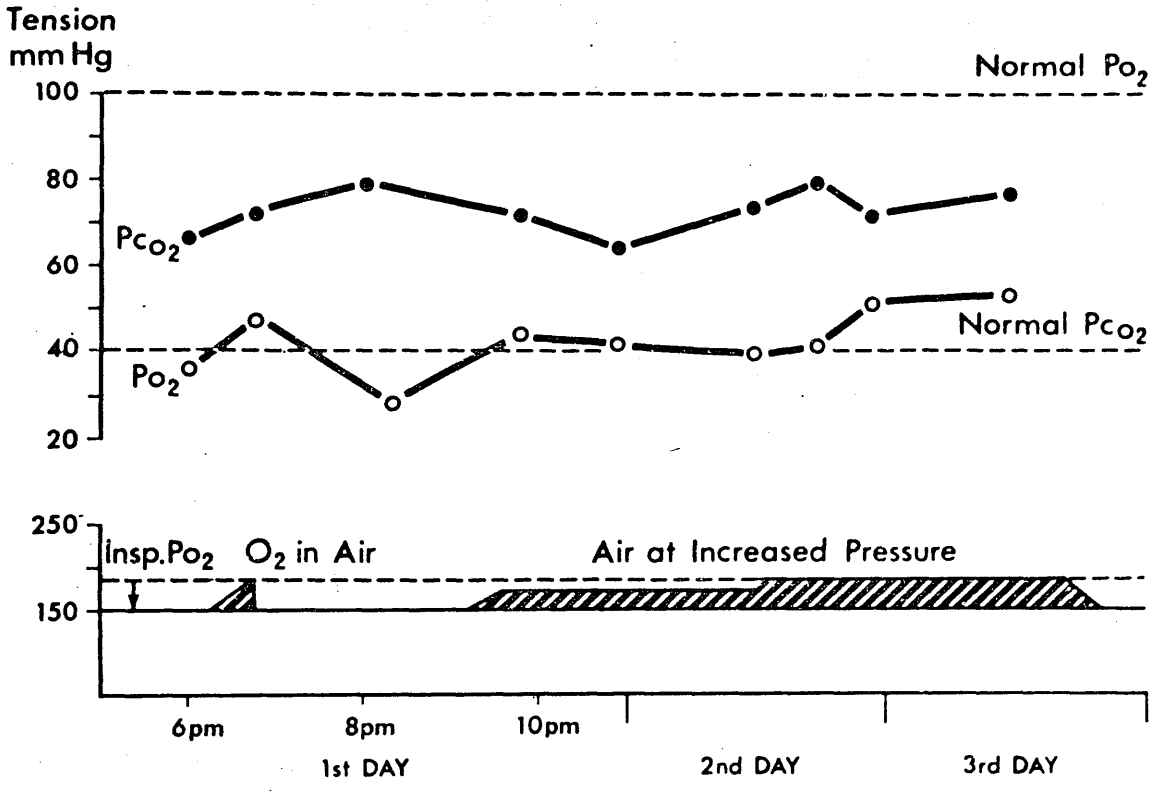

Figure 10.6. Manipulation of chamber pressure to produce optimal arterial blood gas values over a prolonged period of time.

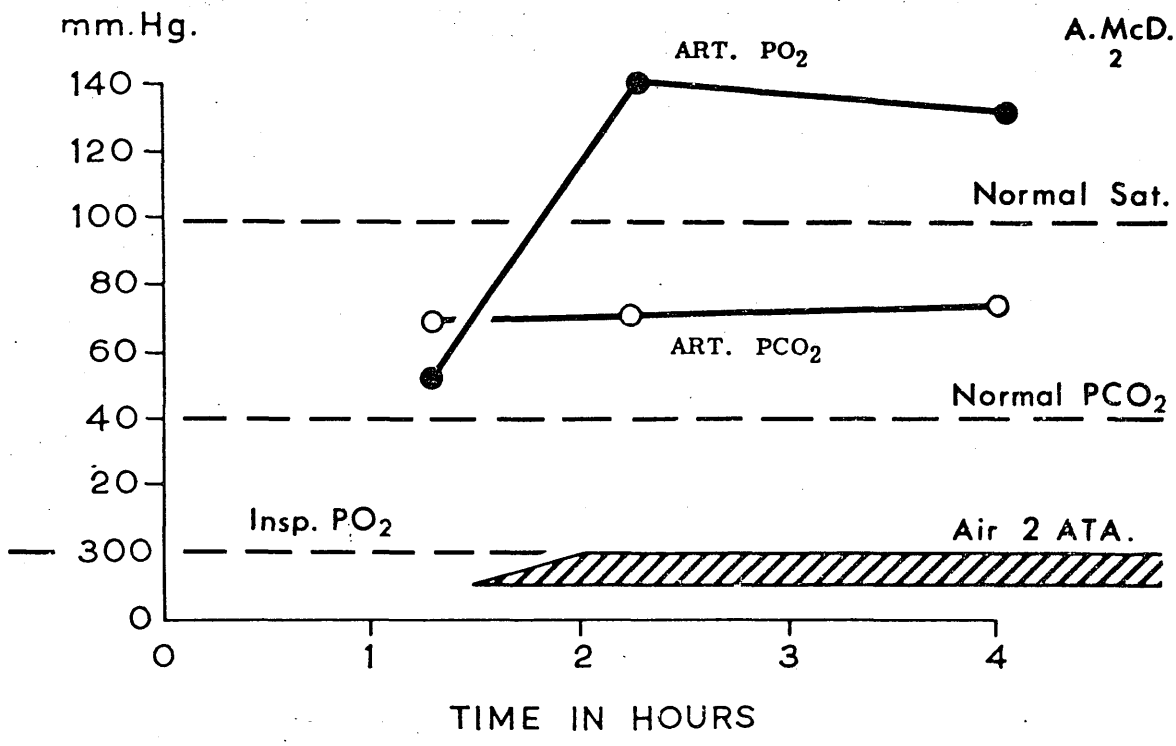

Figure 10.7. Evaluation of effect of time on arterial blood gas values in a patient with chronic respiratory failure during air breathing at 2 ATA.

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SPONTANEOUS REVERSION OF VENTRICULAR FIBRILLATION

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EXTERNAL cardiac massage combined with external defibrillation has resulted in the resuscitation of patients who would otherwise have died from ventricular fibrillation or asystole.

In ventricular asystole cardiac massage, either external or internal, will often restore sinus rhythm and good cardiac output; but in ventricular fibrillation this is unusual (Wetherill and Nixon 1962, Semple and Dall 1962). We describe here a case of spontaneous reversion of ventricular fibrillation.

Case-report

A 58-year-old engineer with a 3-day history of transient episodes of retrosternal pain on exertion was admitted on April 29, 1963, at 1.15 P.M. on account of severe constricting chest pain of 4 hours' duration, radiating to the throat and accompanied by cold sweating and breathlessness.

The patient was mildly shocked with pallor and sweating, orthopnœa, and cyanosis of lips and ears. The pulse-rate was 72 per minute, and the rhythm was regular with fair volume. The blood-pressure was 110/70 mm. Hg; the heart sounds were soft but normal, with no added sounds. There was no evidence of congestive cardiac failure, but chest examination revealed bilateral basal crepitations. The electrocardiograph showed transmural anteroseptal myocardial infarction and sinus rhythm (fig. 1).

At 2 P.M. on the same day the peripheral pulses disappeared and breathing stopped. Within a minute effective external cardiac massage and artificial ventilation with a Brook airway were begun. The electrocardiograph showed ventricular fibrillation (fig. 2a). After 5 minutes, the trachea was intubated, and satisfactory oxygenation was obtained by means of a semi-closed circuit. External defibrillation was attempted at minutes 15, 18, and 20 of resuscitation with voltages of 320, 440, and

590 without electrocardiographic evidence of reversion to sinus rhythm (fig. 2b). 20 ml. of an 8·4% solution of sodium bicarbonate (1 mEq. per ml.) was then administered into the left external jugular vein, and about 2 minutes later, without further electrical defibrillation, spontaneous reversion to sinus rhythm was noted on the electrocardiogram (fig. 2c). The radial pulse immediately became palpable, and soon afterwards the rate was 90 per minute and the blood-pressure was 100/60 mm. Hg. About a minute later the patient gagged on the endotracheal tube, and after its removal he became fully conscious and answered questions quickly and correctly.

External cardiac massage was maintained for 25 minutes, and at no time did the pupils dilate.

A further 80 ml. of a similar strength of sodium bicarbonate was given intravenously, and, as a prophylactic measure, procainamide 250 mg. 4-hourly by mouth. Analysis of a sample of capillary blood, taken an hour later, by means of the micro-Astrup apparatus (Andersen et al. 1960) revealed the following: pH, 7·28; Pco_2, 42 mm. Hg; standard bicarbonate, 19·1 mEq. per litre; base excess—5·2 mEq. per litre.

Using the formula suggested by Astrup (1960) (body-weight [kg.] × 0·3 × base excess) we administered 105 mEq. of sodium bicarbonate intravenously to restore acid-base balance.

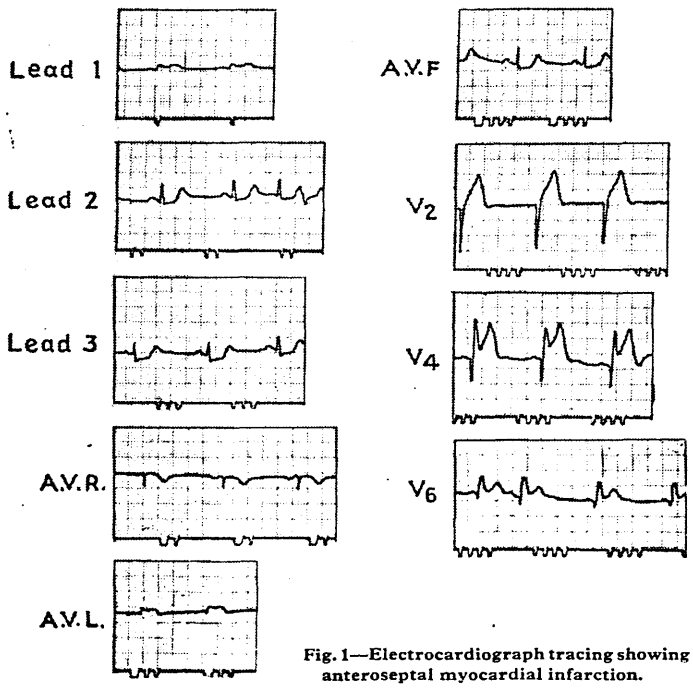

Fig. 1—Electrocardiograph tracing showing anteroseptal myocardial infarction.

Anticoagulant therapy with heparin 10,000 units intravenously was then begun, in addition to intravenous hydrocortisone hemisuccinate 100 mg. 4-hourly and tetracycline 100 mg. 6-hourly.

In the next 8 hours the patient's condition gradually deteriorated with the setting in of congestive cardiac failure and pulmonary œdema, which became more severe with the onset of ventricular tachycardia (fig. 2d). This was associated with acute dyspnœa and precordial pain. After a slow intravenous infusion of 10 mg. of morphine sulphate, 5 mg. of perphenazine, and 0·5 g. chlorothiazide, the peripheral pulses again disappeared. External cardiac massage was repeated, and 20 mEq. of sodium bicarbonate was again injected into the left external jugular vein. Before an electrocardiogram could be recorded the radial pulse returned. A subsequent electrocardiogram revealed sinus rhythm. 5 minutes later, complete consciousness returned. External cardiac massage on this occasion lasted 5 minutes, and once again a corrective dose of sodium bicarbonate was given soon after.

The patient's subsequent progress was entirely satisfactory, and he was discharged from hospital on the 53rd day. There was no evidence of neurological sequelæ or of local mechanical trauma as a result of the external cardiac massage. He is now doing a full day's work.

Discussion

This case illustrates the value of promptly executed external cardiac massage and its efficacy in providing adequate cerebral perfusion for many minutes. Of greater importance perhaps in this case is the demonstration that intensive supportive therapy is needed if patients are to survive for long beyond the period of circulatory standstill. Simple correction of existing metabolic disturbances can do much towards this end.

Metabolic acidosis, resulting from anaerobic glycolysis, and frequently hyperkalæmia are known to follow periods of circulatory arrest (Huckabee 1958, Brooks and Feldman 1962, Ledingham and Norman 1962). Further, Ledingham and Norman (1962) showed that myocardial

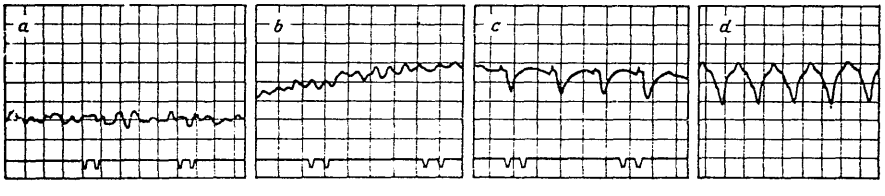

Fig. 2—E.C.G. (lead II): *a*, Ventricular fibrillation.
***b*, Persistence of ventricular fibrillation despite external defibrillation;**
***c*, Reversion to sinus rhythm after administration of sodium bicarbonate;**
***d*, Ventricular tachycardia.**

function is more rapidly restored in dogs that are given a prophylactic dose of sodium bicarbonate intravenously immediately before arrest of the circulation than in dogs not so treated; dangerous arrhythmias were also less common in the postoperative phase in the group of animals treated with bicarbonate. Although externally applied countershock in this patient failed on three occasions to produce reversion to sinus rhythm, this reappeared after the administration of intravenous sodium bicarbonate. In a case reported by Gillespie and Thompson (1963) reference was made to the possible benefit of giving a potassium-glucose insulin combination in the post-arrest phase, but we believe that in gross metabolic acidosis such an infusion can be regarded as only of secondary importance.

There can be little doubt of the urgent need for adequate correction of acid-base imbalance after circulatory arrest, and experience in this hospital with several adult patients has shown that up to 200 mEq. of sodium bicarbonate should be administered empirically as soon as possible after the arrest. Under these conditions ventricular fibrillation, if present, will be more easily corrected with electrical countershock and left ventricular function will improve (Ebert et al. 1962). More precise correction of the metabolic acidosis can wait until after the acute incident has passed. Sodium lactate seems to be contra-indicated because of its slowness of action.

Summary

Ventricular fibrillation in a 58-year-old man with acute myocardial infarction failed to respond to external electrical countershock, but responded to administration of intravenous sodium bicarbonate. A similar response was obtained in a later period of ventricular tachycardia.

We wish to thank Dr. Keith Holloway for his help in the management of this patient; and Dr. J. A. W. McCluskie for permission to present this report.

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Not all cardiac arrest victims have such an uneventful outcome. Of those who are resuscitated some develop evidence of progressive cerebral oedema which is often fatal. Treatment consists of maintaining adequate oxygenation and reducing the oedema with steroids or mannitol. Apparent failure of these agents in a five year old child, who suffered cardiac arrest during surgical correction of a squint, prompted the institution of total body hypothermia to 30 deg C. The details are given in the following case history.

Case Report M.McD. (F/5 yr)

Day 1 (14/1/65)	Operation for convergent strabismus; cardiac arrest - given sodium bicarbonate and after external cardiac massage, blood pressure returned and pupils constricted. Appeared to lighten but did not regain consciousness.
Day 2	Deeply comatose. Cooled to 30 deg C and given oxygen/spontaneous ventilation. Intravenous feeding with 20% laevulose.
Day 3	Conscious level improved - good cough reflex. Chlorpromazine for shivering at 33 deg C. Arterial blood gases (corrected for temperature) were: pH - 7.26: PCO_2 - 40: base excess - -9. Temperature fell to 29.4 deg C.

Day 4 Apparently responding to name. Rewarmed (total duration of hypothermia - 48 hr). Variable conscious level at normothermia.

Day 5 Developed signs of meningism then became opisthotonic (Fig. 10.8). Given 10% dextrose; EEG - multiple, extensive abnormalities; brainstem dysfunction.

Day 7 Open eyes between decerebrate attacks.

Day 14 First day of improvement; laughed.

Day 17 "Watches" conversation; less frequent decerebration.

Day 25 Says "yes" and "no".

Day 33 Counts fingers; left side very spastic.

Month 3 Stands alone

Month 5 Discharged from hospital. Cerebellar ataxia.

Year 2 Ataxic; educationally subnormal but attends original school.

Year 8 Rational, intelligent, attractive, active; residual spasticity left leg.

Year 12 Gainfully employed

Comment

The mechanism of action of hypothermia in the treatment of cerebral oedema is two-fold - reduction of brain volume and reduction of cerebral oxygen consumption. Experimental evidence that total body

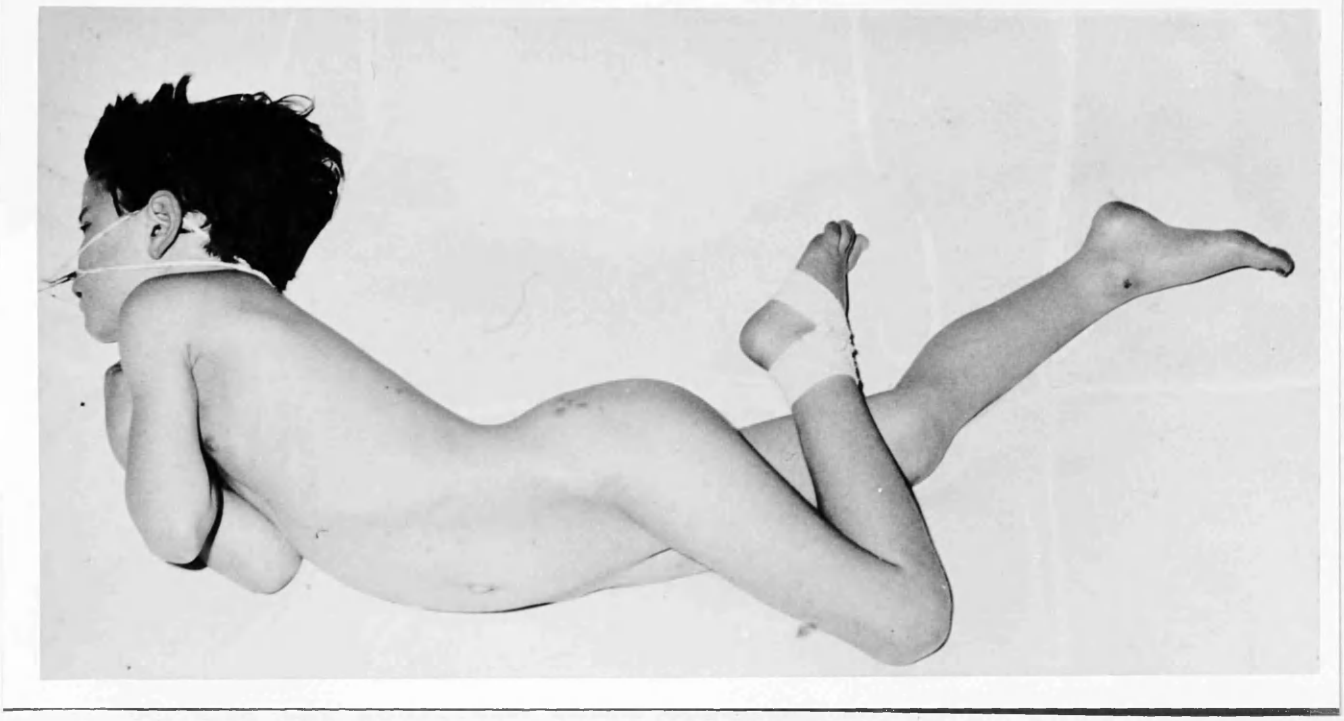


Figure 10.8. Five year old girl with marked opisthotonus five days after cardiac arrest.

cooling reduces the incidence of neurological sequelae following cerebral hypoxia is limited (Rosomoff and Gilbert, 1955; Sluijter, 1967). Favourable results after severe coal gas poisoning have been reported from several centres (Vialard, 1953; Binet et al, 1957, 1959; Craig et al, 1959). Following cardiac arrest an improved prognosis may be expected only if hypothermia is started immediately (Williams and Spencer, 1958; Rosomoff et al, 1960).

In the present case treatment with hypothermia was delayed because the conscious level appeared to improve after resuscitation. Presumably cerebral oedema was developing at this stage. There were no major problems during institution and maintenance of hypothermia at about 30 deg C. Ventilation was somewhat depressed as indicated by the normal arterial PCO_2 but this was regarded as acceptable from the point of view of cerebral oxygenation. The moderate metabolic acidosis resulted from a combination of shivering and possibly the intravenous administration of 20% laevulose (Ledingham and Hanning, 1977). Whether there would have been any advantage in prolonging the period of hypothermia will never be known. The fact that the patient was a young child at the time of the arrest would contribute in a major way to the surprisingly good eventual outcome.

HYPOTHERMIC HYPERBARIC CIRCULATORY ARREST IN HUMAN CARDIAC SURGERY

The results of experimental total circulatory arrest at 28 deg C (chapter 3) had indicated that oxygen at 2 ATA might be of some value in human cardiac surgery, particularly in infants with congenital heart disease. It was also known that 70% of children born with this form of heart disease died if untreated within the first year of life.

Many of these infants were admitted to hospital in cardiac failure which often proved unresponsive to medical treatment. When this failed their only hope of survival was some form of surgical procedure. Operation might be palliative as in the case of banding of the pulmonary artery in cases of ventricular septal defect (VSD) with pulmonary hypertension, or curative where closure of a patent ductus arteriosus (PDA) or VSD was effected. In the best hands, operation on carefully selected infants under one year of age (Bernhard, 1966) might bring about cure or benefit in more than 70%. Operative procedures might be performed:

1) Under normal conditions, e.g., ligation of PDA, banding of the pulmonary artery, or creation of a systemic-pulmonary shunt.

2) Under hypothermia, e.g., creation of an atrial septal defect for transposition of the great vessels, valvotomy for relief of a pulmonary valvular stenosis or closure of an atrial septal defect.

3) Using cardiopulmonary bypass, e.g., complete correction of a Fallot's tetralogy or closure of a VSD. Moderate hypothermia had its limitations allowing the surgeon approximately eight to 10 minutes of circulatory arrest at 28 deg C for the performance of the operation. Cardiopulmonary bypass presented special problems in very small infants.

The role of hyperbaric oxygen in infant cardiac surgery seemed to rest in the hope that the safe period of circulatory arrest might be prolonged at 28 deg C. This in turn would increase the scope for surgery.

Patients and Techniques (2/4/63 - 3/9/63)

Four children in cardiac failure were admitted for surgery. Three were under eight weeks of age. In one the lesion was transposition of the great vessels while two had large VSD's. The fourth patient was a boy of two years of age who was diagnosed as suffering from transposition of the great vessels but who was discovered at operation to have Fallot's tetralogy.

The operations were carried out under halothane anaesthesia with oxygen at 2 ATA as the inspired gas. Hypothermia to around 28 deg C was achieved using surface cooling techniques (Fig. 10. 9). The children were placed in a bath on the operating table and cold water was circulated by means of a pump from a reservoir situated under the operating table. Thoracotomy was performed while the cooling process was in progress, and the temperature to which the child was cooled varied with the behaviour of the heart for it was only when ventricular fibrillation seemed imminent that the circulation was interrupted.

By raising the temperature in the water reservoir, reheating was instituted as soon as the operation was commenced so that at the end of the period of inflow occlusion, reheating was under way. This normally resulted in a rapid restoration of effective cardiac output after a period of inflow occlusion at 28 deg C.

All four children succumbed and Table 10.1 gives details of the procedures involved. In cases 1 and 3 blood loss was a decisive factor resulting in prolonged hypotension. In case 2

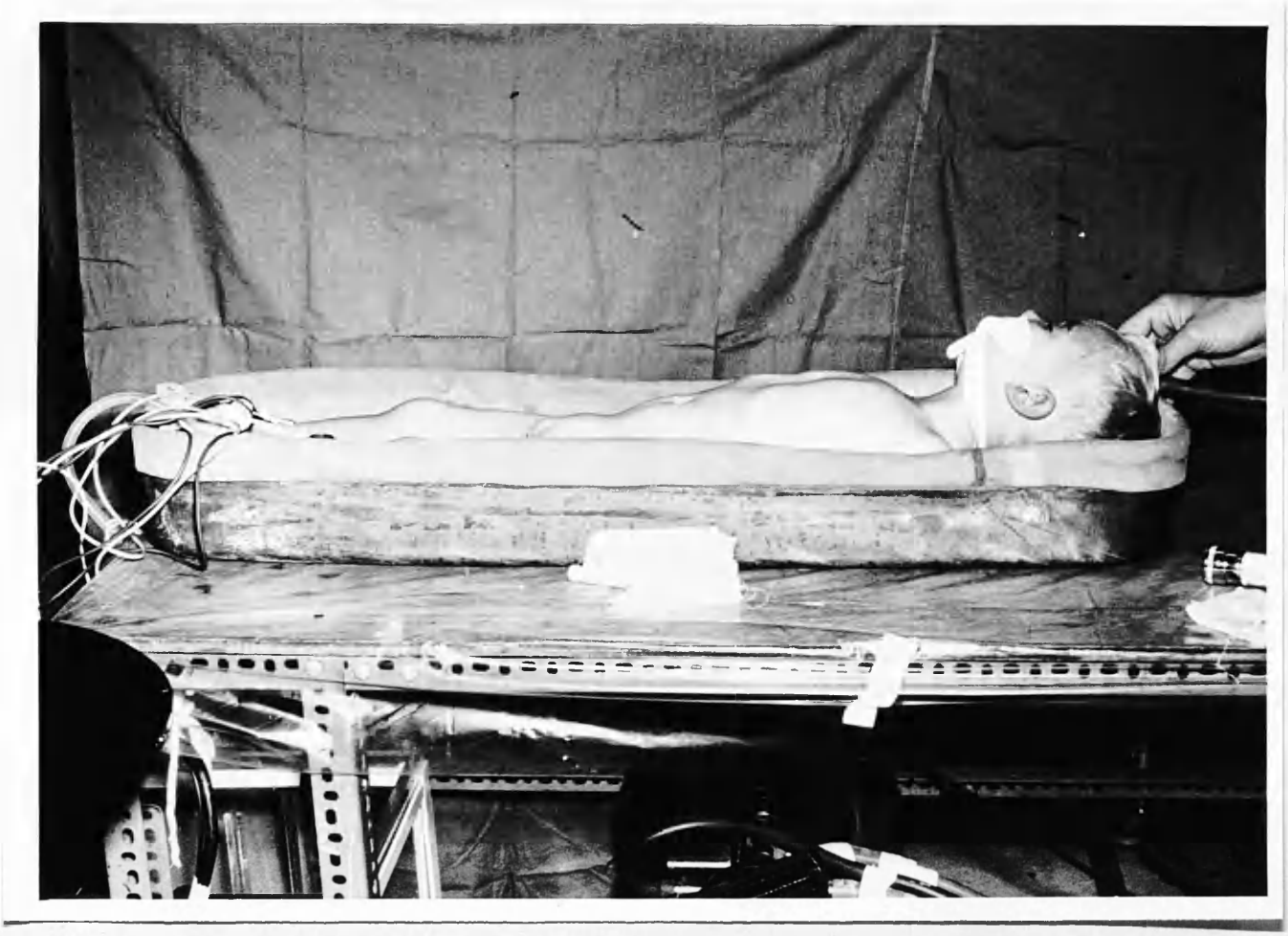


Figure 10.9. Baby in hypothermia bath.

Table 10.1 Surgical correction of congenital heart lesions in four children using oxygen at 2ATA

Age	Heart lesion	Oesophageal temperature (°C)	Period of cardiac arrest (min)	Procedure and remarks	Outcome
5 wks	Transposition of great vessels	28	9	Creation of an A.S.D. Required 230 ml blood	Hypotension: death-end of operation
8 wks	V.S.D.	21.8	12	Closure of V.S.D. Heater failure: 1 hour of cardiac massage	Hypotension: death-end of operation
8 wks	V.S.D.	26.8	13	Closure of V.S.D. 50 min cardiac massage	Hypotension: Blood loss + + + Death - end of operation
2 yrs	Fallot's tetralogy	30	6	Relief of infundibular stenosis	Died 1st post-operative day. Left lung collapse

failure of the reheating mechanism resulted in a drop of body temperature to 21 deg C which necessitated a prolonged period of cardiac massage while the heart was in ventricular fibrillation. At autopsy the ventricular septal defect was (in both cases) satisfactorily closed. The fourth developed a post-operative pulmonary collapse after an apparently successful open infundibular resection.

To draw conclusions from this small number of infants would have been unwise, especially in view of the differences in technique between the experimental and human procedures. These included performing thoracotomy during the actual cooling phase and ventilating the first three babies manually. Both these manoeuvres produced profound alterations in blood pressure, heart rate and rhythm, and acid-base balance of the babies before the arrest phase had begun. This was in marked contrast to the minor changes observed in the animals cooled to a similar temperature. In the fourth child the technique was altered to resemble more closely the experimental approach, including replacement of manual by controlled ventilation. The pre-arrest parameters were all within normal limits and the immediate operative course of this child was entirely uncomplicated.

In view of the disappointing outcome in these four children it was decided to await the results of further experimental work at deeper hypothermia and increased partial pressures of oxygen (Chapter 6). The experimental work, however, failed to demonstrate any additional benefit accruing from the use of hyperbaric oxygen at 20 deg C and, thus, further clinical development was not pursued.

GENERAL COMMENTS AND CONCLUSIONS

These heterogeneous clinical studies largely confirmed the earlier experimental observations. In severe hypoxic hypoxia hyperbaric oxygen was of definite value in elevating arterial PO_2; if the underlying condition was capable of resolution, either spontaneously or in response to treatment, long term benefit might result (Jacobson et al, 1970; Levine, 1970). In ischaemic conditions, however, the advantages of hyperbaric oxygen were not so obvious. In total circulatory arrest, at best only a marginal protective influence was observed. Perhaps more surprising was the negligible effect of hyperbaric oxygen in low flow states, e.g., shock. Although not reported, the author's clinical experience completely substantiates the negligible effects seen in shocked dogs (Chapter 8). Others have also been unimpressed with the

clinical value of excess oxygen in shock (Del Guercio et al, 1966; MacLean et al, 1967).

Chapter 11

Hyperbaric Oxygenation in Resuscitation of the Severely Anaemic Patient

Detailed information concerning resuscitation of the severely anaemic patient is scarce. The potential hazard of transfusion in these patients was recognised by Sharpey-Schafer in 1945 and the risk of congestive cardiac failure with even the most carefully monitored blood transfusion is well known. Attempts have been made to reduce this risk by the administration of packed cells over a prolonged period but this measure does not eliminate the problem in every instance. Further attempts have been made to reduce the fluid load by inducing a diuresis at the time of transfusion (Fisher, 1970). Exchange transfusion also undoubtedly helps to reduce the problems of acute circulatory overload (Fullerton and Turner, 1962). The possibility that hyperbaric oxygenation might be of value in this context has not been explored.

In this chapter data are presented from four severely anaemic patients who received oxygen at 2 ATA in addition to conventional treatment. During the period of acute resuscitation arterial and mixed venous blood gas measurements were made together with haemodynamic monitoring.

Material and Methods

Four patients suffering from severe megaloblastic anaemia were admitted to the Western Infirmary, Glasgow. All were extremely ill and all were given oxygen at 2 ATA during the acute phase of their resuscitation.

Case 1

Mrs J.T. (40 yr) was admitted on 17/2/67 at 1.00 a.m. in a semi-comatose condition. Over the preceding 12 months she had become grossly debilitated with progressive weight loss, dysphagia and anorexia. On the evening of admission the immediate findings were agitation and dyspnoea. Clinical examination revealed a patient with pale, lemon yellow skin, white conjunctivae and palm creases, and a purpuric rash over the chest and arms. Congestive cardiac failure was present and the pulse rate and blood pressure were 108 beats/min and 65/0 mm Hg respectively; a haemic murmur was audible. The relevant haematological data were:

Hb - 1.5 g/100ml

platelets - 20,000/cmm

blood film - macrocytosis, anisocytosis and poikilocytosis of the red cell series (some being nucleated); leucopenia with hypersegmented polymorphs.

The patient was transferred to the pressure chamber but before

pressurisation commenced, and while breathing oxygen through a close fitting, high concentration mask, she had a major convulsion with apnoea of two minutes duration. Recovery occurred spontaneously. Additional noteworthy features were the development of large haematomata at venous sample sites, and bouts of diarrhoea. Blood gas analysis (Table 11.1) revealed a severe metabolic acidosis with compensatory hyperventilation and normal oxygen exchange.

Soon after pressurisation to 2 ATA the patient became alert and the neck vein congestion disappeared. A slow transfusion of 300 ml of packed cells was started at 06.00 hr and continued over about five hours. During a brief period when, for nursing reasons, the oxygen mask was removed a further major convulsion occurred which again responded to the resumption of oxygen breathing. The patient's general condition improved markedly over the next few hours, the metabolic acidosis resolved spontaneously and the oxygen was withdrawn without adverse effect. (Since she remained at 2 ATA the inspired air had a PO_2 equivalent to 40% oxygen at normal atmospheric pressure). Unfortunately while being prepared for decompression the patient suddenly died. Post-mortem revealed a large posterior fossa subarachnoid haemorrhage covering the pons and cerebellum, and associated

Table 11.1 Blood pressure and arterial blood gas data in Case 1.
T = transfusion packed cells

Time (hr)	Ambient pressure	Inspired gas	Mean arterial blood pressure (mmHg)	PO_2 (mmHg)	PCO_2 (mmHg)	pH (units)
04.00	Normal pressure	AIR	60	109	19	7.15
05.10	2ATA	OXYGEN	85	900	19	7.25
06.20	"	"	80	880	20	7.39
07.30 (T)	"	"	70	850	22	7.42
10.20	"	"	90	820	29	7.44

tonsillar herniation.

Case 2

Mr D.B. (60 yr). This very obese man was admitted on 28/8/68 in a semi-comatose condition with gross congestive cardiac failure and profound anaemia. There was a long-standing history of epilepsy controlled by phenobarbitone. Clinical examination revealed extreme pallor, skin purpura and fundal haemorrhages. The relevant haematological data were:

Hb - 3.7 g/100ml (PCV - 10%)

platelets - 20,000/cmm

reticulocytes - 5%

marrow biopsy - megaloblastic changes, erythroid hypoplasia and maturation arrest.

Initial treatment consisted of packed cells, Vit B_{12} and folate but with no response in spite of simultaneous frusemide administration. Exchange transfusion was performed in the pressure chamber with oxygen at 2 ATA (Table 11.2); there was some improvement in the clinical features of cardiac failure. Blood gas analysis revealed poor pulmonary gas exchange with only a modest increase in arterial PO_2 in response to hyperoxygenation. After slow infusion of 550 ml packed cells (with simultaneous withdrawal of 350 ml of the patient's blood) decompression to normal

Table 11.2 Blood pressure and arterial blood gas data in Case 2.
T = exchange transfusion

Time	Ambient pressure	Inspired gas	Mean arterial blood pressure (mmHg)	Heart rate (beats/min)	PO_2 (mmHg)	PCO_2 (mmHg)	pH (units)
13.37	Normal pressure	AIR	65	116	40	27	7.47
14.20	"	OXYGEN	65	108	164	30	7.42
14.40	"	"	66	116	174	35	7.44
15.25	2ATA	"	65	108	520	42	7.42
16.00 (T)	"	"	65	108	364	43	7.43
23.45	"	"	65	100	400	41	7.41
10.30	"	"	75	90	324	37	7.36

atmospheric pressure was accomplished without difficulty.

The patient's general condition improved temporarily thereafter but severe thrombocytopenia with malaena continued and repeated blood transfusion was necessary to maintain an adequate haemoglobin. Six weeks later bronchopneumonia developed and the patient died. Post-mortem showed an old subdural haematoma, cerebral infarction, gut haemorrhages and acute tubular necrosis; the bone marrow appearances were unchanged from the earlier examination. The persistent marrow failure was attributed to a combination of anti-epileptic drugs and possibly radiotherapy treatment which followed removal of a seminoma 24 years before.

Case 3

Mrs E. McF. (66 yr). This unfortunate lady was admitted in a dirty, disorientated state on 10/7/69. Mild congestive cardiac failure was present together with severe pernicious anaemia. The relevant haematological data were:

Hb - 2.0 g/100ml (PCV - 8%)

platelets - 30,000/cmm

bone marrow biopsy - megaloblastic changes

Treatment with B_{12}, folate, frusemide and blood transfusion was initiated but the features of cardiac failure became more

pronounced.

Some four days after admission exchange transfusion was performed while the patient breathed oxygen at 2 ATA (Table 11.3). A good response to this treatment was obtained (500 ml infused, 1200 ml withdrawn) over a period of three and a half hours. Initial blood gas analysis revealed normal oxygen exchange and arterial PO_2 rose to over 1000 mm Hg with oxygen at 2 ATA. Although cardiac output was not measured, the arterial/mixed venous content difference was small and mixed venous PO_2 reached over 400 mm Hg. Decompression to normal atmospheric pressure and return to the Intensive Therapy Unit were achieved without difficulty and two further units of packed cells were given. At this time the serum potassium was noted to be 2.1 mmol/l and oral potassium supplements were immediately prescribed.

The patient responded well to B_{12} and folate and was discharged in good health shortly afterwards.

Case 4

Mrs J.L. (66 yr) was admitted on 28/6/71 for investigation of anaemia and diarrhoea. Pyrexia was attributed to concomitant urinary tract infection. Haematological investigations confirmed

Table 11.3 Blood pressure and arterial/mixed venous blood gas data in Case 3
T = exchange transfusion

Time (hr)	Ambient pressure	Inspired gas	Mean arterial blood pressure (mmHg)	Heart rate (beats/ min)	CVP (cm/ sal.)	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	paH (units)	Arterial O_2 content (ml/100ml)	PvO_2 (mmHg)	$PvCO_2$ (mmHg)	pvH (units)	Venous O_2 content (ml/100ml)
12.15	2ATA	AIR	46	-	-	182	36	7.55	3.28	-	-	-	-
12.35	"	OXYGEN	-	-	-	902	35	7.56	5.44	-	-	-	-
14.15	"	"	70	84	+7	1035	30	7.53	5.83	394	37	7.53	3.91
14.50	"	"	46	84	0	1000	28	7.63	5.88	461	33	7.56	4.26
16.45 (T)	"	"	60	84	+1	970	29	7.68	5.95	206	49	7.39	3.66
17.35	Normal pressure	"	54	90	+3	322	29	7.61	4.08	48	39	7.55	2.88

a megaloblastic anaemia with a haemoglobin of 3.8 g/100ml and haematocrit of 10%; the platelet count was 60,000/cmm.

Two days after admission, drowsiness and disorientation became marked and in spite of the degree of anaemia the skin appeared cyanosed. Blood gas analysis revealed an arterial PO_2 of 55 mm Hg, PCO_2 of 37 mm Hg and pH of 7.50 units. Exchange transfusion in the pressure chamber was arranged. Catheters were inserted into the radial artery and the right atrium for arterial and central venous pressure measurements and for ease of withdrawal of blood samples. Cardiac output was measured using a standard dye dilution technique. From the above measurements, the following additional data were derived as described in chapter 8; total body oxygen availability, extraction and consumption; external cardiac work; systemic vascular resistance (Figs. 11.1, 11.2 and 11.3).

At 2 ATA breathing oxygen, arterial blood gas analysis indicated values for PO_2 of 900 mm Hg, PCO_2 28 mm Hg and pH 7.57 units. During the first hour of OHP there was an apparent improvement in the patient's mental state coincident with a small increase in oxygen availability from 183 ml/min to 239 ml/min (which occurred in spite of a fall in cardiac output from 3.8 l/min to 3.2 l/min).

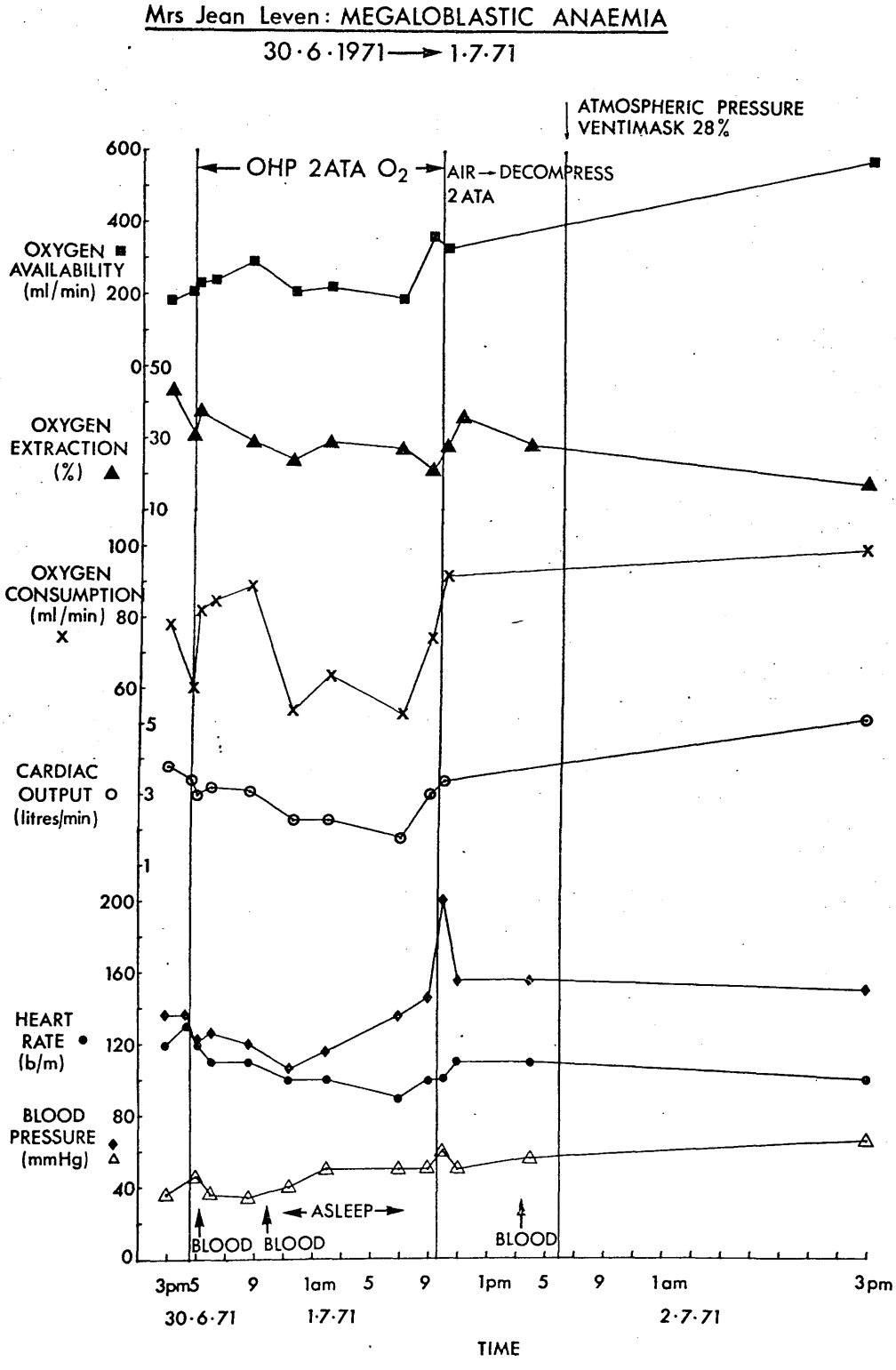


Figure 11.1. Changes in oxygen exchange values, cardiac output, heart rate and blood pressure in a patient with severe megaloblastic anaemia ; blood transfusion whilst breathing oxygen at 2 ATA.

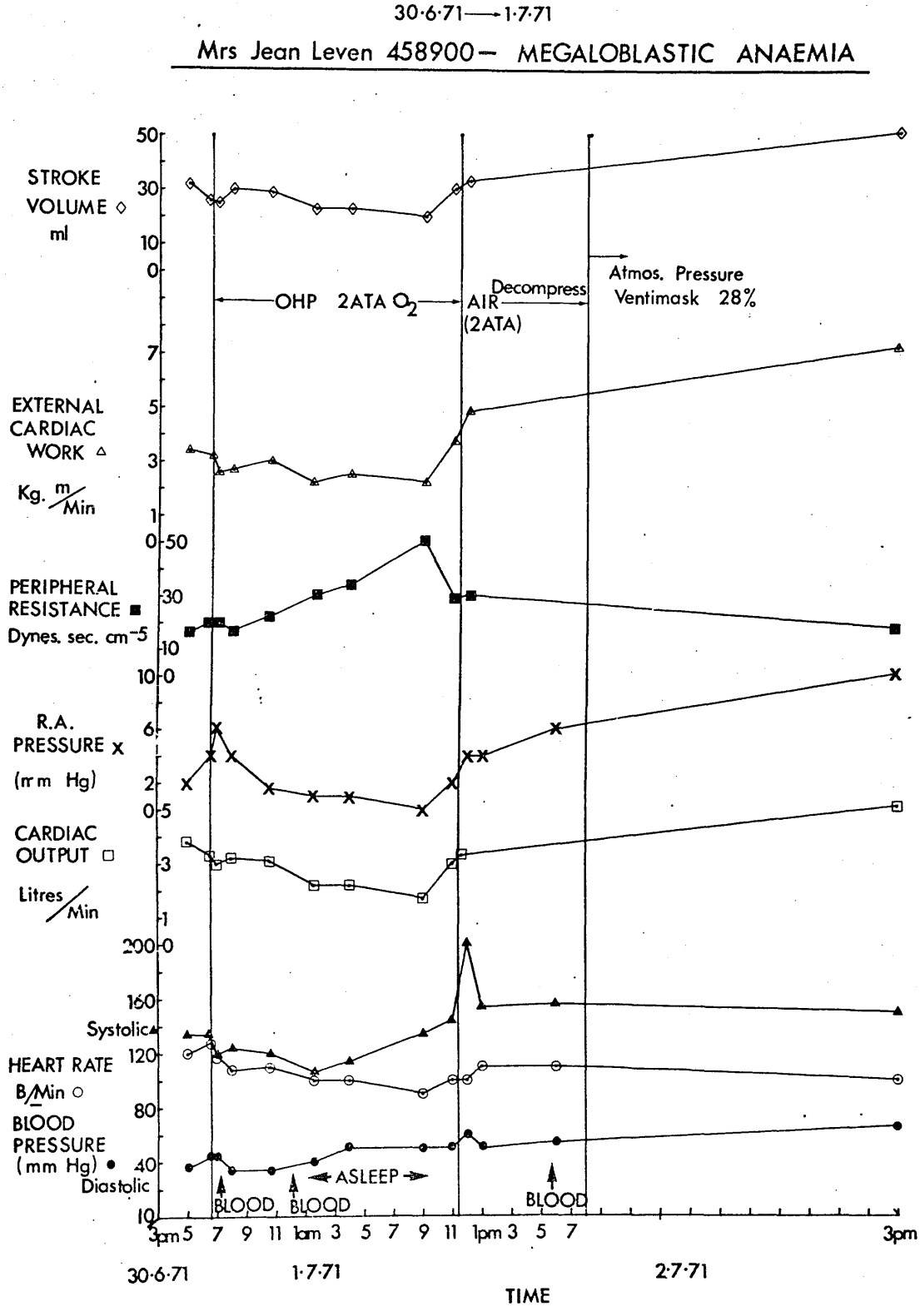


Figure 11.2. Changes in various cardiovascular parameters in a patient with severe megaloblastic anaemia; blood transfusion whilst breathing oxygen at 2 ATA.

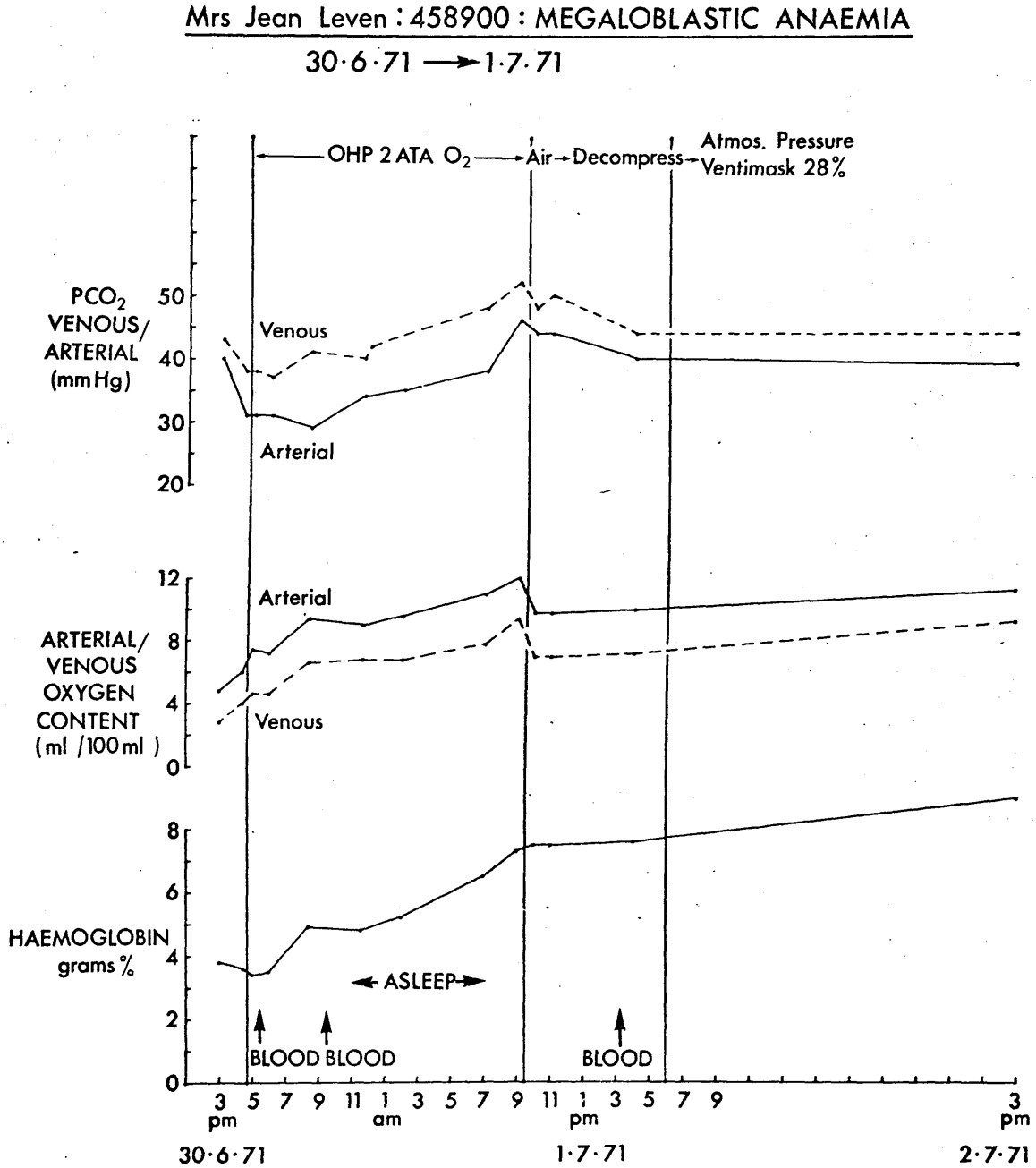


Figure 11.3. Arterial and venous PCO2, oxygen content and haemoglobin in a patient with severe megaloblastic anaemia; blood transfusion whilst breathing oxygen at 2 ATA.

Over the same period pulse rate fell slightly while blood pressure and systemic vascular resistance remained unchanged. Thereafter two additional factors complicated interpretation of the data - the administration of packed cells (600 ml over 30 hr.) and sleep (9 hr as indicated in figs.). In view of the haemodynamic stability during infusion of the first unit of packed cells it was decided not to proceed with the original plan of exchange transfusion.

Coincident with the increase in haemoglobin there was a steady fall in cardiac output due to a decrease in both heart rate and stroke volume; right atrial pressure and arterial blood pressure changes were minor; calculated systemic vascular resistance increased substantially; oxygen availability remained unaltered since the rise in haemoglobin was matched by the fall in cardiac output. There was a marked increase in cardiac output when the patient awoke. Total body oxygen consumption appeared to increase initially with the increase in oxygen availability, fell during sleep and rose again when the patient awoke. The arterial and venous oxygen content and PCO_2 returned progressively towards normal.

After 17 hours of oxygen breathing at 2 ATA (during which arterial

PO_2 fluctuated between 750 and 900 mm Hg), the oxygen mask was removed and the patient breathed first air at 2 ATA, and later 28% O_2 via a ventimask system at normal atmospheric pressure. Right atrial pressure, cardiac output and oxygen availability rose steadily throughout this period while oxygen extraction and systemic vascular resistance fell. The change in oxygen consumption was unremarkable.

The only other findings of note during the later period of resuscitation were hypokalaemia (lowest value 2.1 mmol/l) and troublesome diarrhoea. The patient eventually made a full and complete recovery.

Discussion

Chronic anaemia would cause tissue hypoxia were it not for two important compensatory mechanisms (see chapter 1). Moderate degrees of anaemia are associated with an elevation of 2:3 diphosphoglycerate and a decrease in haemoglobin oxygen affinity (Finch and Lenfant, 1972). When haemoglobin falls below 7 g/100ml cardiac output and blood volume increase. In the normal course of events, therefore, oxygen delivery is relatively well maintained. In the severely anaemic patient, however, particularly if coronary artery disease co-exists, the work load on the myocardium may become excessive. Cardiac failure results and

oxygen delivery to vital organs such as the brain and kidney, is critically reduced.

Attempts to transfuse these patients with red cells can present difficulties. In anaemic patients with a high cardiac output and normal venous pressure, Duke, Herbert and Abelmann (1964) showed that transfusion was associated with a slight decrease in heart rate and increases in stroke volume, cardiac output and arterial pressure; venous pressure remained normal. On the other hand, in patients with a high cardiac output and elevated venous pressure, transfusion was accompanied by a slight decrease in heart rate and decrease in stroke volume and cardiac output; both arterial and venous pressure rose as did haematocrit. If, at this stage, blood was removed, stroke volume and cardiac output rose, venous pressure fell to pretransfusion levels and haematocrit remained unchanged. In the treatment of severe anaemia in pregnancy, exchange transfusion has been shown to lower mortality significantly (Fullerton and Turner, 1962).

Diuretics may also help to prevent the complications of circulatory overload and pulmonary oedema (Ledingham, 1964), and some have suggested that these agents may dispense with the need for venesection.

The present studies have shown that oxygen administration at 2 ATA can increase both arterial PO_2 and oxygen availability although the increase in oxygen availability is not as great as might have been anticipated because of the associated fall in cardiac output. This latter effect is a well-documented response to hyperbaric oxygen and in the short-term is related to a fall in heart rate mediated via the vagus (Whalen et al, 1965). Nevertheless oxygen delivery to the tissues appears to be increased and in this study there was evidence of improved cerebral function (cases 1 and 4), improved cardiac function (cases 1, 2, 3 and possibly 4), and improved metabolic function (elimination of acidosis - case 1, increased oxygen consumption - case 4).

Mortality in severe megaloblastic anaemia has been attributed to circulatory overload, for the reasons previously cited, or to hypokalaemia (Palva and Kaipainen, 1970). Two of the present patients demonstrated the fall that may occur in serum potassium during treatment (Lawson et al, 1970) and energetic replacement may be necessary. The fall in potassium is due to the sudden increase in intracellular requirement for the cation brought about by the haemopoietic stimulus of Vitamin B_{12} therapy. Whether hypokalaemia alone is responsible for sudden death in

severe anaemia is uncertain but it seems more reasonable to consider a combination of effects which also includes a critical reduction in myocardial oxygen availability and acidosis. The hypoxic basis of the latter has been demonstrated by Coronata and Cohen (1969) in a patient whose acidosis disappeared after transfusion of red cells.

It is concluded that hyperbaric oxygen at 2 ATA can provide improved tissue oxygenation in the severely anaemic patient and may prevent death while the patient is being resuscitated by conventional means.

Chapter 12

TREATMENT OF THE FAT EMBOLISM SYNDROME

The fat embolism syndrome remains a diagnostic and therapeutic enigma (Wright, 1971). The original description of the syndrome is that of cyanosis, dyspnoea, pulmonary crepitations, petechiae and cerebral manifestations (including coma) occurring in a previously healthy patient with a recent fracture (Peltier, 1965). Reports of mortality approaching 85% with this combination of clinical features (Sevitt, 1960; Ashbaugh and Petty, 1966) are probably no longer relevant, but the multiplicity of therapeutic regimens (Freeman, 1962; Denman et al, 1964; O'Driscoll and Powell, 1967; Larson, 1968; Mokkhavesa et al, 1969) suggests that no single method has proved to be convincingly effective. Recently the importance of correction of hypoxaemia has become increasingly accepted (Galloon and Charkravarty, 1967; Ross, 1970) although in many of the clinical reports the simultaneous administration of other forms of treatment complicates interpretation of the results.

This chapter presents data from a prospective study of 11 consecutive patients with the fat embolism syndrome admitted to an Intensive Therapy Unit (ITU). The aim of the study was to examine the truth of the suggestion that the cause of death

from the fat embolism syndrome was 'almost invariably the hypoxia secondary to the effects of pulmonary fat emboli' (Lancet, 1972) and that provided this hypoxia could be corrected, the patient would survive, usually without any sequelae (Benatar et al, 1972).

Personal interest in the fat embolism syndrome was stimulated by reports that oxygen administration (at inspired partial pressures above those required simply to correct hypoxaemia) might be of benefit as a form of treatment (Warren, 1946; Harman and Ragaz, 1950; Love and Stryker, 1957). Experience with one elderly patient with severe fat embolism who was treated with oxygen at 2 ATA prompted the author to reconsider the basic disturbance of pulmonary gas exchange in this syndrome and to determine whether it was necessary to do more than correct the existing hypoxaemia. In the event, re-exploration of the potential therapeutic role of hyperbaric oxygenation was not required.

MATERIAL AND METHODS

A single patient who was severely hypoxaemic and exhibited most of the related features of fat embolism was treated with oxygen

at 2 ATA (11/5/65) for a period of four hours.

The main series consisted of 11 adult patients, apparently suffering from the fat embolism syndrome, who were admitted to the Intensive Therapy Unit (ITU) of the Western Infirmary, Glasgow, between 1969 and 1978. This represents the total number of patients admitted to the unit during that period who had a relevant clinical history and associated signs and symptoms. Most of the patients were referred from the Orthopaedic Departments of the Western Infirmary and neighbouring hospitals.

The aim of treatment was to maintain arterial PO_2 as near as possible within the normal range and, otherwise, to apply only routine supportive measures.

RESULTS

The single patient (male/75 yr) was drowsy and mildly hypotensive (90/65 mm Hg) on admission to the pressure chamber and arterial blood gas analysis revealed the following data: PO_2 - 32 mm Hg; pH - 7.57 units; PCO_2 - 20 mm Hg; base excess - +1 meq/l (the inspired gas was air and the patient was breathing spontaneously). On exposure to oxygen at 2 ATA the patient's conscious level lightened, arterial blood pressure rose and he became restless. Repeat arterial blood gas analysis showed: PO_2 - 408 mm Hg; pH - 7.54 units; PCO_2 - 25 mm Hg; base excess - 0 meq/l. After a three and a half hour period of hyperbaric oxygenation, decompression to normal atmospheric pressure was carried out and

repeat blood gas analysis (while the patient breathed oxygen at high concentration) was as follows: PO_2 - 42 mm Hg; pH - 7.47 units; PCO_2 - 18 mm Hg; base excess - -8 meq/l.

Comment

The data from this patient confirmed the observations, reported in chapter 10 (p.236), concerning the ability of hyperbaric oxygen to increase arterial PO_2 in patients with severe pulmonary oedema. Clearly, lower inspired oxygen concentrations could be used to correct the hypoxaemia in most patients suffering from fat embolism and since alternative methods were available to eliminate pulmonary oedema, the question was whether hyperbaric oxygen had any additional advantage to offer. One possibility was that OHP might be beneficial in dealing with cerebral oedema secondary to fat emboli obstructing the brain vessels, if indeed this factor was of clinical importance.

Main Series

A description of the injury sustained by each of the patients in the main series is contained in Table 12.1 from which it can be seen that nine of the 11 patients had fractures of the lower limbs. In two of the patients the syndrome appeared to

Table 12.1

FAT EMBOLISM

DESCRIPTION OF INJURY

Patient (Series No. & Date)	Age (yr)	Sex	History	Injury
J.H. (1) 21.9.69	24	M	RTA	femur
D.B. (2) 24.5.70	24	M	RTA	femur tibia clavicle nose
W.M. (3) 14.9.70	21	M	RTA	tibia
J.C. (4) 2.7.71	26	M	RTA	femur tibia metatarsals
J.T. (5) 31.10.71	71	M	Post-op	Aortic aneurysm bifurcation graft
M.H. (6) 29.9.72	72	F	RTA	pelvis femur tibia ulna
H.M. (7) 9.2.73	66	M	Agricult. accident	pelvis ribs
I.S. (8) 14.11.74	17	F	Stabbing (L) loin	(L) kidney, pancreas, stomach, liver
A.B. (9) 30.12.74	20	F	RTA	pelvis femur
A.McC.(10) 28.1.75	61	F	RTA	ribs pelvis tibia
G.W. (11) 4.7.78	20	M	RTA	tibia knee

follow extensive retroperitoneal soft tissue injury. The clinical and laboratory data at the time of admission to the ITU, or soon thereafter, (Table 12.2 and 12.3) indicate the severity of hypoxaemia and the frequency of major cerebral manifestations observed in this series. Anaemia was a consistent finding.

The clinical and laboratory findings in each of the patients have been summarised and are presented together with relevant figures.

Table 12.2

FAT EMBOLISM

CLINICAL DATA ON ADMISSION

Patient (Series No.)	Cerebral features	Resp. Rate (/min.)	Cyanosis	Lung Creps	Petechiae (site)	H.R. (/min.)	Temp. (°C)	Time of onset (Day)
J.H. (1)	Coma	22	+	+	-	160	37.2	2
D.B. (2)	Irritability:Confusion	40	+	+	+ (Neck)	140	37.6	2
W.M. (3)	Gross confusion	20	+	+	+ (trunk)	105	38.6	2
J.C. (4)	Agitation:Confusion	48	+	+	+ (axilla)	130	37.6	1
J.T. (5)	Confusion	30	+	+	+ (axillae)	140	36.5	1
M.H. (6)	Coma	35	+	+	+ (trunk: conjunctiva)	100	38.2	1
H.M. (7)	Coma	18	+	+	+ (neck: conjunctivae)	120	34.0	1
I.S. (8)	On ventilator	on ventil-ator	Profound	Yes	+ (chest: neck conjunctivae)	110	38.2	3
A.B. (9)	On ventilator	on ventil-ator	-	+	+ (chest)	150	38.2	3
A.McC. (10)	Confused	35	+	+	+ (chest)	110	38.2	4
G.W. (11)	Drowsiness	60	+	+	+ (neck)	106	38.2	3

Table 12.3

FAT EMBOLISM

LABORATORY DATA

Patient (Series No.)	Chest X-Ray	PaO_2 (mmHg)	Base deficit (meq/L)	Fat (site)	Hb (G)	Ca (mmol/l)	Platelets (/cmm)
J.H. (1)	POS	40	-3	Neg.	8.4	Norm	-
D.B. (2)	POS	40	-2	-	8.8	-	135,000
W.M. (3)	POS	40	0	Pos(SP) Neg(UR)	7.6	1.9	150,000
J.C. (4)	POS	53	0	-	9.2	-	-
J.T. (5)	POS	53	-3	-	9.2	2.0	25,000
M.H. (6)	POS	40	-2	Pos(SP) Neg(UR)	7.8	1.8	40,000
H.M. (7)	?	40	-14	Neg(UR)	10.1	2.2	30,000
I.S. (8)	POS	40 (on IPPV: 100%O_2	0	Neg	8.9	2.0	55,000
A.B. (9)	POS	110 (on IPPV)	-1	Neg	10.3	1.9	25,000
A.McC. (10)	?	56	-3	Neg(UR)	7.1	2.2	60,000
G.W. (11)	POS	60	-1	Neg	7.2	1.9	110,000

Case 1 J.H. Male/24 yr
Admitted 21/9/69

DAY	COMMENT	TREATMENT
1	Road traffic accident: facial lacerations: compd # nose simple # Ⓛ femur	Resuscitation Routine surgery General anaesthesia
2	Sudden onset: coma dyspnoea cyanosis Arterial PO_2 - 49 mm Hg (air/spont) Chest X-ray - pulmonary oedema	OXYGEN:IPPV tracheostomy mannitol
6	Chest - Clinical/radiological improvement Δ A-a PO_2 ↓	OXYGEN reduced
12	Much improved	OFF IPPV
16	General condition good Chest X-ray - residual congestive changes	Discharged from ITU
30	Chest X-ray clear	

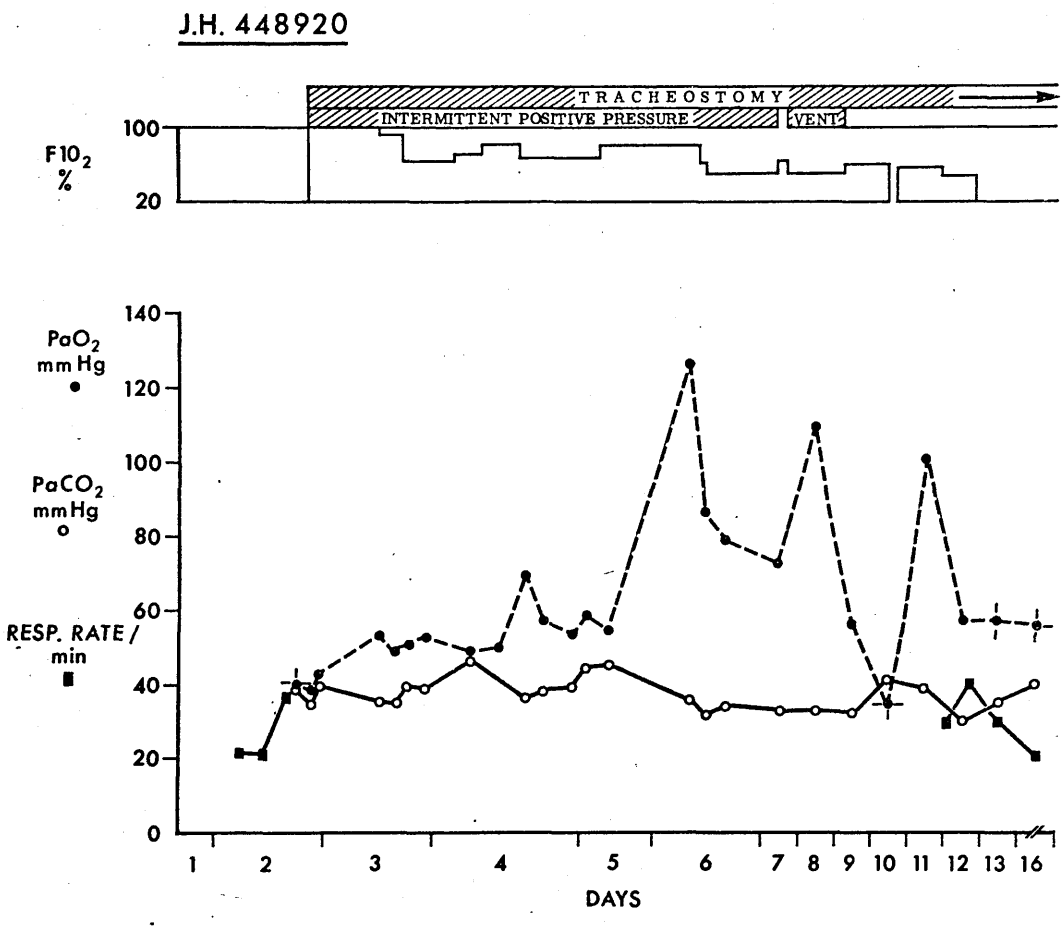


Figure 12.1a. Case 1. Respiratory and blood gas data.

J.H.: Age 24 448920

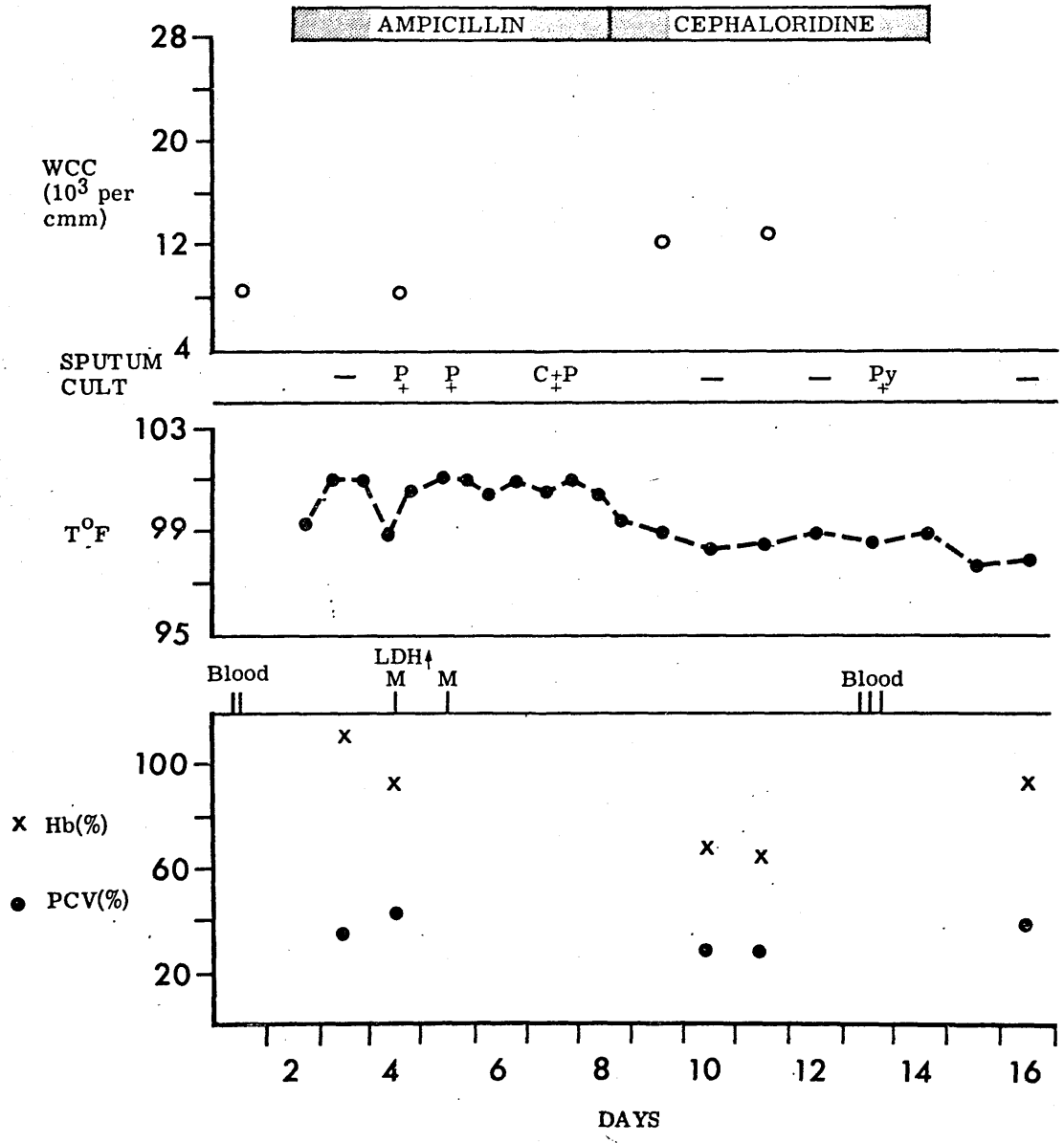


Figure 12.1b. Case 1. Haematological and bacteriological data.

p. proteus
c. coliforms
Py. pseumomonas pyocyanea
m. mannitol
LDH. lactate dehydrogenase

Comment

This patient required 100% oxygen for the first 24 hours of his stay in the ITU and was not independent of the ventilator for nearly 10 days. Throughout the first four days of his illness, the patient's neurological status gave cause for grave concern. There were no localising signs but there was clinical evidence of raised intracranial pressure for which treatment with intravenous mannitol was given. On day 7, the patient became alert and was able to communicate, and there was no regression in his conscious level thereafter. Other clinical features of note included:

(1) A coliform respiratory infection, which occurred on day 8 and was successfully treated with cephaloridine.

(2) Anaemia, normochromic and normocytic in type, for which blood transfusion was required.

Case 2 D.B. Male/24 yr
Admitted 24/5/70

DAY	COMMENT	TREATMENT
1	Road traffic accident facial lacerations: simple # (R) clavicle, (R) femur/patella, (L) tibia	Resuscitation Routine surgery General anaesthesia
2	Sudden onset: agitation dyspnoea cyanosis petechiae Arterial PO_2 - 67 mm Hg (on oxygen at high concn.) Chest X-ray - widespread patchy opacities	OXYGEN Heparin
4	Clinical/radiological features unchanged Arterial PO_2 - 40 mm Hg (air/spont.)	OXYGEN: aggressive physiotherapy
8	Clinical/radiological improvement	OFF OXYGEN
10	Chest X-ray normal Arterial PO_2 - 95 mm Hg (air/spont.)	Discharged from ITU

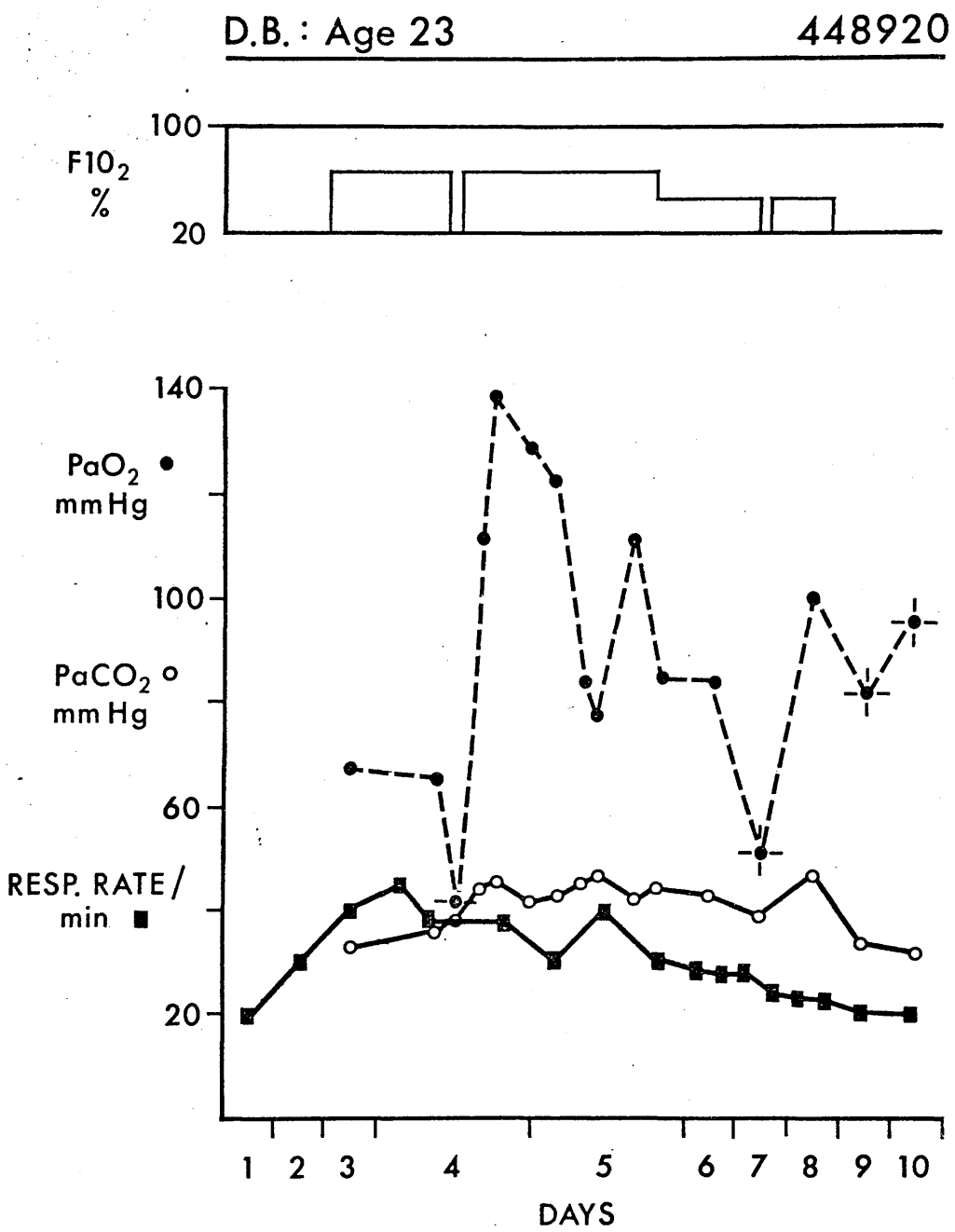


Figure 12.2a. Case 2. Respiratory and blood gas data.

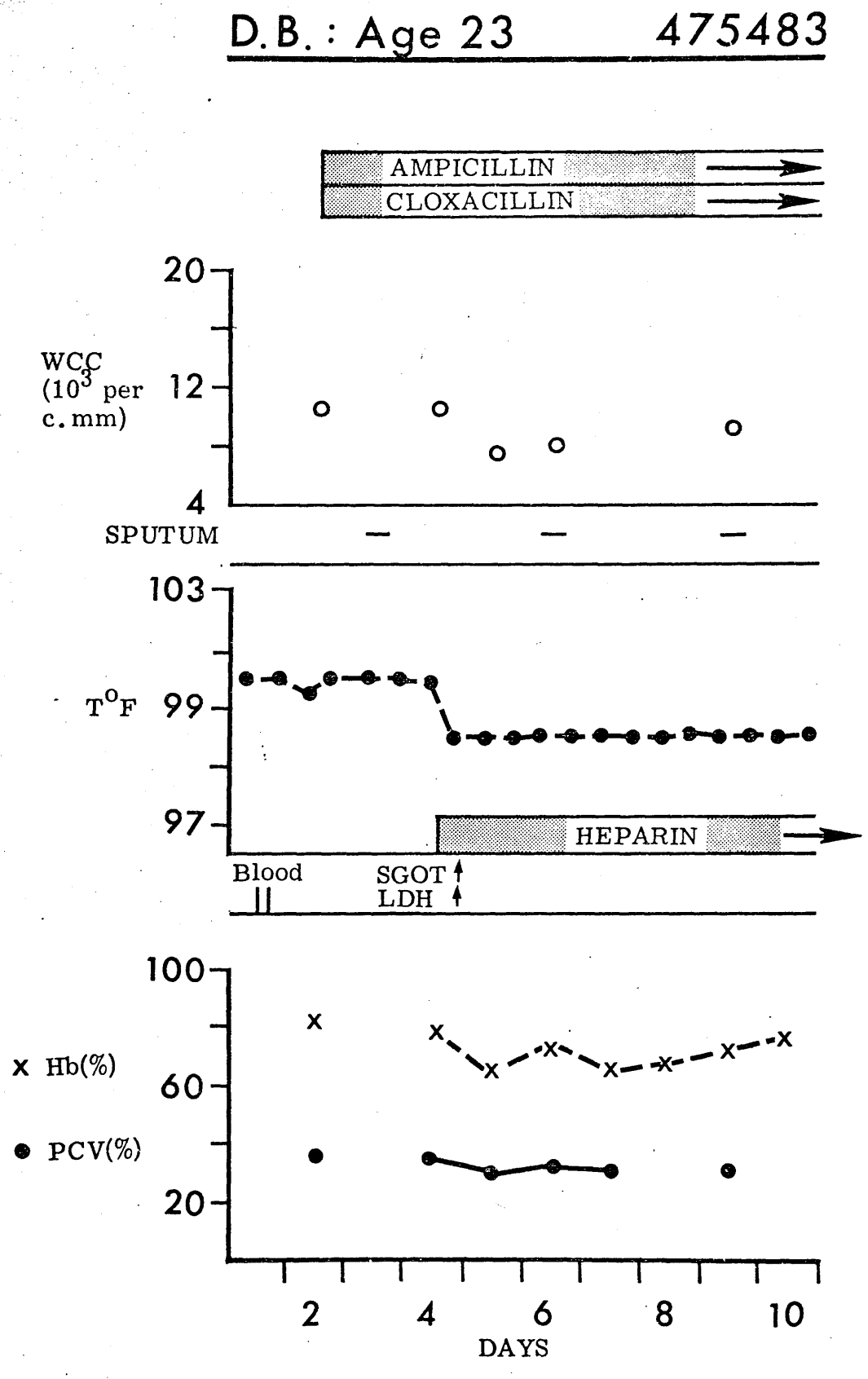
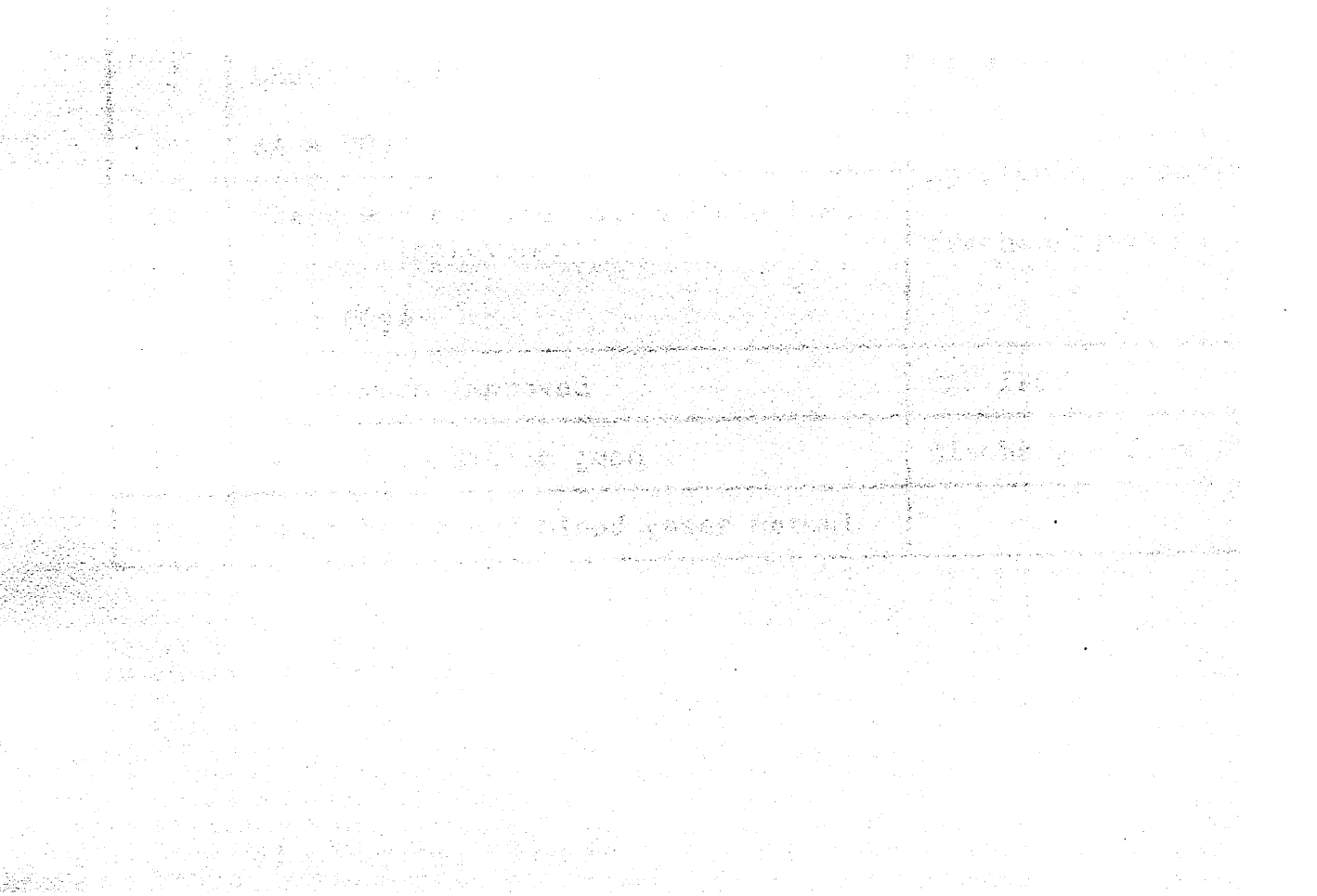


Figure 12.2b. Haematological and bacteriological data.
SGOT - serum glutamic oxalacetic transaminase.

Comment

This was the least severely ill patient of the series. Nevertheless hypoxaemia was marked and oxygen was required for nearly one week. Without oxygen the patient became cyanosed and extremely agitated. Haemoptysis (note also case 11) was noted during the first three days and heparin was commenced when an alternative diagnosis of pulmonary embolism was being considered.



Case 3 W.M. Male/21 yr
Admitted 14/9/70

DAY	COMMENT	TREATMENT
1	Road traffic accident: Simple # Ⓛ tibia	Long leg plaster general anaesthesia
2	Sudden onset: confusion/drowsiness dyspnoea cyanosis petechiae Arterial PO_2 - 53 mm Hg (air/spont.) Chest X-ray - 'snowstorm lung'	OXYGEN
3	Chest - clinical deterioration $\Delta A\text{-}a\ PO_2 \uparrow$	IPPV Aprotonin (trasylol) →
11	Chest - slow clinical/radiological improvement $\Delta A\text{-}a\ PO_2 \downarrow$	tracheostomy
15	Chest much improved	OFF IPPV
17	General condition good	Discharged from ITU
20	Chest X-ray and blood gases normal	

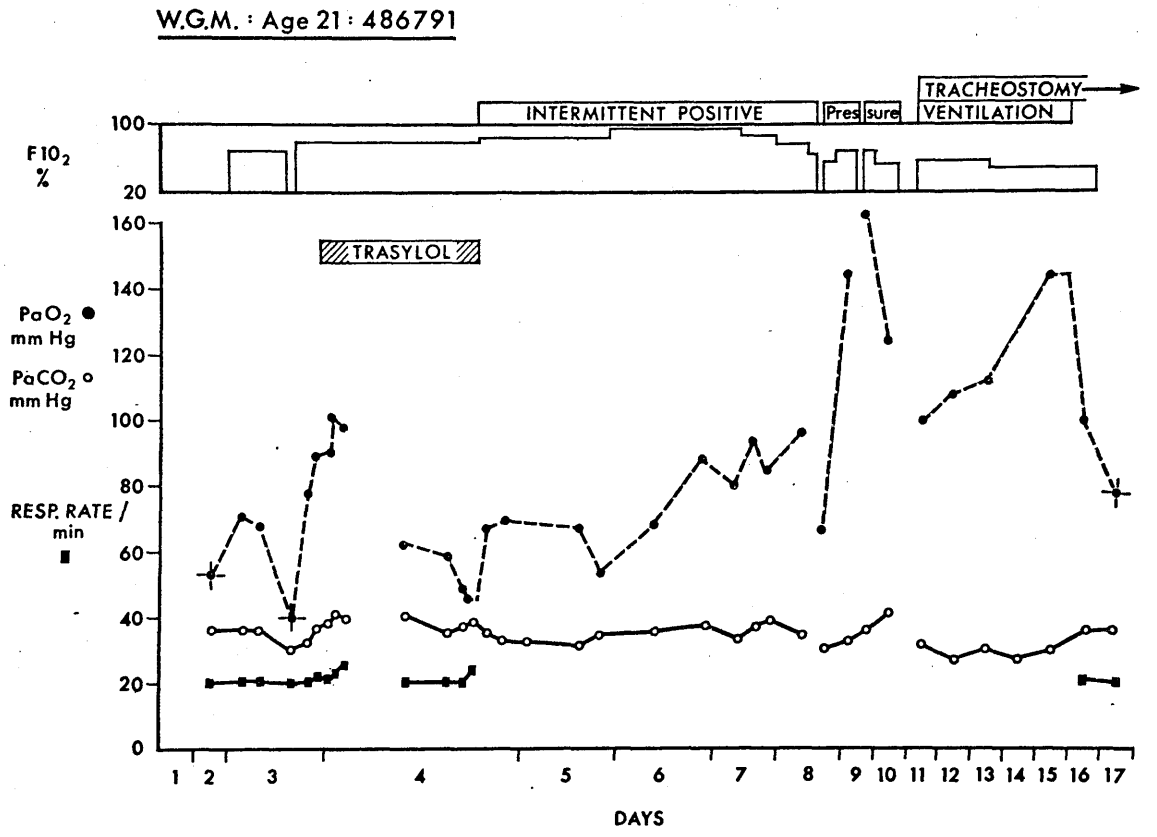


Figure 12.3a. Case 3. Respiratory and blood gas data.

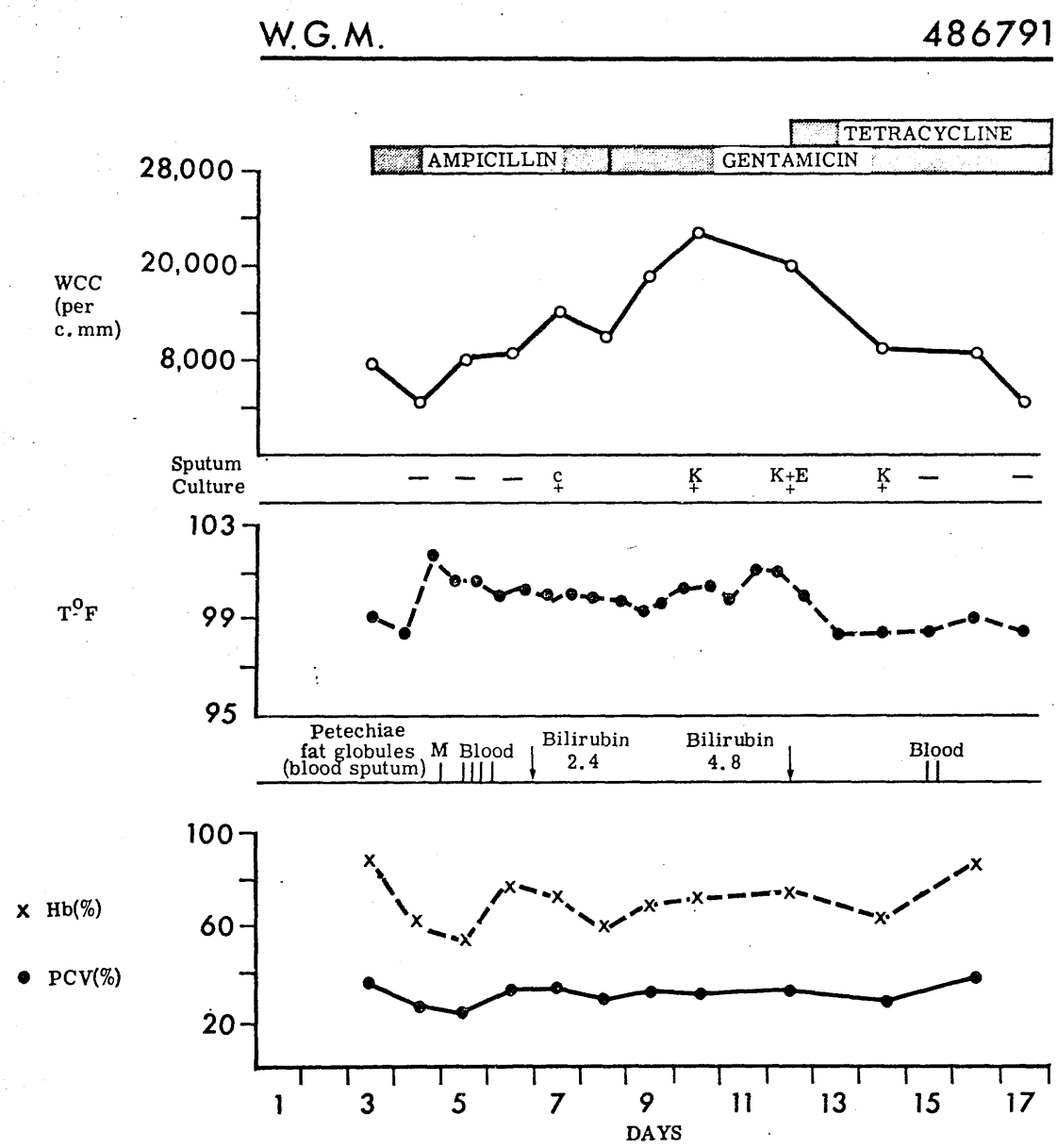


Figure 12.3b. Case 3. Haematological and bacteriological data.

c - coliforms m - mannitol
K - Klebsiella
E - enterococci

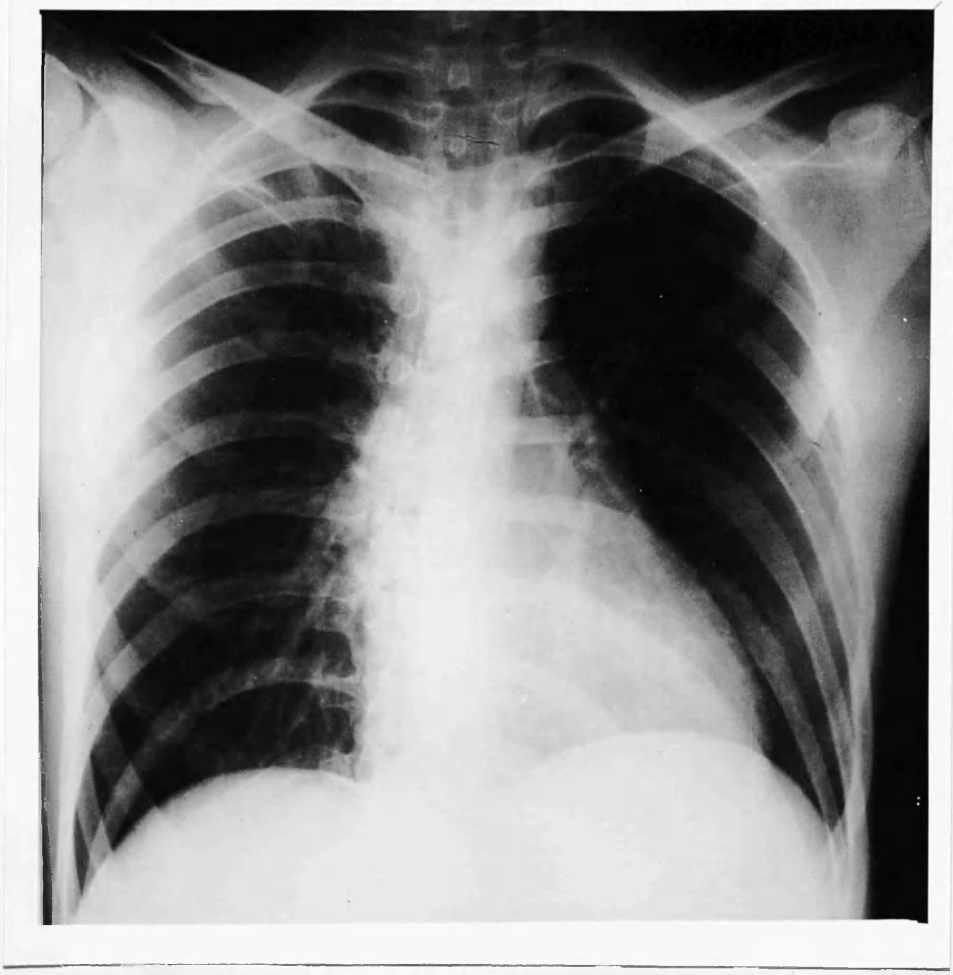
Comment

During the first day in the ITU (day 4 from the date of admission) an increase in the inspired oxygen concentration to about 75% produced a rise in arterial PO_2 to 100 mm Hg. On the basis of information such as that contained in figure 12.9, a course of the broad spectrum proteinase inhibitor, aprotonin (Trasylol), in a dose of 50,000 KIU hourly was given. The drug was singularly without effect. Indeed the progressive deterioration in arterial PO_2 and in the patient's conscious level during this period prompted the institution of intermittent positive pressure ventilation (IPPV). This experience helped to demonstrate the importance of early IPPV, preferably before the onset of major pulmonary gas exchange disturbances.

Another lesson was learned between days 8 to 10. On these days premature attempts were made to discontinue IPPV and on each occasion the patient became rapidly dyspnoeic and the arterial blood gases deteriorated. With hindsight it was realised that these were episodes of acute pulmonary oedema probably relating to the continuing presence of pulmonary vascular and alveolar abnormalities (see Discussion). Whatever the cause of the disturbance, weaning from the ventilator in subsequent cases was considered with greater circumspection, apparently to

good effect.

The further clinical course of this patient was complicated by a brief Klebsiella chest infection and the usual combination of anaemia, thrombocytopenia and hypocalcaemia. The sequence of changes in the chest radiograph (12.4 a,b,c) is characteristic of the changes observed in all the patients of the series.



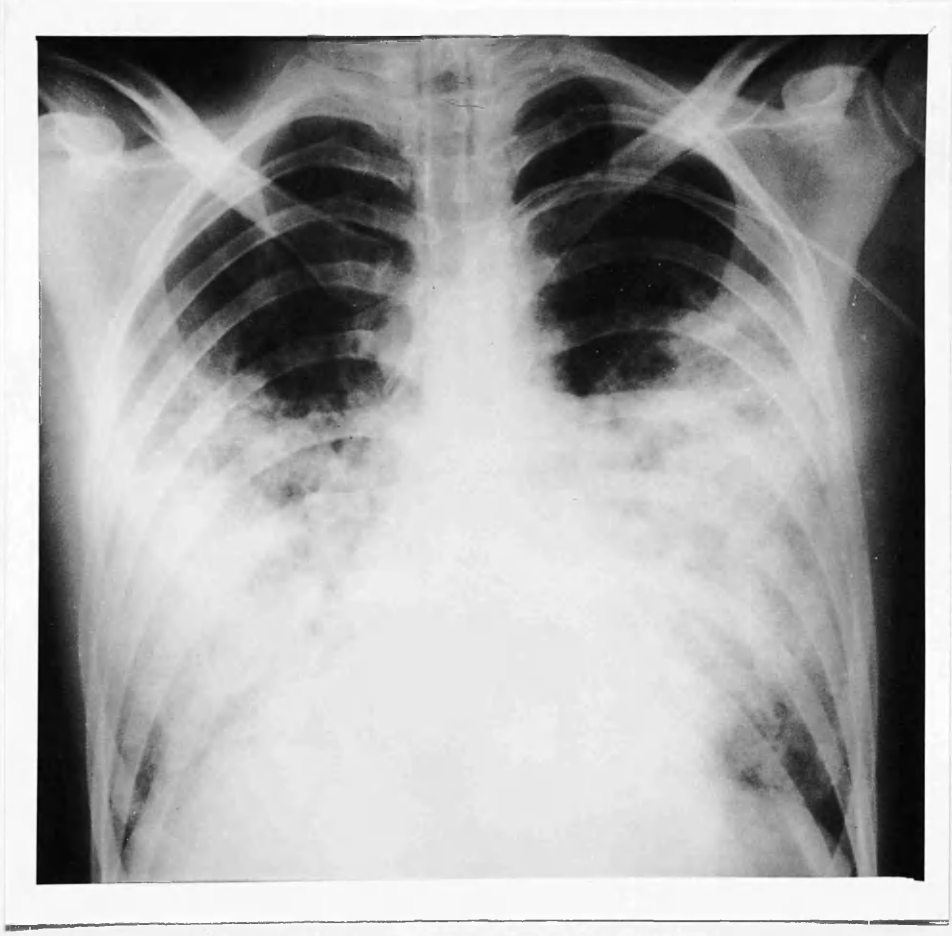


Figure 12.4. Chest radiographic appearances (a) on day of injury - normal (b) on 4th day after inju y - 'snowstorm lung'

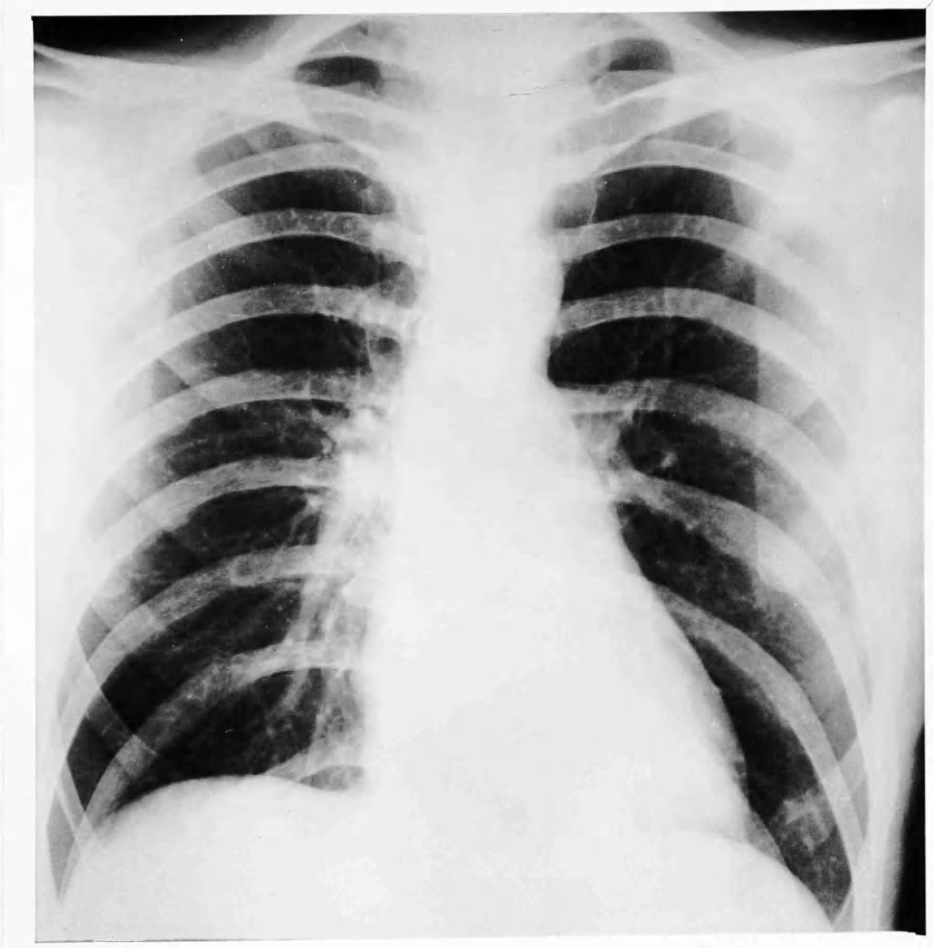


Figure 12.4 (cont'd). Chest radiographic appearances
(c) two months later - normal

Case 4 J.C. Male/26 yr
Admitted 2/7/71

DAY	COMMENT	TREATMENT
1	Road traffic accident: simple #Ⓡ femur/tibia, matatarsals both feet; compd.#Ⓡ patella Recovery from anaesthesia: - confusion/agitation dyspnoea cyanosis petechiae Arterial PO_2 - 53 mm Hg (air/spont.) Chest X-ray - widespread pulmonary oedema	Resuscitation Routine surgery General anaesthesia OXYGEN:IPPV tracheostomy
5	Chest - clinical/radiological improvement Δ A-a $PO_2\downarrow$	OFF IPPV
6	Chest X-ray - clear blood gases almost normal	Discharged from ITU

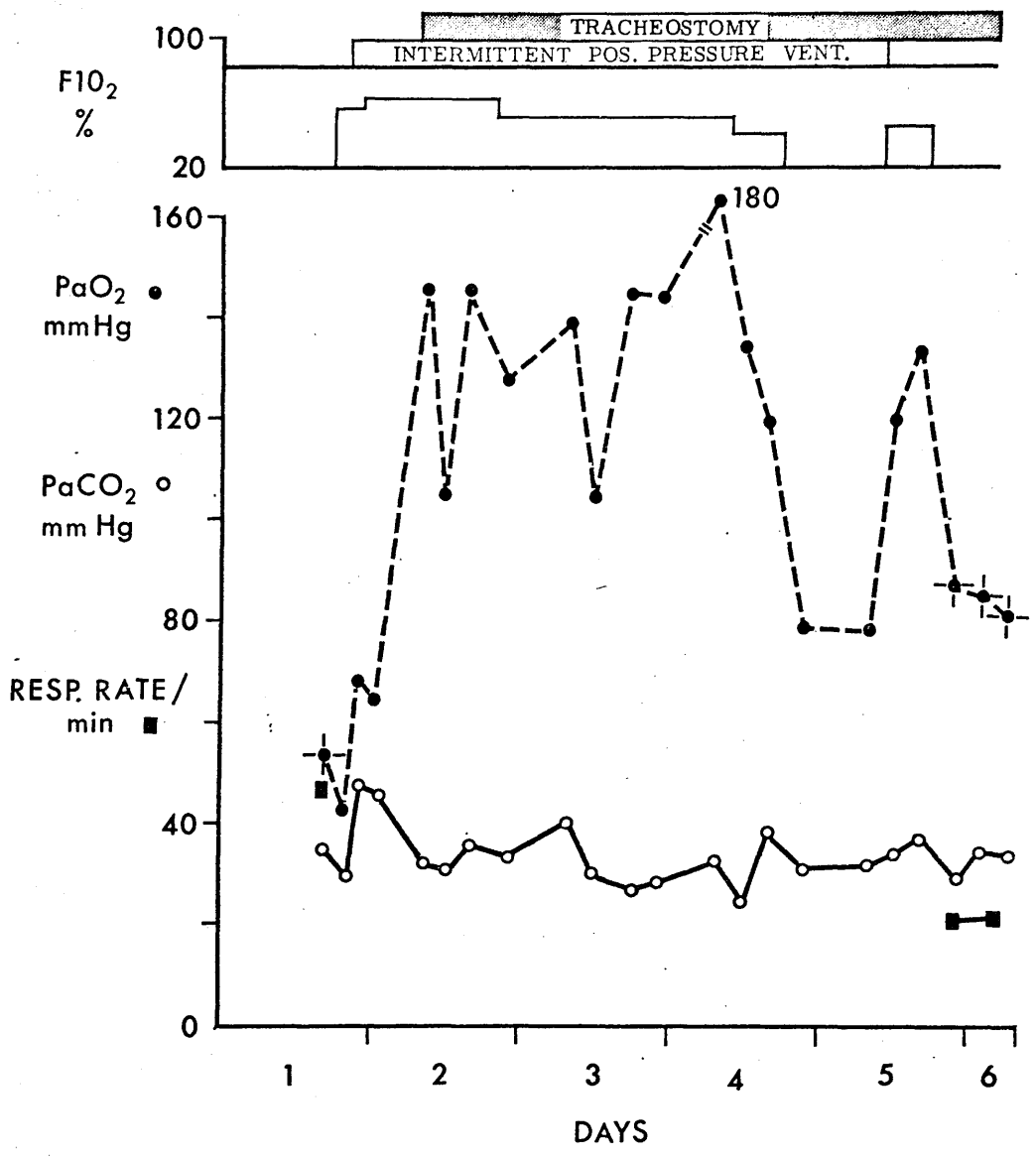


Figure 12.5a. Case 4. Respiratory and blood gas data.

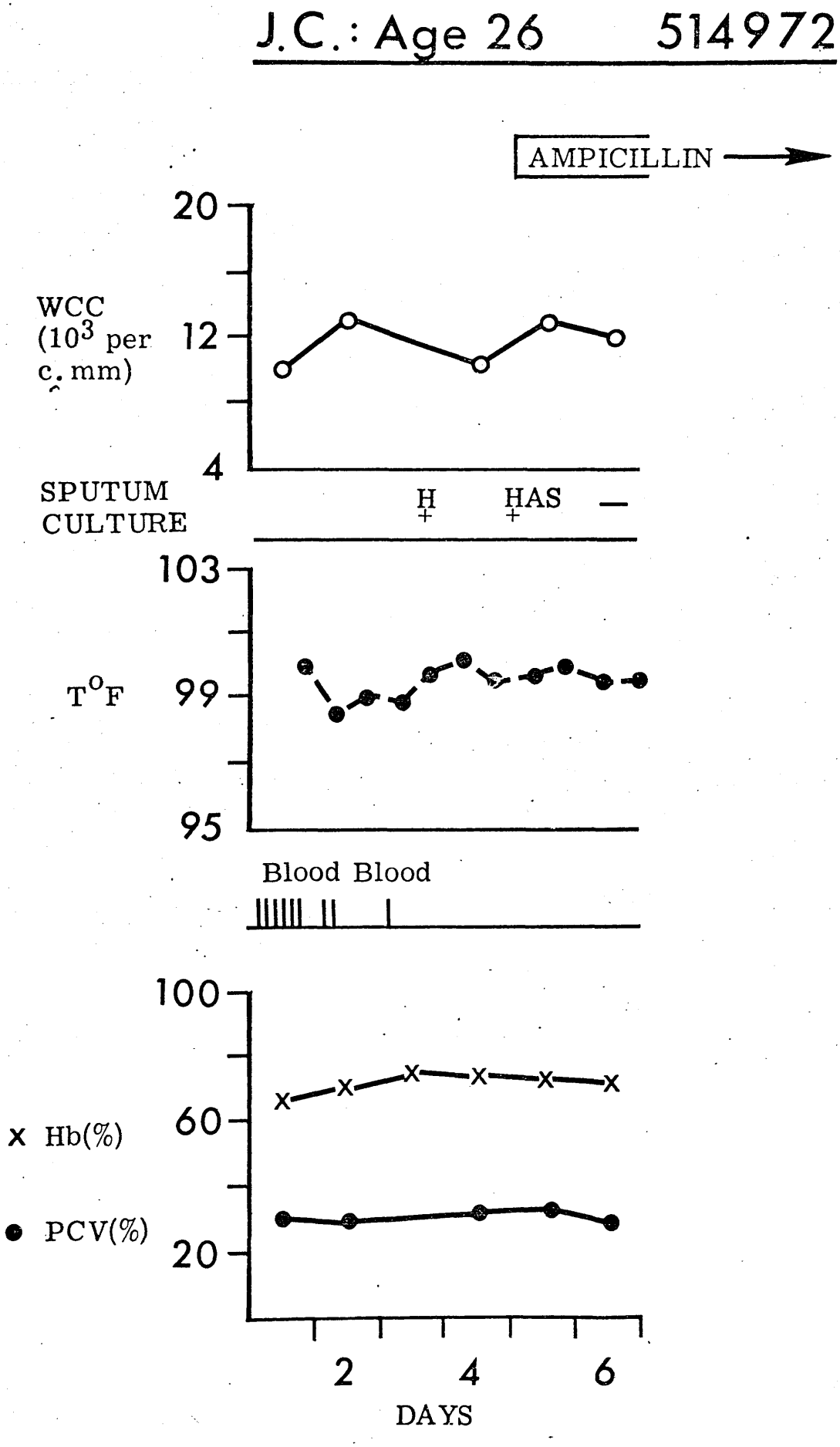
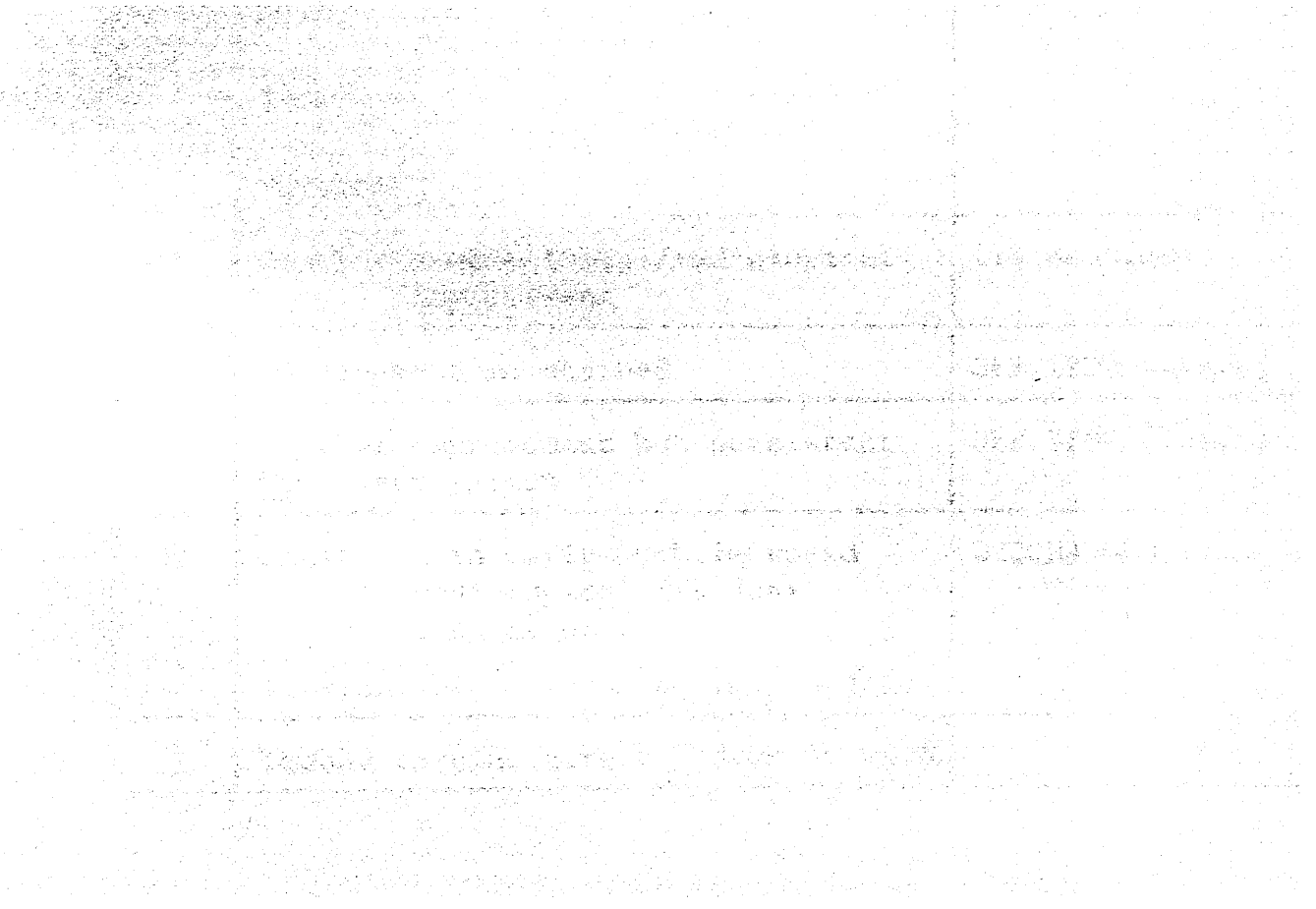


Figure 12.5b. Case 4. Haematological and bacteriological data.
H - haemophilus AS - aerobic streptococci.

Comment

This patient became confused and agitated during recovery from anaesthesia, and was reintubated and ventilated in haste because of the speed of deterioration in his clinical condition. The subsequent course of treatment was uneventful and no major infection ensued.



Case 5 J.T. Male/71 yr
Admitted 31/10/71

DAY	COMMENT	TREATMENT
1	Ruptured aortic aneurysm	Resuscitation Insertion bifurcation graft
2	Sudden onset : confusion dyspnoea cyanosis Arterial PO_2 - 53 mm Hg (air/spont.) Chest X-ray - widespread parenchymal nodulation	OXYGEN: antibiotics: frusemide; digoxin
5	Chest - clinical/radiological deterioration Arterial PO_2 - 52 mm Hg (oxygen at high concn.) Petechiae	IPPV
13	Chest - slow clinical/radiological improvement	tracheostomy
16	Improvement maintained	OFF IPPV (start)
22	Further improvement but persistent hyperventilation	OFF IPPV (final)
30	Chest - clinically much improved radiological residual changes only Arterial PO_2 - 74 mm Hg (air spont.)	DISCHARGED from ITU
33	Sudden cardiac arrest - died in ward	

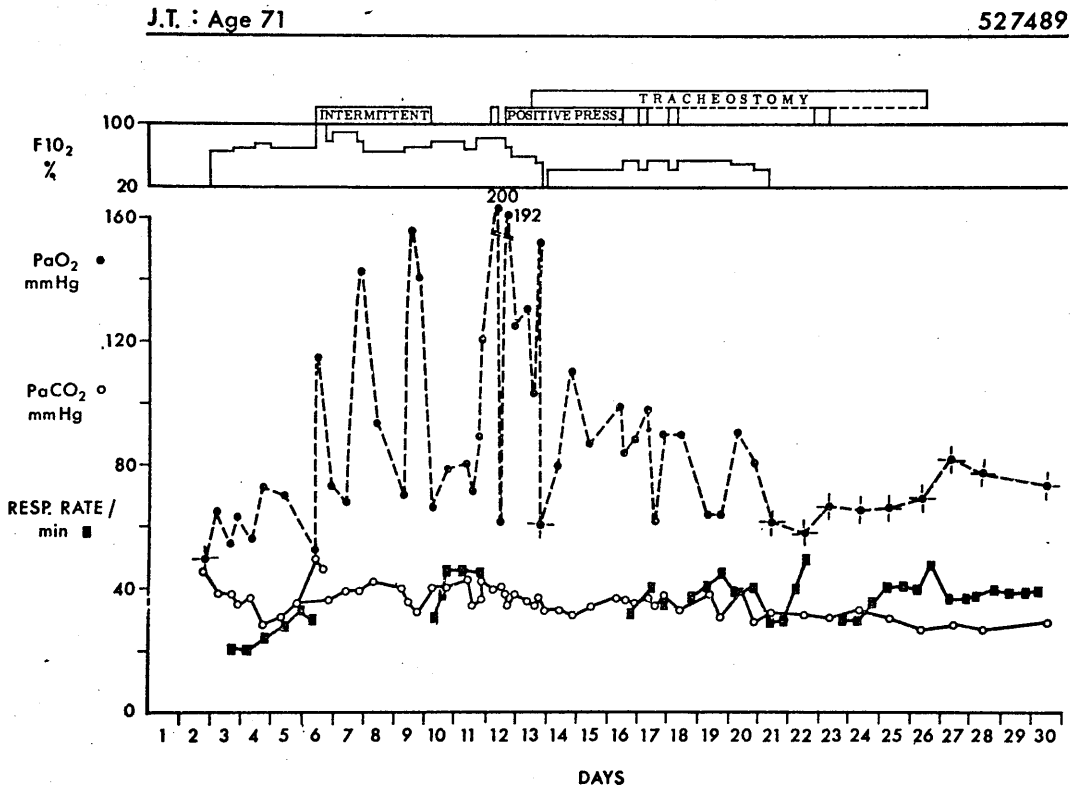


Figure 12.6a. Case 5. Respiratory and blood gas data.

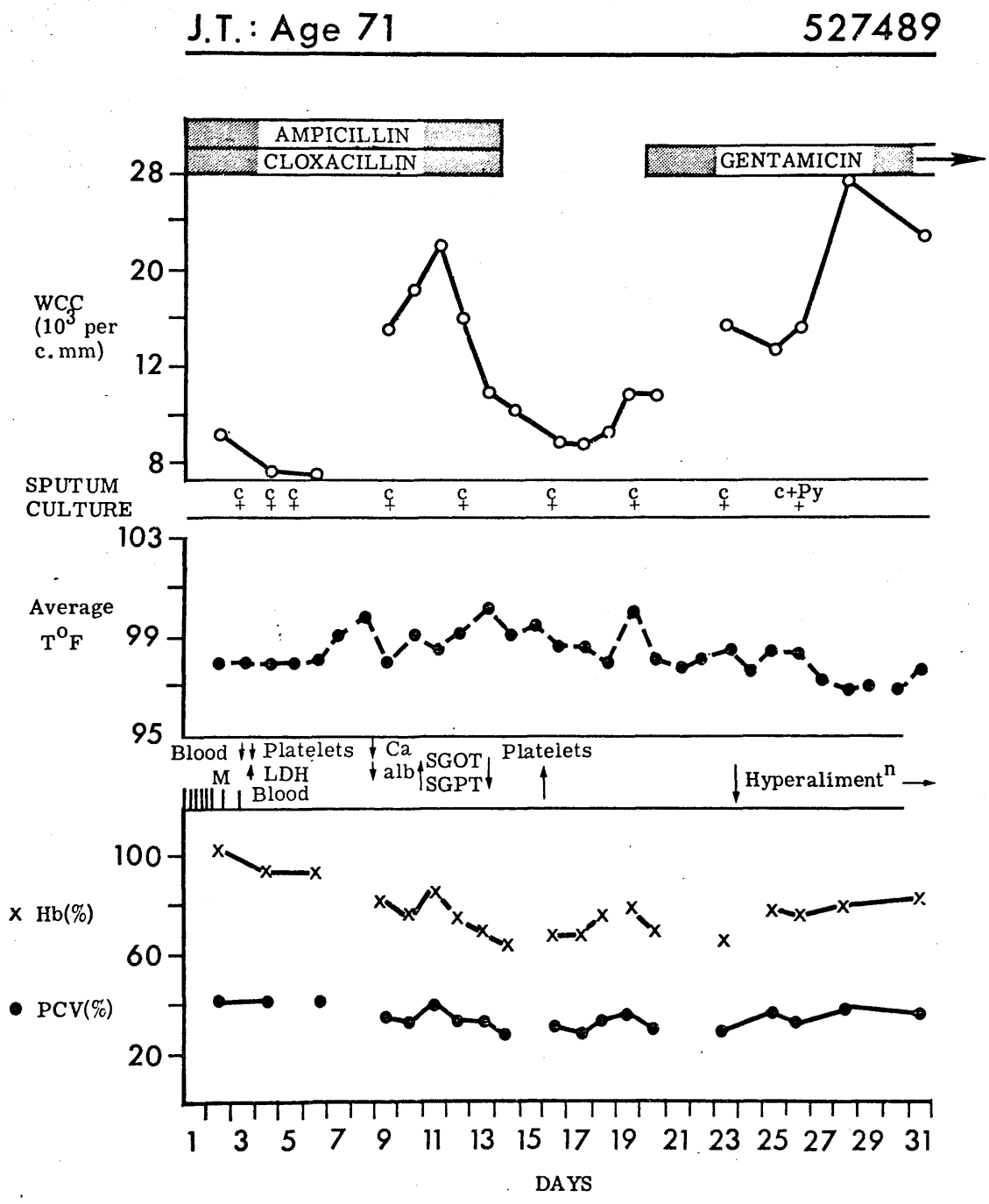


Figure 12.6b. Case 5. Haematological and bacteriological data.
c - coliforms: Ca - calcium:
Py - pseudomas pyocyanea: m - mannitol
SGOT - serum glutamic oxalacetic transaminase
SGPT - serum glutamic pyruvic transaminase

Comment

This patient was one of the two without bone fractures. At operation on the day of admission a Teflon graft was inserted for ruptured aortic aneurysm. Between days 2 and 5 he developed all the features of the fat embolism syndrome including very convincing petechiae. The subsequent clinical course was protracted before successful weaning from the ventilator was achieved. Hyperventilation was a striking feature during the weaning process although no single cause was detected apart possibly from residual infection. Cachexia was also present and a course of intravenous hyperalimentation was given; (the importance of the latter in the management of long-stay ITU patients was just being appreciated at this time).

Three days after return to the ward the patient had a sudden cardiorespiratory arrest from which he did not recovery. No autopsy was performed.

Case 6 M.H. Female/72 yr
Admitted 29/9/72

DAY	COMMENT	TREATMENT
1	Road traffic accident; simple # pelvis, femur, tibia and ulna Sudden onset: coma dyspnoea petechiae Arterial PO_2 - 58 mmHg (oxygen at high concn.) Chest X-ray - widespread 'fluffy' opacities	Resuscitation Skeletal traction Local anaesthesia OXYGEN
4	Unconscious Chest - clinical/radiological deterioration Δ A-a PO_2 ↑	IPPV/PEEP Tracheostomy Gentamicin Digoxin, frusemide
9	Chest - clinical/radiological improvement Δ A-a PO_2 ↓	
11	Continued respiratory improvement Conscious level only fair	OFF IPPV/PEEP (start)
12 - 25	Recurrent pulmonary infection	Carbenicillin
26	Improvement	OFF IPPV (final)
37	Much improved: lucid, active	Discharged from ITU

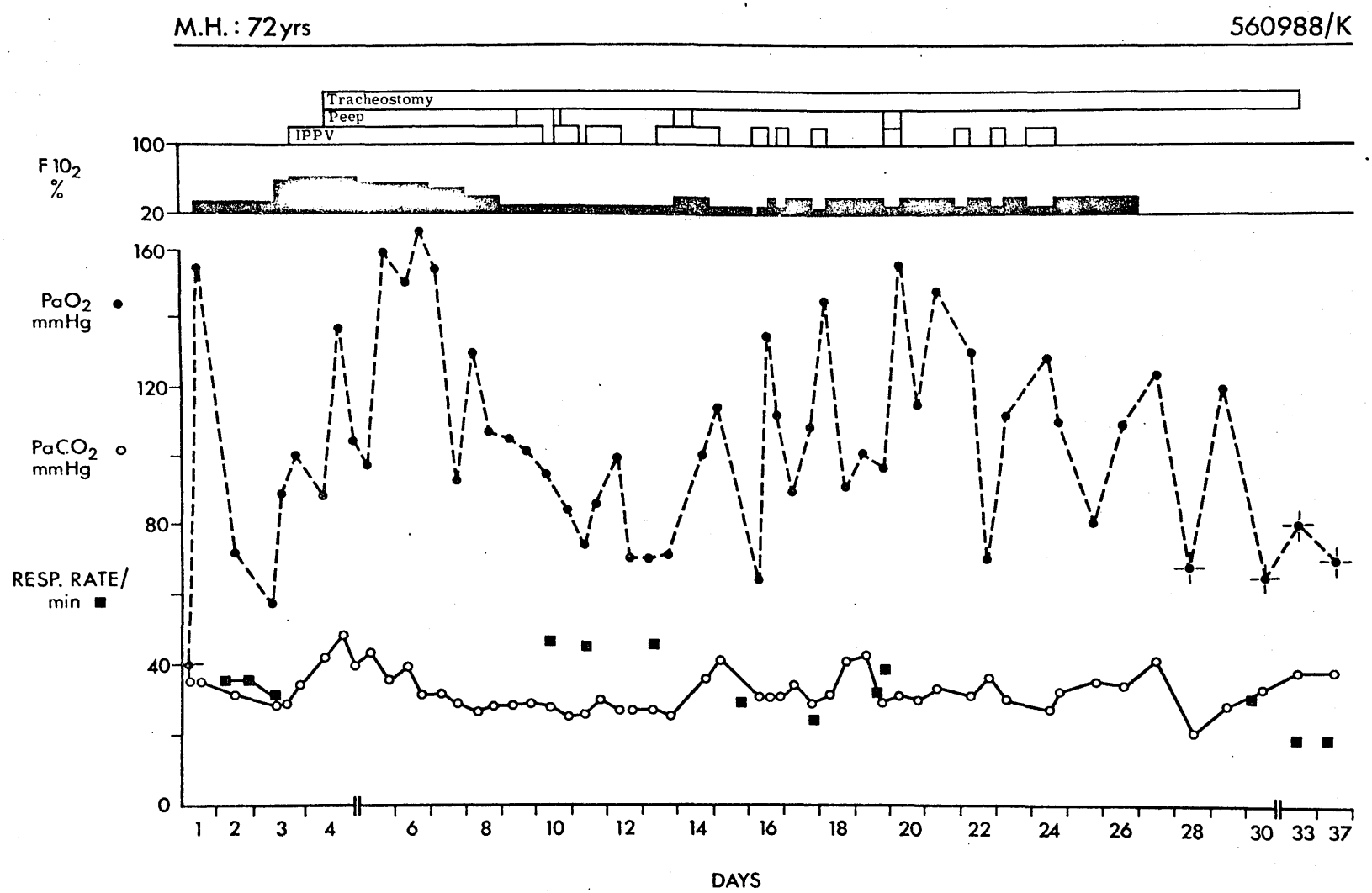


Figure 12.7a. Case 6. Respiratory and blood gas data.

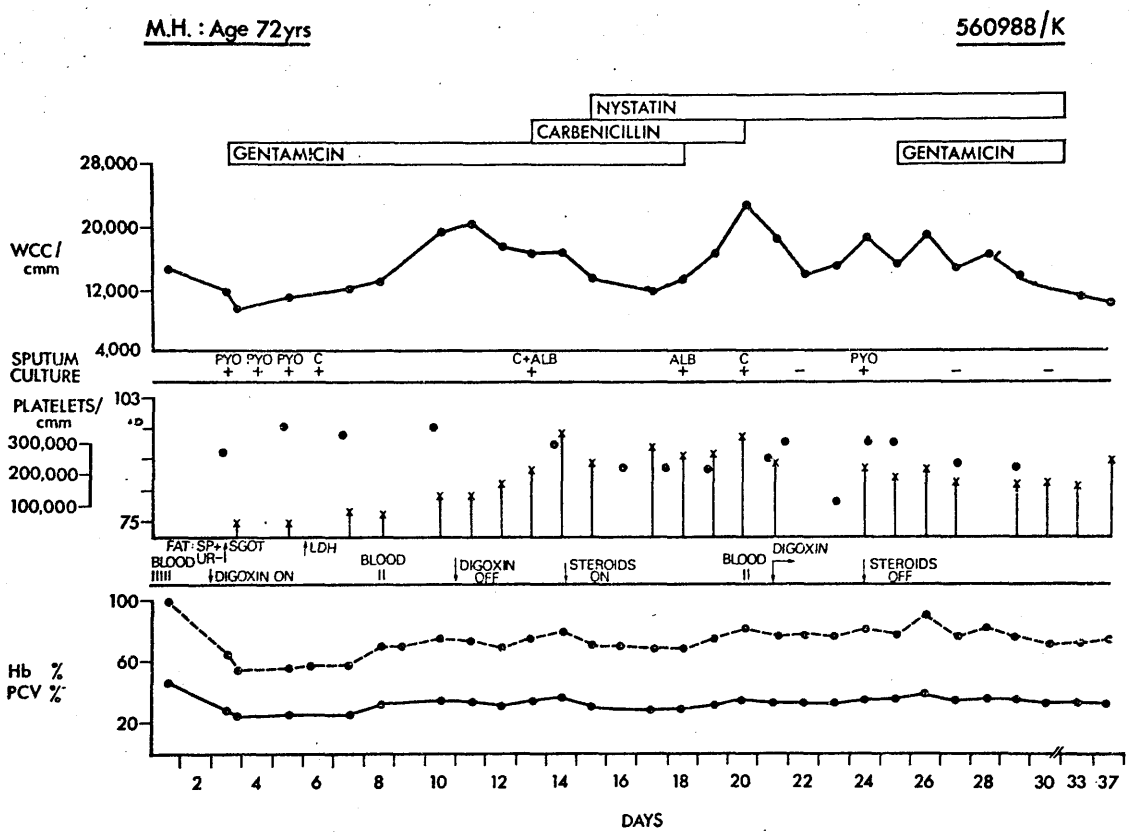
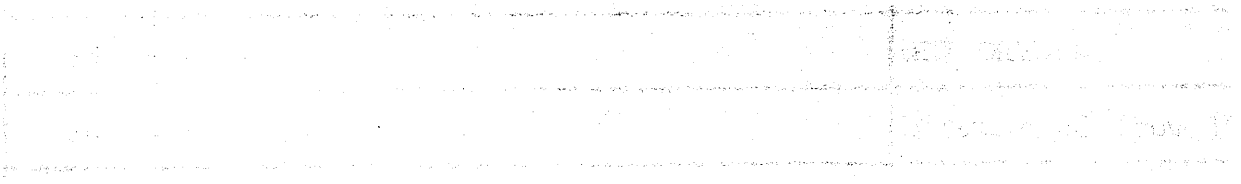


Figure 12.7b. Case 6. Haematological and bacteriological data.
PYO - pseudomas pyocyanea.
CALB - candida albicans
SGOT - serum glutamic oxalacetic transaminase
C - coliforms

Comment

This patient was the eldest of the series and during the acute phase of resuscitation was extremely ill. On admission to the ITU she was comatose; in common with the other patients of the series no head injury had been sustained and conscious level was apparently normal at the time of admission to hospital. The initial response to IPPV was slow and for the first time in the series, positive end-expiratory pressure (PEEP) was added to the ventilator regimen with gratifying effect. The later clinical course was complicated by recurrent pulmonary infection associated with bronchospasm, the persistence of which prompted the administration of steroids for one week; no obvious benefit resulted. Recovery thereafter was slow but sure.



Case 7 H.M. Male/66 yr
Admitted 9/2/73

DAY	COMMENT	TREATMENT
1	Tractor injury: #pelvis, 3 ribs Sudden onset: hypotension coma dyspnoea cyanosis Arterial PO_2 - 47 mmHg (oxygen at high concn.)	Resuscitation OXYGEN IPPV
5	Petechiae - neck/conjunctivae; frequent dysrhythmias Slow resolution lung lesion; platelets - 35,000/cmm	Tracheostomy Carbenicillin PEEP
14	Cerebral state fair ΔA-a $PO_2\downarrow$	OFF IPPV (start)
20	Mentally clear (Isaiah - Chp. 40 v. 29) Continued slow resolution lung lesion	
24	Much improved	OFF IPPV (final)
28	Well	OFF OXYGEN
30	In good shape	Discharged from ITU

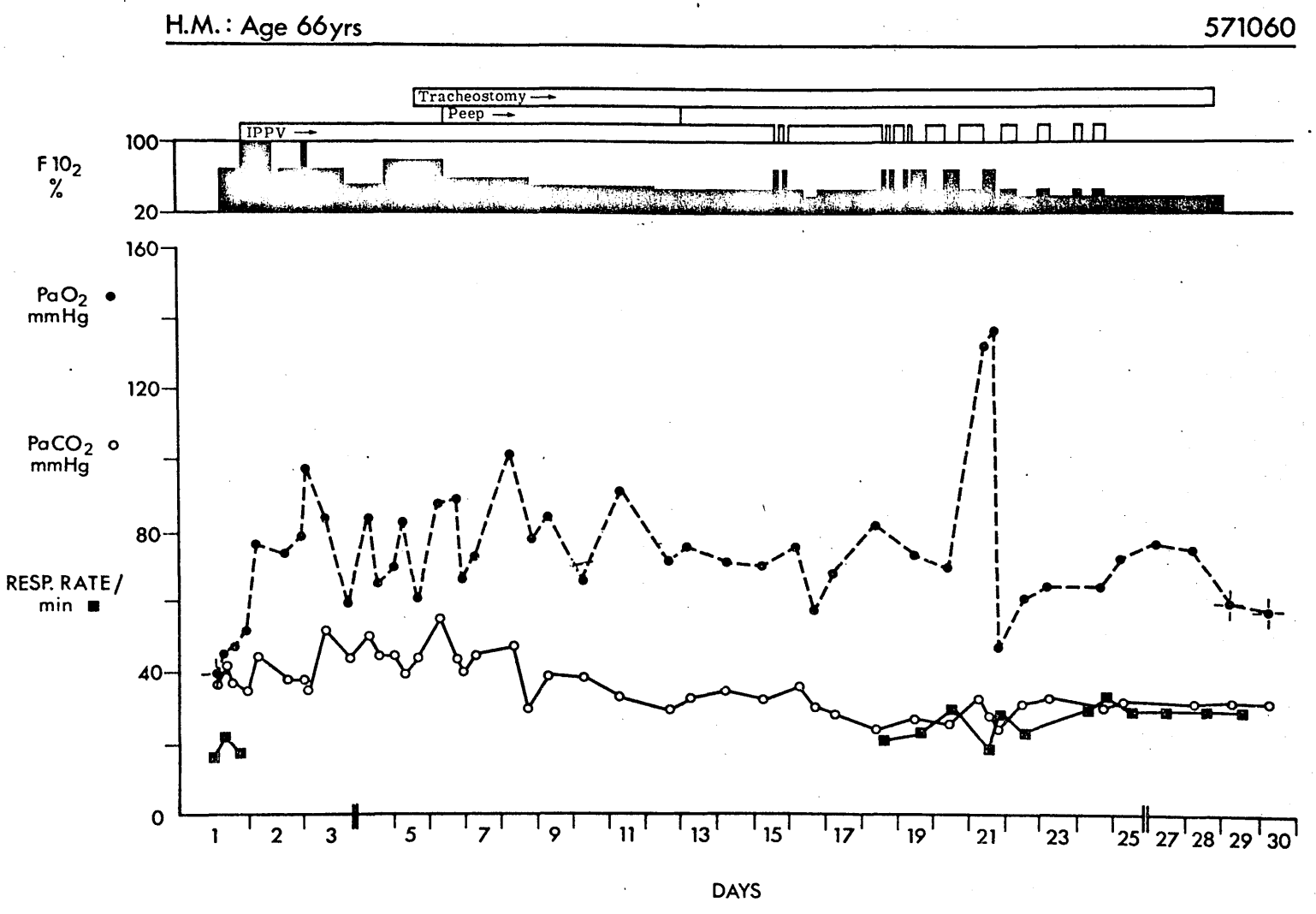


Figure 12.8a. Case 7. Respiratory and blood gas data.

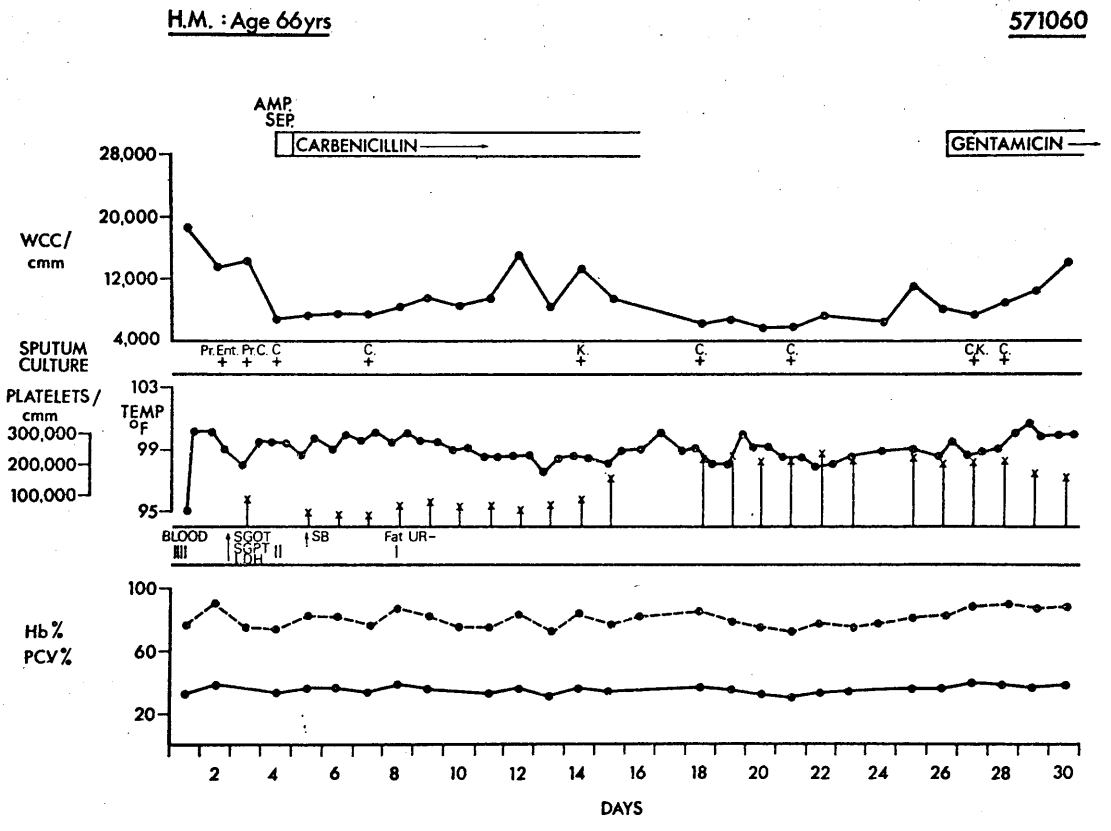


Figure 12.8b. Case 7. Haematological and bacteriological data.
Pr. - proteus. SGOT - serum glutamic oxalacetic transaminase. Ent - enterococci
SGPT - serum glutamic pyruvic transaminase.
c. coliforms. LDH - lactate dehydrogenase
K - Klebsiella. SB - serum bilirubin

Comment

This island crofter/lay preacher was crushed by his tractor which overturned. Within two hours of transfer from Oban the patient's condition rapidly deteriorated and he became shocked. The main features after resuscitation were sustained elevation of the alveolar/arterial PO_2 gradient and protracted thrombocytopenia. Weaning from the ventilator proved difficult apparently because of marked inanition. When the patient finally recovered and was told how fortunate he had been to survive the accident, he indicated that luck was not involved and quoted from Isaiah; 'He giveth power to the faint; and to them that have no might he increaseth strength.' So much for intravenous hyperalimentation.

Case 8 I.S. Female/17 yr
Admitted 14.11.74

DAY	COMMENT	TREATMENT
1	Stab injury (L) kidney, renal artery; stomach, pancreas, liver. Platelets 40,000/mm^3. PaO_2 - 40 mmHg (IPPV/100% O_2). Chest X-ray - massive pulmonary oedema.	(L) nephrectomy; excision tail pancreas; repair stomach, liver Resuscitation: 12½L fluid, IPPV (100% O_2 + PEEP), calcium, steroids, digoxin.
3	AM General condition much improved ΔA-a PO_2 marked↓; platelets 70,000mm^3 PM Petechiae chest/arms; ΔA-a PO_2↑	Ampicillin: frusemide PEEP OFF
4	Tachycardia, fever; platelets 55,000/mm^3. Chest X-ray - extensive pulmonary mottling	PEEP ON Lincomycin/Gentamicin tracheostomy
8	Chest - clinically improving. ΔA-a PO_2 steady↓; X-ray clearing; Platelets 220,000/mm^3. Petechiae neck/conjunctivae - fresh crop	Carbenicillin
11	Continued improvement. DVT (L) leg	PEEP OFF
14	ΔA-a PO_2↓; tachycardia	PEEP ON
17	Sudden marked respiratory deterioration (R) pneumothorax confirmed: B.proteus - trach.asp/L.F.C. - urine	Chest drain
20	Sudden onset (L) apical pneumothorax; recurrence (R) pneumothorax	PEEP OFF; further chest drains. Cloxacillin
23	Very ill; Ps.pyocyanea-trach. asp/urine; air leak +++ both chest drains	Chloramphenicol/cotrimoxazole, digoxin
32	Continues very ill; sustained fever; ? L subphrenic abscess	Carbenicillin
36	Improved; Ps. sepacia-trach. asp: trach. ulceration	OFF IPPV (start)
38	Pain (L) lumbar region	
43	In fair shape; WCC remains high	OFF IPPV (final)
45	Fluctuant, tender swelling (L) loin	
47	General condition fair	Drainage (L) perinephric/subdiaphragmatic abscess
50	General condition good	Discharged from ITU

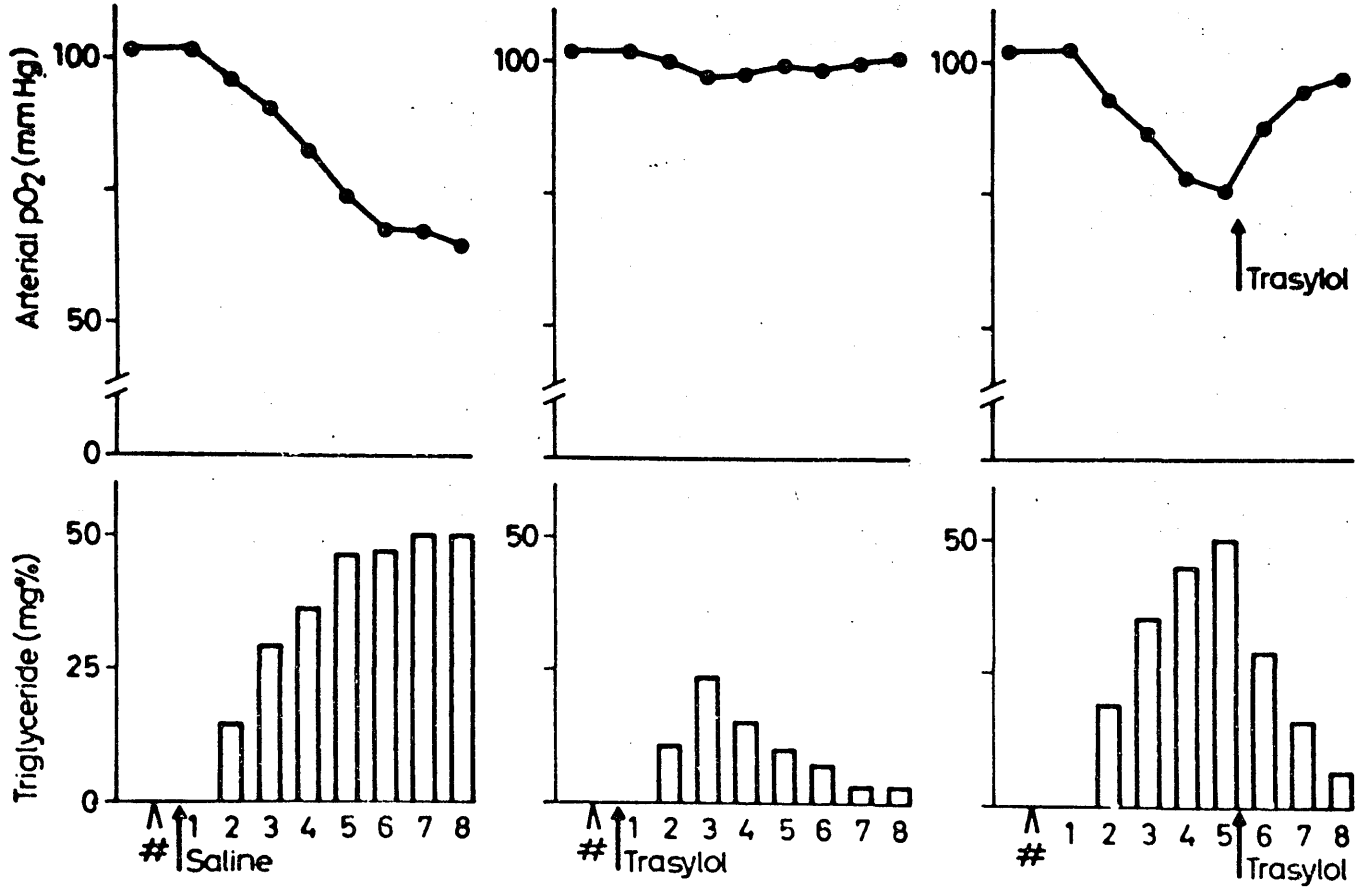


Figure 12.9. Fat globules and arterial PO2 in 30 dogs subjected to trauma.

Comment

This unfortunate girl had extensive retroperitoneal soft tissue injury and was in a parlous condition for the first 36 hours after injury but then markedly improved. The appearance of features of the fat embolism syndrome was rapid and the lungs were the principal focus of attack. As in previous cases recurrent pulmonary infection proved a major problem, further complicated in this instance by pulmonary barotrauma with sequential bilateral pneumothoraces. When the respiratory sequelae had been overcome, surgery was required for a large left perinephric abscess. Thereafter the patient's recovery was full and complete.

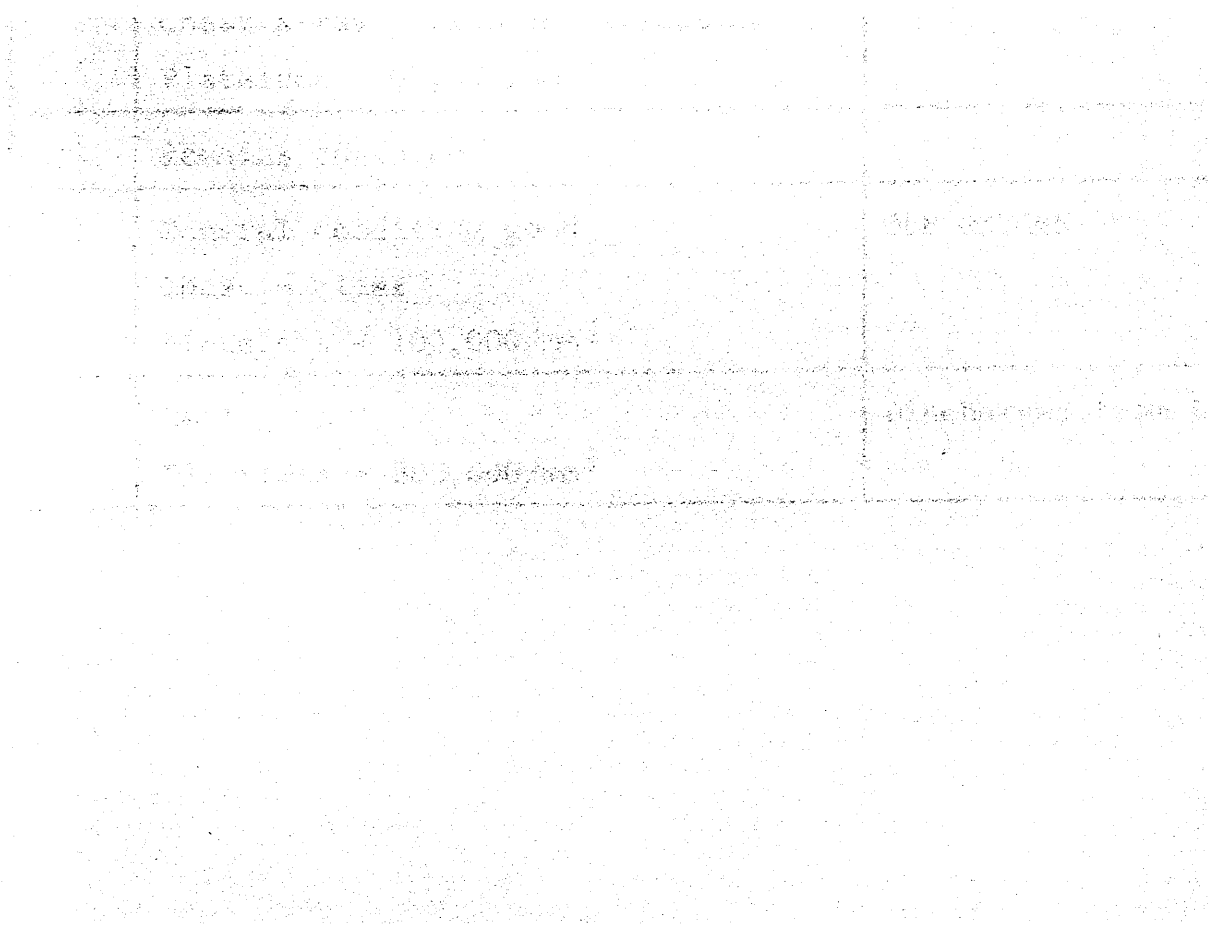
Follow-up studies have revealed only minor residual pulmonary problems and the patient has successfully completed her training as a nurse. The differential diagnosis in this case was the most difficult of the series and it would be impossible to exclude other possible causes of acute respiratory distress e.g., overtransfusion and shock.

Case 9 A.B. Female/20 yr
Admitted 30/12/74

DAY	COMMENT	TREATMENT
1	Road traffic accident: simple # pelvis, (R) femur; compd # (L) femur	Resuscitation Routine surgery General anaesthesia IPPV
2	Tried off IPPV - unsuccessful: Platelets - 25,000; bleeding tendency: Hb 4G, PaO_2 - 110 mmHg (IPPV/100% O_2)	Blood Coagulation factors Thymoxamine Recommence IPPV
4	Petechiae (upper chest) Chest X-ray - diffuse mottling	Tracheostomy Blood
6	Platelets 45,000; jaundice +++ ΔA-a $PO_2\downarrow$	Gentamicin
9	General condition much improved Fever (41°C): jaundice +++	OFF IPPV
15	General condition good	Remanipulation (R) femur General anaesthesia
16	Recovered well from surgery	Discharged from ITU

Comment

This was the second patient in the series who presented with features of the fat embolism syndrome during recovery from general anaesthesia. The response to IPPV and oxygenation was gratifying and no major complications ensued.

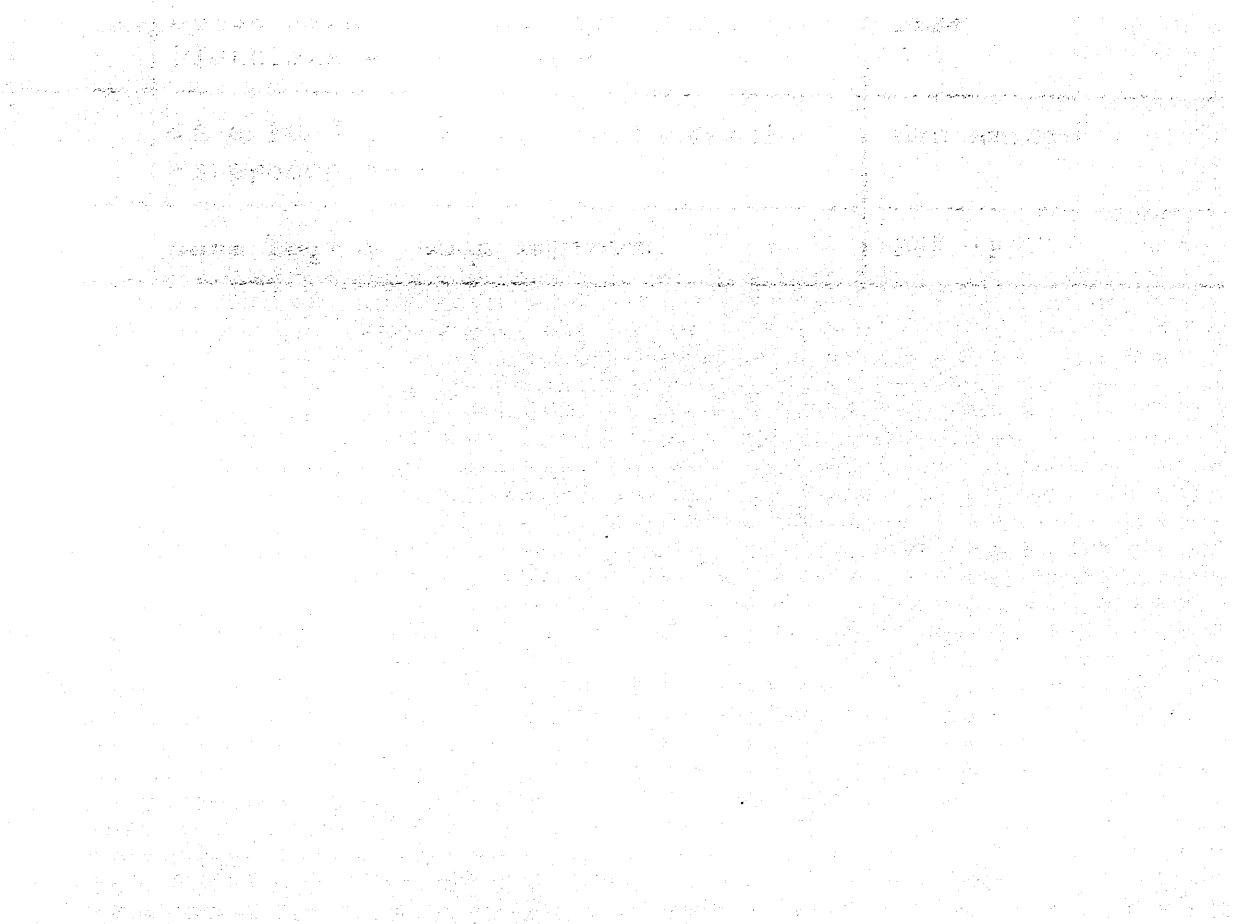


Case 10 A.McC. Female/60 yr
Admitted 28/1/75

DAY	COMMENT	TREATMENT
1	Road traffic accident: Simple # ribs, pelvis, tibia	Resuscitation
3	Sudden onset: confusion cyanosis petechiae Arterial PO_2 - 56 mm Hg (air/spont.) Chest X-ray - fine opacification Platelets - 60,000/mm^3	OXYGEN physiotherapy
5	Remains confused	
8	General condition good Chest - clear Platelets - 100,000/mm^3	OFF OXYGEN
12	Well Platelets - 305,000/mm^3	Discharged from ITU

Comment

The principal presenting feature in this instance was confusion which was not immediately relieved by correction of hypoxaemia. Pulmonary gas exchange was closely monitored for three days by which time the patient had become lucid and it was clear that oxygen therapy was no longer required to maintain an adequate arterial PO_2.



Case 11 G.W. Male/20 yr
Admitted 4/7/78

DAY	COMMENT	TREATMENT
1	RTA: simple #Ⓡ tibia, rupture ligaments Ⓛ knee	Resuscitation Routine surgery General anaesthesia
3	Sudden onset: drowsiness dyspnoea petechiae EMI scan - diffuse oedema	
4	Arterial PO_2 - 60 mm Hg (air): haemoptysis. Chest X-ray - 'snowstorm lung' Platelets - 110,000/cmm	OXYGEN IPPV PEEP
10	ΔA-a $PO_2\uparrow$; fever; leucocytosis Ps.pyocynea-sputum	Gentamicin
15	ΔA-a $PO_2\downarrow$; much improved	OFF IPPV

Comment

As in case 3, this young man had a relatively minor injury to the lower limbs and was apparently making a routine recovery when his condition rapidly deteriorated. So striking were the cerebral manifestations that he was transferred to the regional Neurosurgical Institute for an Emiscan examination although there was no history of head injury. Mild diffuse cerebral oedema was noted but by this time the respiratory features were obvious and the diagnosis was not in doubt. Haemoptysis was present for the first three days (note also case 2).

The disturbance of pulmonary gas exchange responded slowly to IPPV augmented by positive end-expiratory pressure. A relatively short-lived respiratory infection responded to antibiotics and the patient's recovery was uneventful.

Treatment

A summary of the treatment, together with the outcome in each case, is presented in table 12.4. All the patients recovered from the acute condition and were discharged from the unit. Only one patient failed to make a long-term recovery (Case 5). After acute resuscitation, treatment consisted exclusively of oxygen and IPPV (in the later cases with PEEP). Heparin,

Table 12.4

FAT EMBOLISM
TREATMENT AND OUTCOME

PATIENT (SERIES NO.)	TREATMENT						Outcome
	Initial blood (units)	Antibiotics (Day Commenced)	Oxygen (days)	IPPV (days)	PEEP (days)	Drugs (days)	
J.H. (1)	2	Amp. (2): Ceph.	11	9	-	Mannitol (2)	Survival
D.B. (2)	2	Amp. Clox. (2)	7	-	-	Heparin (5)	Survival
W.M. (3)	4	Amp. (3): Gent: Tetr.	14	12	-	Aprotonin (1)	Survival
J.C. (4)	6	Amp. (5)	4	3	-	-	Survival
J.T. (5)	6	Amp. Clox. (1): Gent.	23	19	-	Mannitol (1) Frusemide Digoxin (10)	Survival
M.H. (6)	5	Gent. (3): Carb: Nystat.	26	21	7	Frusemide Digoxin (25+) Steroids (7)	Survival
M.H. (7)	4	Amp. Sep, (4): Carb.	28	24	8	-	Survival
I.S. (8)	12	Amp. (3): Gent/Linc (4): Carb. (8): Clox. (20): Chloram/Cotrimox (23): Carb. (32)	43	43	13	Frusemide Digoxin (21)	Survival
A.B. (9)	18	Amp. (-2): Clox. (-2): Gent. (3): Clox. (7): Magnapen (18).	7	6	-	Digoxin	Survival
A.McC. (10)	4	Pen. (-3): Amp. Clox. (4)	4	-	-	-	Survival
G.W. (11)	0	Gent. (10)	11	11	6	-	Survival

trasylol and a brief course of low dose hydrocortisone was given in one patient each, and appeared to be without effect. Antibiotics were given only when there was bacteriological confirmation of respiratory infection.

Discussion

The difficulty of making a definitive diagnosis of fat embolism is well recognised. Stainable fat in the sputum is common in pneumonia (Nuessle, 1951) and there are considerable technical problems associated with the demonstration of fat in the urine (Ross, 1970). The technique of Gurd (1970) in which pathological fat globules in venous blood could be detected both qualitatively and quantitatively has not been substantiated (Nolte et al, 1974); estimation of fatty acids and serum lipase is likewise unhelpful and may be misleading (Ross, 1969). All the other clinical aids, many of which have been mentioned in the present study, are too non-specific to be of diagnostic value. In particular, the so-called characteristic "snowstorm" appearance of the chest radiograph is not pathognomonic of fat embolism. Similar radiographic appearances may be present in any condition leading to acute pulmonary oedema and vascular congestion (Ashbaugh et al, 1967). The fall in platelets and calcium could be explained inter alia on the basis of intravascular coagulation which

appears to be a feature of fat embolism, but these are also common findings in patients with fractures (Ross, 1970) or major sepsis (Ledingham and McArdle, 1978). The anaemia, which was present in all 11 patients of this study, has been observed before in the fat embolism syndrome and has been attributed in part to haemodilution (for which there is more than one cause after trauma) and in part to intrapulmonary haemorrhage (Peltier, 1965). A haemolytic element may also be present with elevated serum bilirubin and urobilinogen in the urine. Superadded infection, if severe, can lead to bone-marrow depression.

In the absence of specific clinical and laboratory data, some authors have accepted that hypoxaemia without other explanation following long fracture is diagnostic of the fat embolism syndrome (Wright, 1971). Occasionally patients without fractures present with identical features (Herndon, Riseborough and Fischer, 1971) although the two included in this study had extensive soft tissue injury. The lack of specific diagnostic criteria in the fat embolism syndrome has led to the suggestion that it should be regarded simply as a variant of the acute adult respiratory distress syndrome (Ashbaugh et al, 1967). In the author's view this suggestion has much to recommend it.

The pathophysiology of the fat embolism syndrome is another controversial issue. The two main theories are (a) the mechanical, which suggests that fat, liberated at the site of fracture, is carried via the venous system to the lungs (Sevitt, 1962) and (b) the physico-chemical, which postulates that the normally stable emulsion of fats in the blood stream becomes unstable, producing an aggregation of chylomicrons into fat globules of more than 8 u in diameter (Evarts, 1965). The latter have been shown to act as emboli of blocking small capillaries (Harman and Ragaz, 1949). Most experimental work supports the view that the bone-marrow is the source of the emboli (Lancet, 1972) and Hallgren and his colleagues (1966) showed, in dogs, that the triglyceride of emboli recovered from the lung had a composition similar to that of bone-marrow but unlike that of chylomicron fat.

In an experimental study (Bruecke et al, 1971), a biphasic physiological response was observed to follow the intravenous injection of the triglyceride, triolein. During the first three hours pulmonary vascular obstruction was considered to

have been the cause of a 60% fall in cardiac output and a 30% increase in physiological dead space. Thereafter parenchymal damage was associated with marked hypoxaemia which the authors attributed to ventilation/perfusion inequalities rather than right to left shunt. The parenchymal lesion took the form of widespread alveolar oedema and haemorrhage caused possibly by oleic acid released by hydrolysis of triolein. Free fatty acids are known to be toxic to tissues (Baker, Pazell and Peltier, 1971), and particularly to capillaries (Fonte and Hausberger, 1971). This effect may be caused by displacement of lipoproteins from cell walls and their subsequent destruction (Elkes, 1949) or by removal of calcium from cell walls (Jefferson and Necheles, 1948). Hypocalcaemia is certainly a feature of the fat embolism syndrome although, as previously mentioned, disseminated intravascular coagulation may also consume calcium together with platelets, with subsequent release of intensely vasoactive substances, such as 5-hydroxtryptamine and histamine. Either of these mechanisms could lead finally to diminished lung surfactant activity and the formation of hyaline membranes (Peltier, 1965; Ashbaugh et al, 1967).

Hypoxaemia is clearly of fundamental significance in the fat

embolism syndrome. Its presence accounts for most of the clinical features of the syndrome and its elimination should be the main (and possibly exclusive) aim of treatment. The view has been expressed that hypoxaemia cannot explain the cerebral manifestations observed in some patients in that the administration of oxygen does not always relieve these symptoms (Sevitt, 1972). This argument is used to support the claim that cerebral fat emboli may also be of clinical significance. However, it should be appreciated that raising the inspired oxygen concentration may not always correct a critical reduction in oxygen availability to the brain in a patient with a low cardiac output and a low haemoglobin concentration. Both these factors may be present in the acute phase of the fat embolism syndrome and furthermore the associated hyperventilation, although not synonymous with hypocapnia, may diminish cerebral blood flow. In addition, if hypoxaemia has been present for any length of time, with or without the presence of fat emboli in the cerebral vessels, cerebral oedema may result. Under these circumstances, the conscious level in a previously comatose patient may not improve immediately in response to oxygen administration.

Four procedures would appear to be of importance in treatment -

oxygen administration to provide prompt relief of hypoxaemia (Baker, 1976), intermittent positive pressure ventilation to prevent progressive deterioration in pulmonary gas exchange (Galloon and Chakravarty, 1967), positive end-expiratory pressure to reduce the shunt effect (Suter, Fairley and Isenberg, 1975; Gilston, 1977) and sedation, combined with muscle relaxants, to reduce cerebral metabolic rate and eliminate the strong afferent drive arising most probably from the stretch, or "J", receptors in the lung (Guz et al, 1970). The optimal arterial PO_2 would appear to be about 100 mm Hg - high enough to counteract any hypoperfusion effect secondary to cerebral oedema. Other treatment is purely secondary to the main aim of achieving and maintaining adequate tissue oxygenation. Digoxin may be necessary when evidence of cardiac failure is present and diuretics may be used to complement the effects of positive pressure ventilation, particularly in the event of inadvertent positive fluid balance. The judicious use of intravenous fluids may promote an improvement in cardiac output.

This study indicates that adoption of a therapeutic regimen which is designed simply to relieve hypoxaemia and support

pulmonary gas exchange can be consistently successful. Nevertheless rigorous attention to detail is mandatory, with avoidance of any factor which might precipitate the re-appearance of pulmonary oedema. To this end total elimination of voluntary muscle movement during the acute phase of the condition is considered important as is avoidance of premature weaning from the ventilator. In the latter connection the chest radiograph and the platelet count would appear to be of predictive significance.

Intensive care methods such as those described above have reduced the mortality in the fat embolism syndrome. A precise comparison of results between different groups of patients is difficult because of the variable severity of the syndrome. Nevertheless all the patients in the present study had both systemic and pulmonary signs and symptoms, in spite of which all survived. In other recent reports the mortality varied from 25 to 32% (Thomas and Ayyar, 1972; Baker, 1976; Wildsmith and Masson, 1978).

Evidence that other forms of treatment are necessary in the fat embolism syndrome is lacking. These include corticosteroids

(Ashbaugh and Petty, 1966; Fischer et al, 1971), ethanol (Hermann, 1932), heparin (Sage and Tudor, 1958), low molecular weight dextran (Evarts, 1970), clofibrate (Cole, 1971), aprotonin (Morl, 1967), hypothermia (Larson, 1968) and hyperbaric oxygen. The side effects of these various drugs (Baker, 1976) would seem to be worth avoiding in the treatment of a condition which almost always regresses spontaneously and completely (Lancet, 1972).

Chapter 13

Treatment of Accidental Hypothermia: A Prospective Clinical Study

Accidental hypothermia is the term used to describe the patho-physiological state in which an unintentional reduction in central temperature to below 35 deg C has occurred (BMA Special Committee, 1964; Royal College of Physicians Committee, 1966). It is thus distinguished from hypothermia induced for the safer conduct of major cardiovascular surgery or for other therapeutic purposes. Accidental hypothermia may arise as a result of (1) exposure to adverse climatic conditions (Pugh, 1966); (2) immersion in cold water (Keatinge, 1969; Golden, 1973) and (3) drug ingestion, intercurrent illness and impaired thermoregulation (Duguid, Simpson and Stowers, 1961). In the prospective clinical study which forms the basis of this chapter, the author's experience of a group of patients falling into the third category is described. The main aim of the study was to determine the effect on outcome of a more aggressive approach to treatment.

Mortality amongst patients suffering from this form of accidental hypothermia is high - 40 to more than 80% (Mills, 1973) - and although some advances have been made within the past decade there is still no generally agreed treatment policy (Gregory and Doolittle, 1973). A number of key issues remain unresolved

including the optimum rate of rewarming, the requirement for intravenous fluids, the role of oxygen administration and positive pressure ventilation, and the indications for drugs. The treatment programme to be described owes its evolution to earlier laboratory studies of induced hypothermia modified in the light of experience with patients suffering from accidental hypothermia. The effect of treatment has been to eliminate mortality during the rewarming period. Overall mortality is also lower than in previously published series and is related to the underlying precipitating factor or disease rather than to hypothermia.

During the period of the prospective study a number of hypothermic patients were treated by others in the same institution along conventional, i.e., less aggressive, lines. This group of patients did not constitute a properly planned control group but the opportunity was taken to determine their fate on a retrospective basis.

MATERIAL AND METHODS

During the period from 1963 to 1978, 44 patients suffering from accidental hypothermia were referred from the Medical Units and the Accident and Emergency Department of the Western Infirmary,

Glasgow. Since 1968 the patients received their initial treatment in the Intensive Therapy Unit (ITU).

On admission, preliminary assessment was made of the patient's general condition and arterial blood samples were withdrawn for measurement of sodium, potassium, chloride, calcium, urea, creatinine, amylase, glucose, enzymes and osmolality, in addition to haemoglobin, haematocrit, white cell and platelet count and, on occasion, coagulation screen; blood gas analysis was performed using standard electrodes at 37 deg C and the usual convention was adopted (as described in chapter 9) of correcting for the difference in temperature between the electrodes and the patient (Severinghaus, 1966). A chest radiograph and full lead ECG were performed. Radial artery and central venous catheters were inserted for measurement of heart rate, systemic arterial and central venous blood pressure; thermocouples were placed in the rectum and on the great toe for measurement of central and peripheral temperatures; heart rate, arterial pressure, temperatures and lead II of the ECG were continuously displayed on a bedside monitor. Respiratory rate and inspired oxygen concentration were recorded in the spontaneously breathing patient and more detailed information in those being ventilated. Bladder catheterisation permitted accurate measurement of urine

output. No exhaustive investigation was carried out at this stage to uncover the cause of hypothermia.

Occasionally more sophisticated measurements were performed including cardiac output, mixed venous PO_2 and pulmonary artery pressures, which were used in conjunction with the more routine measurements to calculate such derived data as systemic vascular resistance, pulmonary vascular resistance, oxygen consumption, intrapulmonary shunt and alveolar/arterial PO_2 difference. A Swan-Ganz catheter (Swan et al, 1970; Lancet, 1978), passed via a peripheral vein into the pulmonary artery, was used to make the primary measurements.

Rewarming was achieved in all but two of the patients by means of a radiant heat cradle applied over the torso (Fig. 13.1); the skin of the torso was protected by a thin sheet. Active rewarming was discontinued at about 35 deg C to allow for the usual spontaneous further rise in temperature of 2 to 3 deg C. The two patients not rewarmed by this method had thoracotomy and mediastinal irrigation with warmed fluids. Intravenous fluids were administered to reduce haemoconcentration, to restore circulating blood volume, and to maintain arterial pressure, central venous pressure and urine output at satisfactory levels; any fluids thus administered were warmed before infusion.

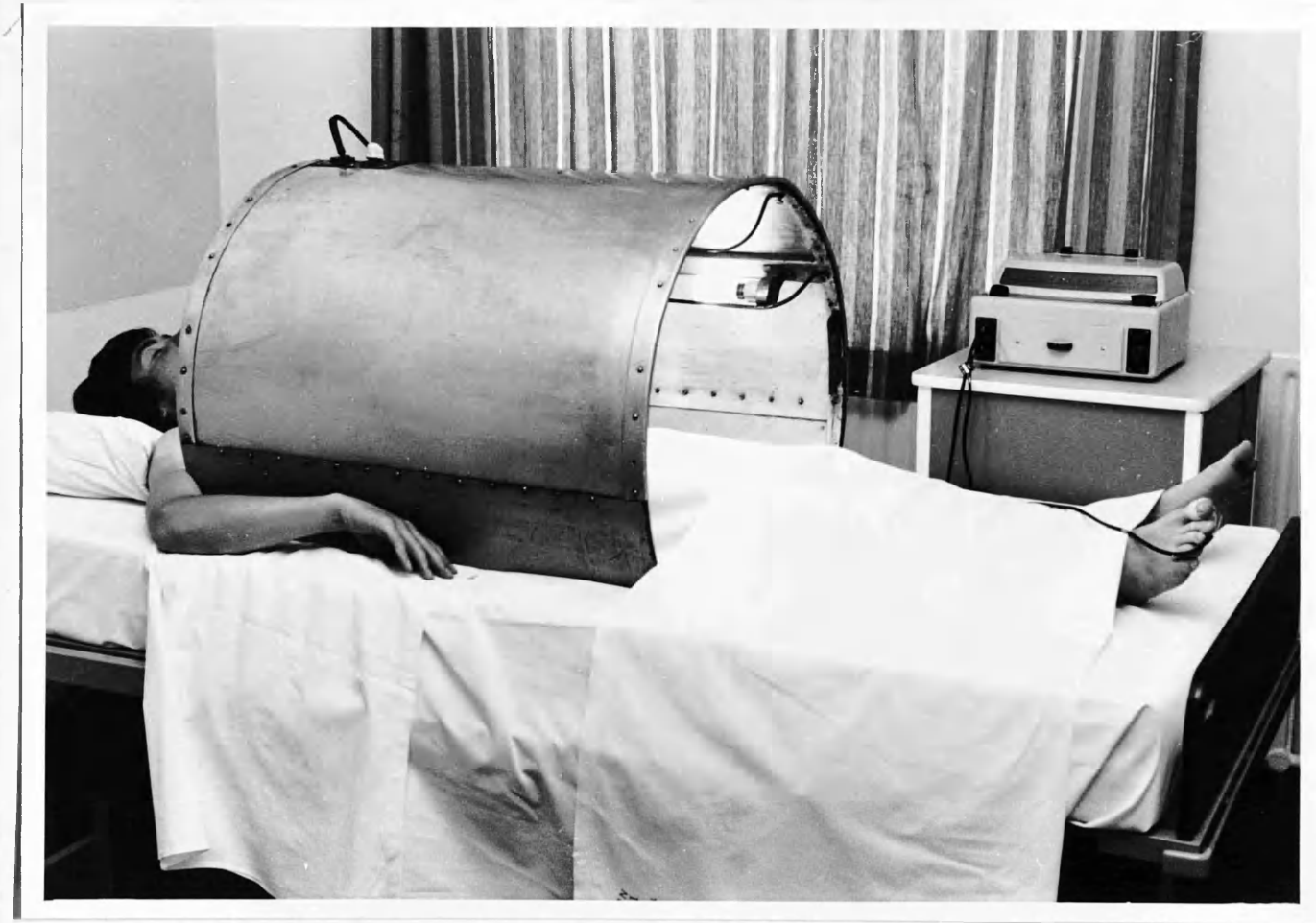


Figure 13.1. Heat cradle applied over torso leaving limbs unheated.

Oxygen was administered to maintain arterial PO_2 (corrected for temperature) within the normal range; indications for intermittent positive pressure ventilation (IPPV) included (1) a combination of hypoxaemia and arterial PCO_2 in excess of about 35 mm Hg (corrected for temperature) (2) evidence of deteriorating pulmonary gas exchange (3) coma and (4) cardiovascular instability. Throughout rewarming careful observation was made of the cardiovascular and respiratory parameters outlined above and appropriate action instituted when required; biochemical and haematological disturbances were likewise detected early and remedied. No special consideration was given to the fact that the patient was hypothermic other than that hypotension was more frequently tolerated without recourse to pharmacological agents, and arterial PCO_2 was maintained at levels below the normal range in patients being ventilated.

The patients were 'followed up' for a period of one month after the episode of hypothermia. Post-mortem examination was performed in nine of the 12 patients who died.

For the purposes of the retrospective study the hospital coding system was utilised. A total of 89 patients appeared to fulfil the required diagnostic criterion. Seventy seven adequate case

records were recovered from which a preliminary analysis was made.

RESULTS

The mean age of the 44 patients in the prospective study was 60 ± 3 years (mean ± S.E.) and the majority were in the fifth to seventh decades (Fig. 13.2); 24 were female and 20 male. The commonest months for admission were December and March (Fig. 13.3) and the lowest individual recorded core temperature ranged from 20.0 to 34.3 deg C (Fig. 13.4); all but seven (84%) were below the "medically significant primary hypothermia" level of 32.2 deg C (Hockaday and Fell, 1969).

The precipitating factors and associated conditions are listed in tables 13.1 and 13.2. In 57% of the patients drugs appeared to be the predominant precipitating factor. In the remainder an assortment of acute and chronic medical ailments was found, with cardiovascular accidents and endocrine diseases being most numerous.

Clinical and Laboratory Data

The clinical and laboratory data corresponding to the lowest recorded temperature are illustrated in figures 13.5 to 13.16.

Heart rates tended to be slower at lower temperatures (Fig. 13.5)

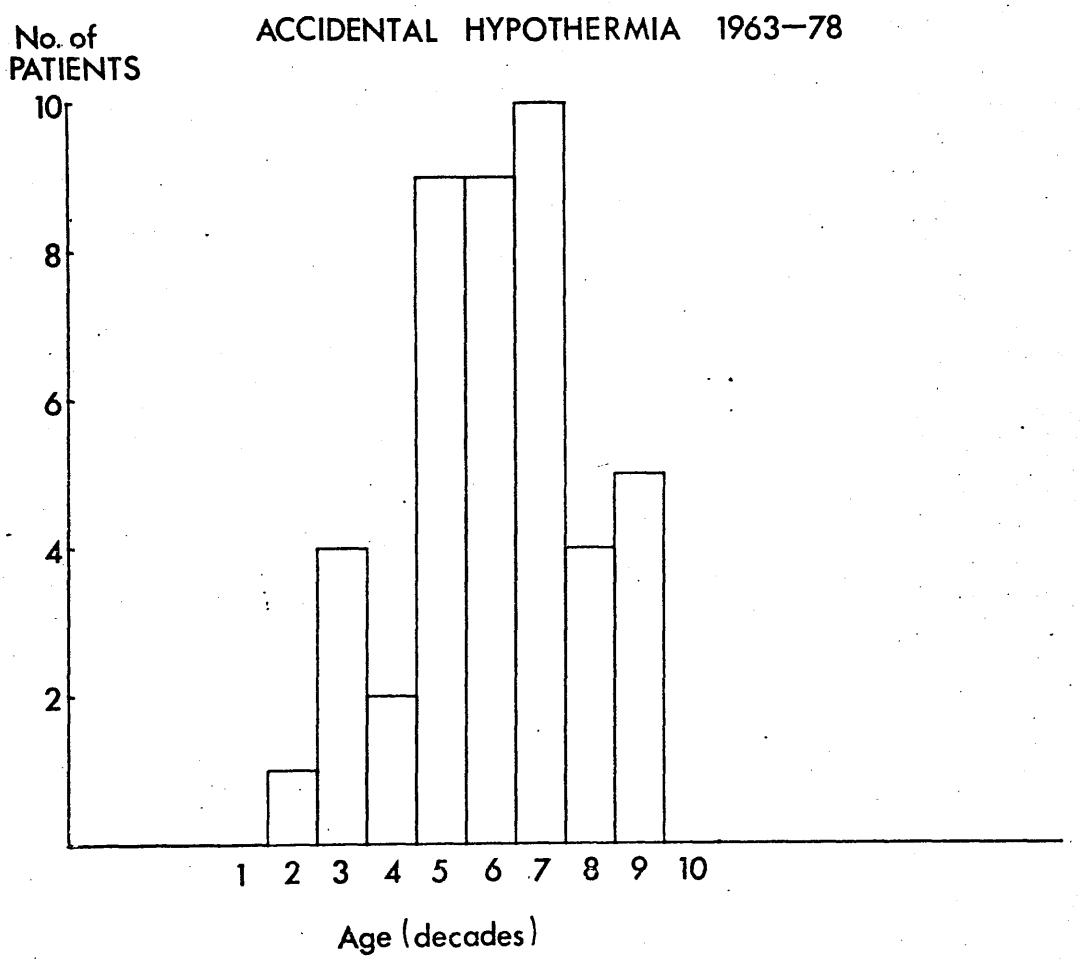


Figure 13.2 Age of patients suffering from accidental hypothermia.

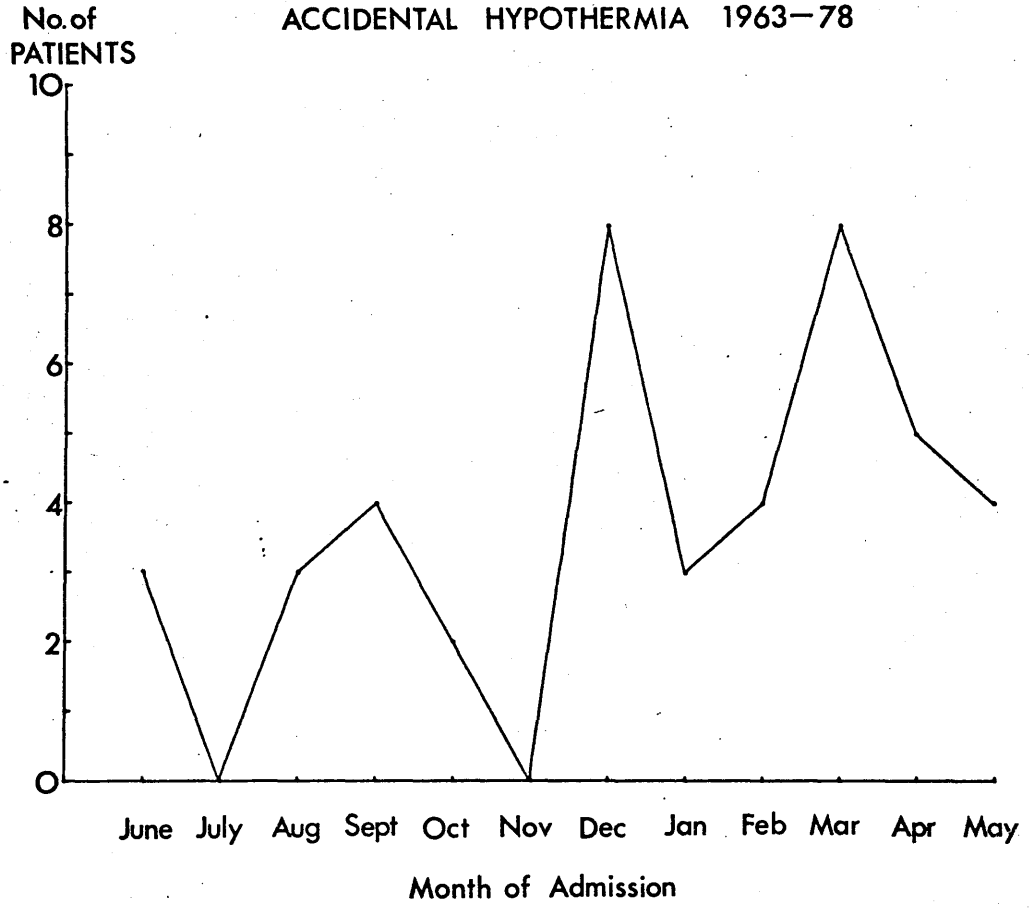


Figure 13.3. Month of admission.

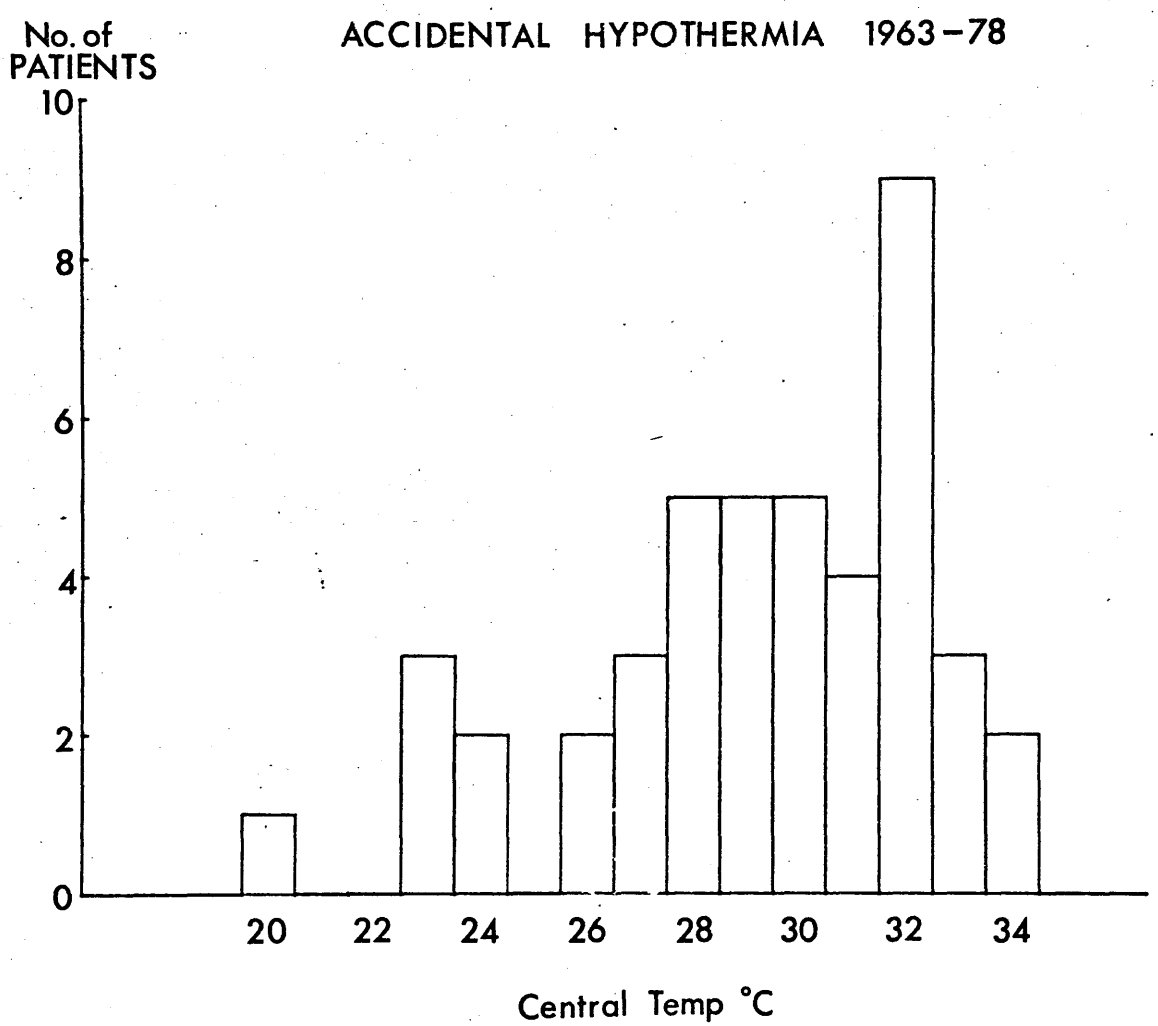


Figure 13.4. Lowest recorded core temperatures.

Table 13.1

ACCIDENTAL HYPOTHERMIA

Precipitating factors

Drugs	barbiturates	long-acting	$2^{+NI,PH}$
		other	$8^{+A,TRI}$
	others		8 (T/A,PH,M^2,F,TRY,D,T)
Alcohol			4 ($+N^2$)
Coal gas poisoning			3
			TOTAL 25

cardiovascular accident	4
endocrine disease	4
malnutrition/dehydration	3 ($+A^2$)
malignancy	2
myocardial infarction	1
pneumonia	1
old age	1
injury	1
skin disease	1
mentally defective	1
	TOTAL 19

A - alcohol
D - diazepam
F - fluphenazine
M - meprobamate
N - nembutal
NI- nitrazepam
PH - phenothiazine
T - tryptazole
TRI - trichloral
TRY - tryptophan

Table 13.2

ACCIDENTAL HYPOTHERMIA

Associated conditions

Psychiatric			20
None			8
alcohol			3
anaemia			3
cardiovascular	cerebrovascular accident	2	3
	myocardial infarction	1	
respiratory			2
malnutrition			1
infection			1
poisoning			1
malignant			1
multiple			1

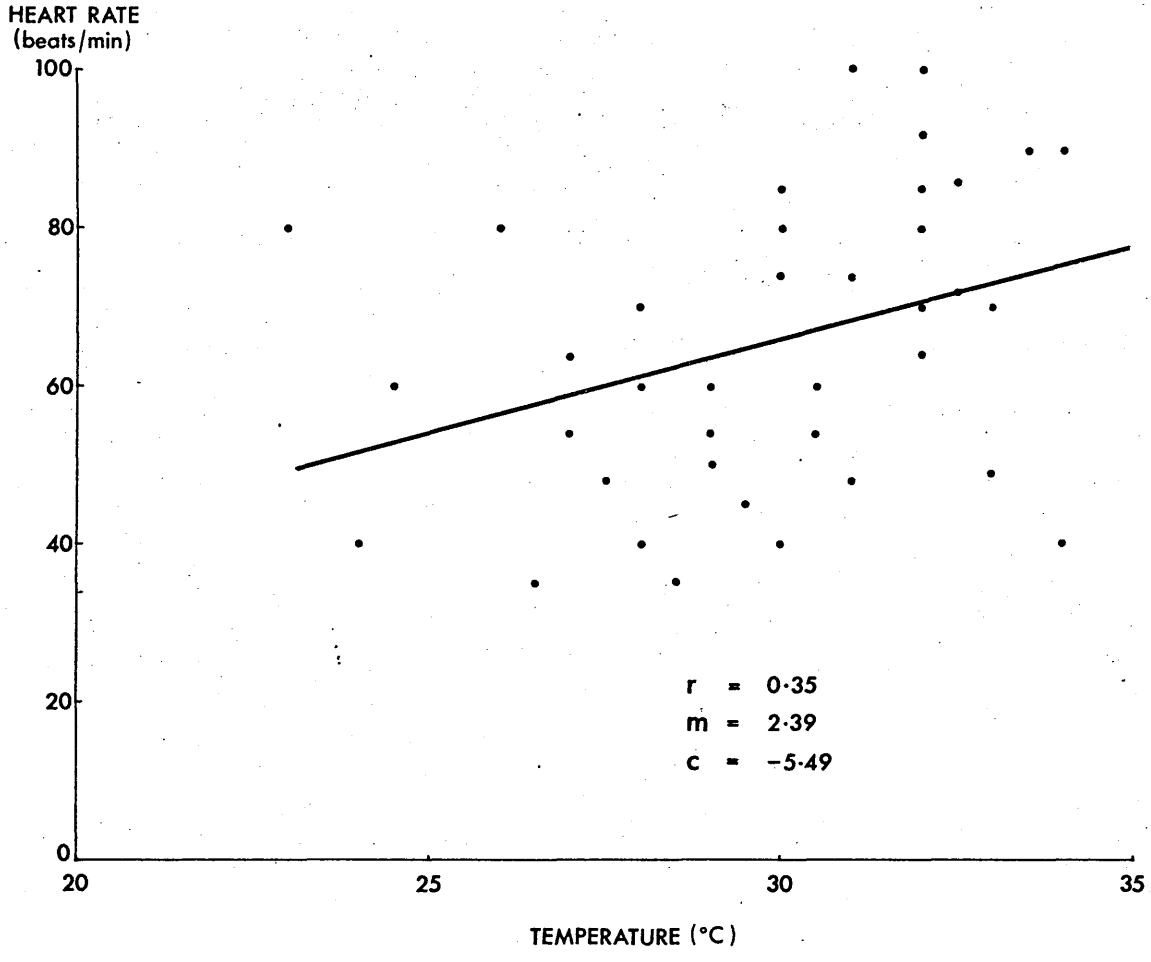


Figure 13.5. Heart rate at lowest temperature.

but the relationship was not as striking as might have been expected. There was no consistent relationship between arterial blood pressure and temperature (Fig. 13.6) although in 10 of the early patients, initial blood pressure on admission was found to be unrecordable. (This occurred at a time before intra-arterial pressure measurement became routine). Of the 34 patients whose admission ECG record had been retained, more than 50% had dysrhythmias (Table 13.3); two of the three patients with ventricular fibrillation survived. The clinical details of one of these patients were published (see following reprint and Fig. 13. 7).

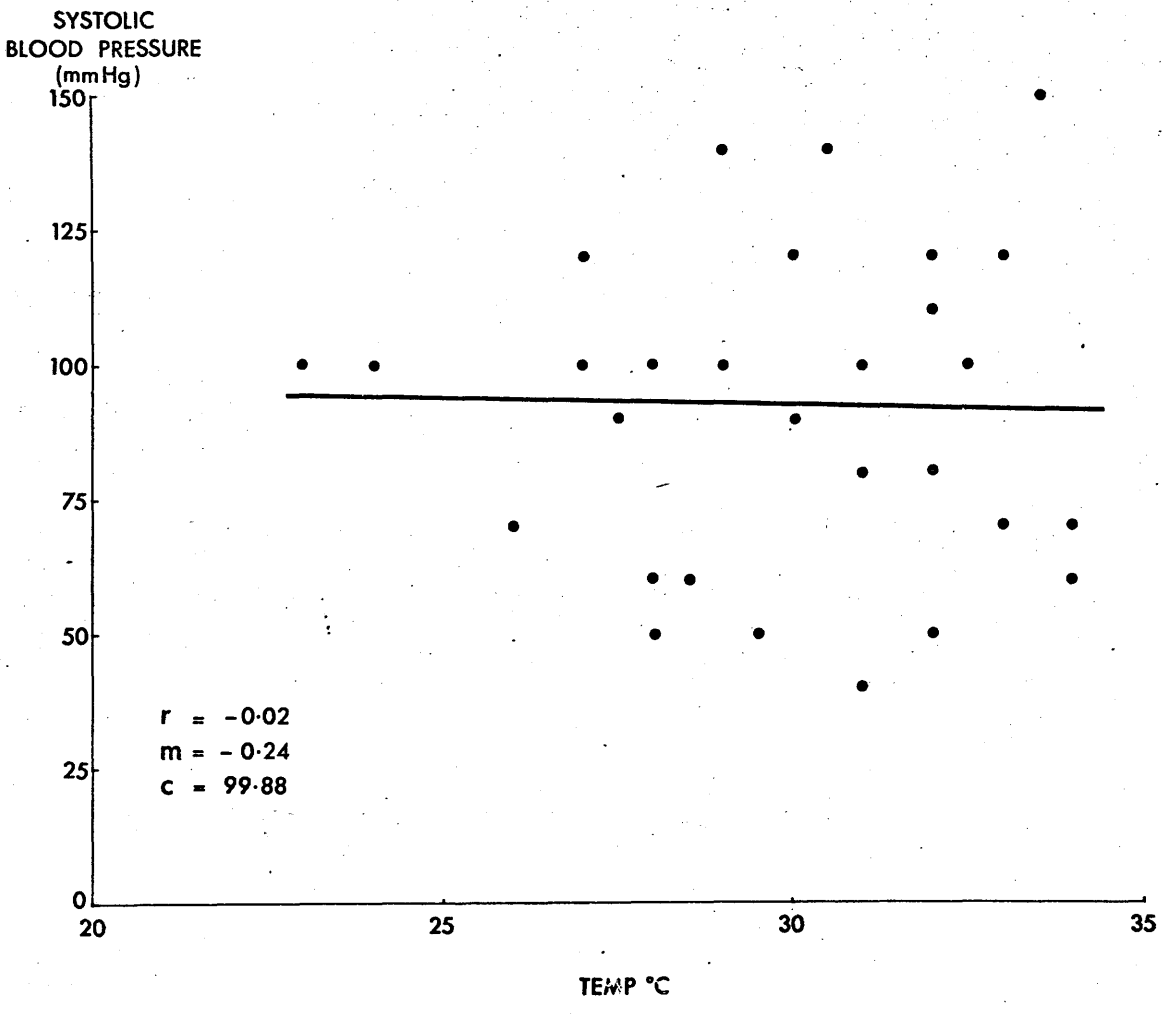


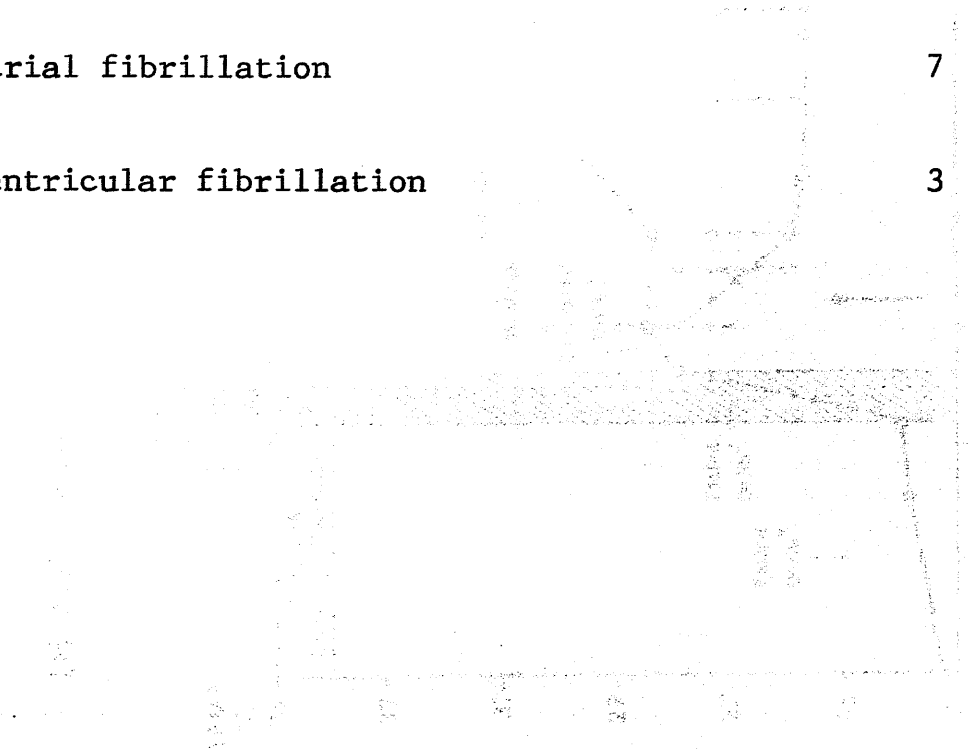
Figure 13.6. Systolic blood pressure at lowest temperature.

Table 13.3

ACCIDENTAL HYPOTHERMIA

Prevalence of dysrhythmias on admission

Total no. ECG recordings	34
dysrhythmias	19
sinus bradycardia (<60 beats/min)	9
atrial fibrillation	7
ventricular fibrillation	3



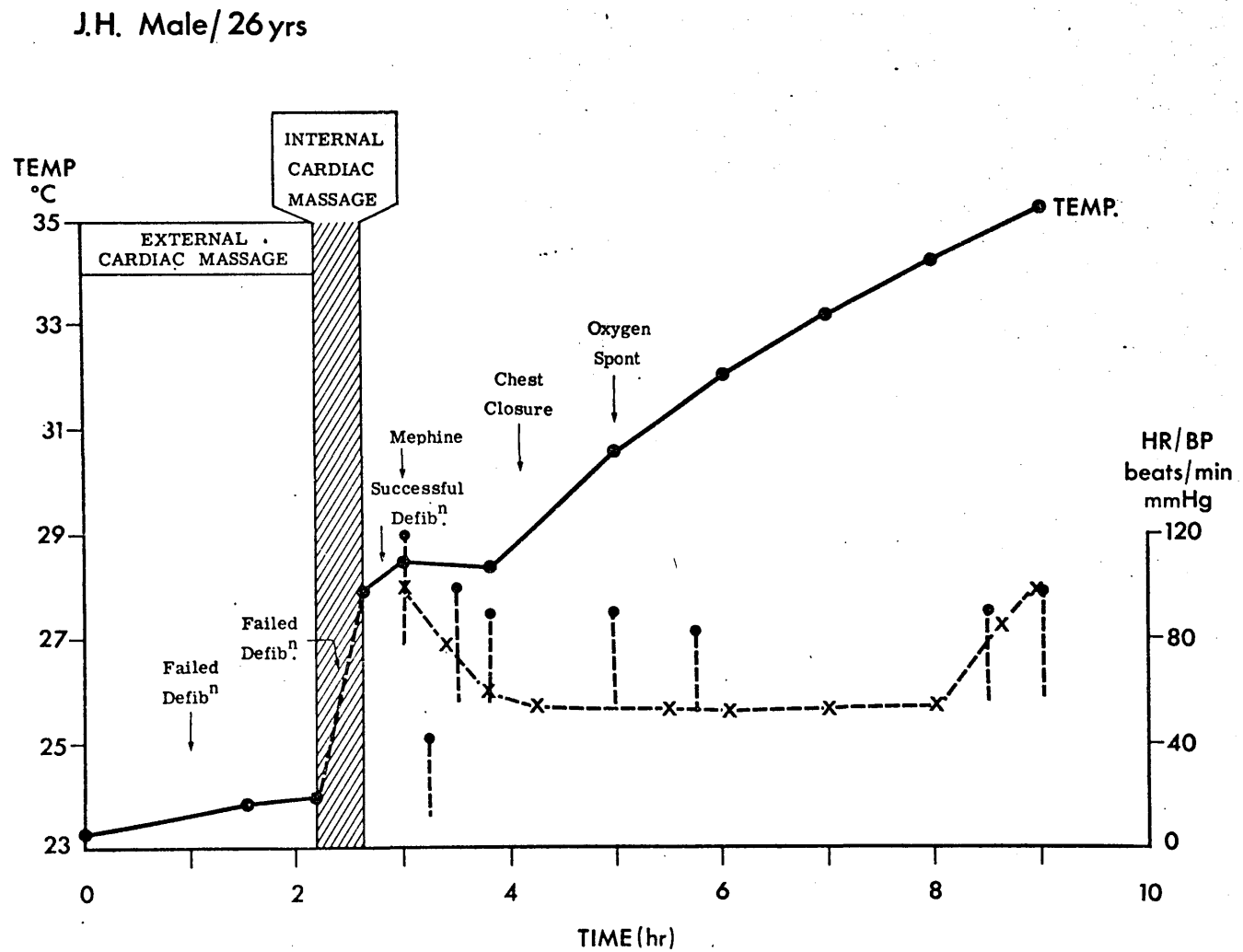


Figure 13.7. 26 year old male who survived a temperature of 23°C after more than 2 hours of external cardiac massage and 40 minutes of internal cardiac massage. Electrical defibrillation was successful at 28°C.

SEVERE HYPOTHERMIA WITH BARBITURATE INTOXICATION

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SEVERE HYPOTHERMIA WITH BARBITURATE INTOXICATION

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DESPITE improvements in the care of the unconscious patient, barbiturate intoxication still carries a mortality of around 5%; and, if only severe cases are considered, the mortality is much greater (Maher et al. 1962). The majority of the deaths are probably due to respiratory and cardiovascular depression, or to the consequences of prolonged unconsciousness. Lee and Ames (1965) have reported a high incidence of hypothermia in severe barbiturate intoxication, particularly with intermediate-acting drugs. They noted several episodes of cardiac arrest in asystole, often associated with intubation.

We report the present case because of the severity of the hypothermia (23°C), the associated cardiac complications, and the somewhat unusual resuscitative measures which became necessary. In addition, observations were made on barbiturate clearances during profound hypothermia.

Case-report

A 27-year-old man was admitted to the infirmary on May 4, 1965, with a history of having taken 50 capsules of ' Sodium Amytal ' (sodium amylobarbitone), 50 tablets of cyclobarbitone, and a considerable amount of alcohol some 12 hours previously. On admission he was deeply unconscious, but blood-pressure and respiration seemed adequate. Reflexes were absent, and an endotracheal tube was inserted without difficulty. Gastric lavage was not undertaken in view of the time interval since the ingestion of the drugs. A few minutes later the patient

suddenly became apnœic, cyanosed, and pulseless. External cardiac massage and artificial ventilation were immediately begun.

At this time the rectal temperature was 23°C. The serum-barbiturate level was 5·7 mg. per 100 ml., blood-urea 23 mg. per 100 ml., electrolytes and blood-count normal. The electrocardiogram (E.C.G.) showed coarse ventricular fibrillation (fig. 1).

The problem was therefore one of severe hypothermia with barbiturate and alcoholic intoxication as the precipitating

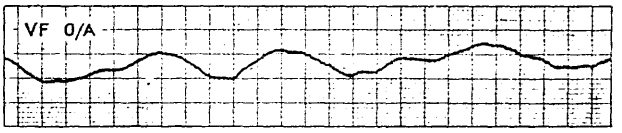

Fig. 1—E.C.G. on admission, showing coarse ventricular fibrillation.

factors. Ventricular fibrillation is a common cause of death in animals and probably in man during hypothermia (Hegnauer 1959), but to our knowledge has not been recorded in barbiturate intoxication.

Continuous monitoring of the electrocardiograph (E.C.G.), blood gases, and temperature was established. A heat cage was placed over the lower trunk; 100 mg. of hydrocortisone and 300 mEq. of bicarbonate were given intravenously. Successive attempts at external defibrillation with 240, 480, and 750 volts were unsuccessful; at the highest voltage a few beats of sinus rhythm appeared, but the rhythm reverted to ventricular fibrillation almost at once (fig. 2).

External cardiac massage was continued for 2 hours, but the external heating was ineffective, the œsophageal temperature at the end of this time being only 24°C. Thoracotomy was therefore done in order to warm the mediastinal region directly to a temperature at which the heart might be expected to remain permanently defibrillated. After the chest had been opened, internal cardiac massage was begun, along with repeated irrigation of the mediastinum with physiological saline solution at 40°C. In 35 minutes, the mediastinal temperature

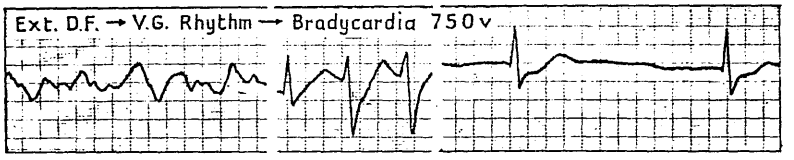

Fig. 2—E.C.G. showing transient reversal to sinus rhythm with external defibrillation (750 volts).

had reached 28°C, and the fibrillation had changed from the atonic type associated with anoxia to the vigorous type found when the myocardium is adequately oxygenated (Wiggers 1940). Internal defibrillation at 125 volts was successful in restoring sinus rhythm at the second attempt, and this proved permanent (fig. 3).

Once it was obvious that heart action was likely to remain stable, the chest was closed and external rewarming continued. Pulse and blood-pressure had returned, and spontaneous

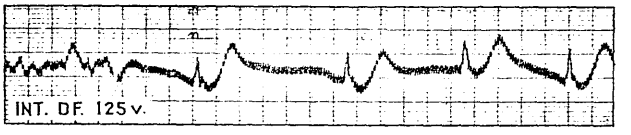

Fig. 3—E.C.G. showing successful conversion to sinus rhythm with internal defibrillation (125 volts).

respiration began about 60 minutes later. Blood-gas analysis at this time confirmed that spontaneous ventilation was sufficient to prevent increasing hypercapnia, but that a very high level of inspired oxygen was necessary to maintain adequate oxygenation. (Arterial blood-gas data with the patient breathing 90% oxygen spontaneously: pH 7·34, P_{CO_2} 39 mm. Hg, P_{O_2} 62 mm. Hg.) The body temperature returned to normal 10 hours after admission—8 hours after thoracotomy. The E.C.G. was by then virtually normal. Chest X-ray showed that the left lung had reinflated successfully.

The patient had been catheterised on admission, and during the hypothermic phase he had exhibited the polyuria normally associated with hypothermia (Wynn 1960). Once the temperature returned to normal, the urine output fell sharply, probably because of the barbiturate intoxication, which now became the major therapeutic problem. The dose of barbiturate ingested had been large, and the blood-level on admission (5·7 mg. per 100 ml.) moderately high for intermediate-acting barbiturate. It therefore seemed likely that unconsciousness might be prolonged—in this case a greater hazard than usual. Once the cardiovascular state seemed satisfactory, cautious forced diuresis was begun as we have previously described (Linton et al. 1964), although the rate of fluid infusion was reduced by half for the first 12 hours to avoid overloading the circulation. No complication occurred, and the patient regained consciousness the next evening, 46 hours after ingestion of the tablets, 34 hours after admission, and after 20 hours of forced diuresis. At this time the serum-electrolytes were normal; blood-urea was 20 mg. per 100 ml., and blood-barbiturate level 1·6 mg. per 100 ml.

Although the patient was permitted to breathe from air from this stage onwards, the arterial oxygen tension only gradually

returned to normal during the next week. On the day after admission it was estimated that 20% of the cardiac output was being shunted through unventilated alveoli.

Apart from an episode of bronchopneumonia 9 days after admission, which quickly responded to tetracycline, the patient had an uncomplicated convalescence. There was no evidence of cerebral damage, and the electroencephalogram was normal. The patient was seen by a psychiatrist, and it emerged that the suicidal attempt was due to adverse social conditions and reactive depression. He was transferred to a psychiatric unit for further care 3 weeks after his original admission.

Discussion

This patient's hypothermia was severe, and with one exception we can find no record of successful resuscitation from a lower temperature (Britton 1930, Talbot et al. 1941, Duguid et al. 1961, Read et al. 1961, McNicol and Smith 1964, Rosin and Exton-Smith 1964). Laufman (1951) recorded the survival of a patient whose temperature was only 18°C, but she lost all four limbs from cold injury. Our patient was a fit young man, and the outdoor temperature on the night he became unconscious was 1°C on the ground and 5°C in the air. He was found in a room in a model lodging-house, fully clothed, and the room temperature did not seem unduly low. However, hypothermia seems to occur very readily in poisoning with the intermediate-acting group of barbiturates (Lee and Ames 1965). Day (1943) has observed that a completely motionless person, even at a temperature as high as 28°C, cannot prevent a slow fall in body temperature. The complete inertia of the severely poisoned patient may therefore explain the occurrence of hypothermia in barbiturate intoxication. In our patient, the vasodilator effect of alcohol may have contributed.

The time spent attempting external defibrillation was probably wasted, for defibrillation is likely to be maintained only when the myocardial temperature is at least 28°C. At this temperature myocardial oxygenation is probably approaching the optimum, and myocardial conduction-time is returning rapidly to normal: both factors contribute to sustained reversion to sinus rhythm.

A patient with a mid-œsophageal temperature as low as 23°C in the presence of ventricular fibrillation could be treated with pump and heat exchanger, or by thoracotomy with direct rewarming of the mediastinum. We chose the

latter technique in order not to lose time while the heart-lung machine was being prepared.

The severe disturbances of metabolic balance often found during the rewarming of patients with accidental hypothermia were largely prevented by the maintenance of adequate blood-pressure and oxygenation both before and after defibrillation. The importance of oxygenation in hypothermia may be underrated because the outward signs of respiratory insufficiency—cyanosis and dyspnœa—are usually absent (Ledingham 1964, McNicol and Smith 1964).

Treatment of the hypothermia and ventricular fibrillation took precedence over any specific treatment for the barbiturate poisoning. The barbiturate poisoning was moderately severe, and it was especially important in this

BARBITURATE CLEARANCE

Specimen no.	Time (hr.)	Volume of urine (ml.)	Barbiturate level (mg. per 100 ml.)		Clearance (ml. per min.)
			Urine	Serum	
1	4	430	49	5·7	15
2	4	90	40	5·5	2·7
3	8	770	46	5·4	14·5

Specimen no. 1: during hypothermia.
„ „ 2: after correction of hypothermia.
„ „ 3: during forced diuresis.

case to reduce the duration of unconsciousness as much as possible, to prevent respiratory complications. Hæmodialysis would have been more effective than forced diuresis in removing barbiturate from the body (Linton et al. 1964), but cautious forced diuresis offered a safer compromise. No difficulties were experienced, and urine excretion was excellent. During the period of hypothermia, and before forced diuresis was begun, the continuing good urine-flow contrasted strikingly with the oliguria which is usual in severe barbiturate intoxication. Polyuria in hypothermia may be due either to inhibition of antidiuretic hormone production, or to insensitivity of the renal tubules to the effects of antidiuretic hormone (Wynn 1960). In uncomplicated barbiturate intoxication production of antidiuretic hormone is increased, producing oliguria (de Bodo and Prescott 1945), and this more usual pattern was seen once the hypothermia was corrected. The table shows that

barbiturate clearance was good during hypothermia; but, once the hypothermia was corrected, both urine-flow and barbiturate clearance fell to very low levels. Forced diuresis restored the clearance to satisfactory levels, and the total amount of barbiturate removed by the modified forced diuresis was 2·2 g. in 20 hours. Thus the duration of unconsciousness was probably much reduced. The effect of hypothermia in inhibiting antidiuretic hormone production seems to overcome the opposite effect of barbiturate intoxication.

Summary

A case of severe barbiturate intoxication, complicated by profound hypothermia (body temperature 23 C) and ventricular fibrillation is reported. Defibrillation was possible only after thoracotomy and direct warming of the mediastinum. Diuresis and barbiturate clearance were good during hypothermia, but, as the body temperature rose, the antidiuretic effect of barbiturate poisoning appeared, and forced diuresis was needed. The patient recovered completely. There is probably only one other recorded case of successful resuscitation from a temperature as low as 23 C.

Our thanks are due to Dr. R. L. Richards for permission to report this case and to the biochemistry department of Glasgow Royal Infirmary for assistance. We should also like to acknowledge the help given by Dr. K. B. Holloway and Dr. W. J. Thomson, of the department of anæsthetics.

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Thirty-nine per cent of the patients had obvious respiratory inadequacy on clinical examination - nine were apnoeic and eight nearly apnoeic. On initial chest x-ray 12 of 30 patients (40%) had patchy opacification (usually bilateral) and five more (a total of 57%) developed radiological changes in the ensuing days (Table 13.4). Blood gas analysis confirmed the frequency and severity of pulmonary gas exchange disturbances. The majority of the patients in whom analysis was performed during spontaneous air breathing had arterial PO_2 values of less than 55 mm Hg (Fig. 13.8) and in those breathing oxygen spontaneously or via a ventilator, the mean alveolar/arterial PO_2 differences were 250 and 350 mm Hg respectively. Mean arterial PCO_2 for the whole group was 32 mm Hg (Fig. 13.9) which accounted for a normal mean arterial pH of 7.38 units (Fig. 13.10) in the presence of a mean base deficit of -9 mmol/l (Fig. 13.11).

The only consistently abnormal finding amongst the serum electrolytes (Figs. 13.12 and 13.13) was hypocalcaemia. The few patients with hyperkalaemia also had elevated blood urea (Fig. 13.14) levels which were a common occurrence. Subsequent events revealed that more often than not the high blood urea levels were prerenal in origin and consistent with other evidence of haemoconcentration including elevated packed cell

Table 13.4

ACCIDENTAL HYPOTHERMIA

Chest Radiograph

On admission		Later (day)	
Normal	18	Normal	2
		Pathological	5 (1(1), 3(2), 1(5))
Pathological	12		

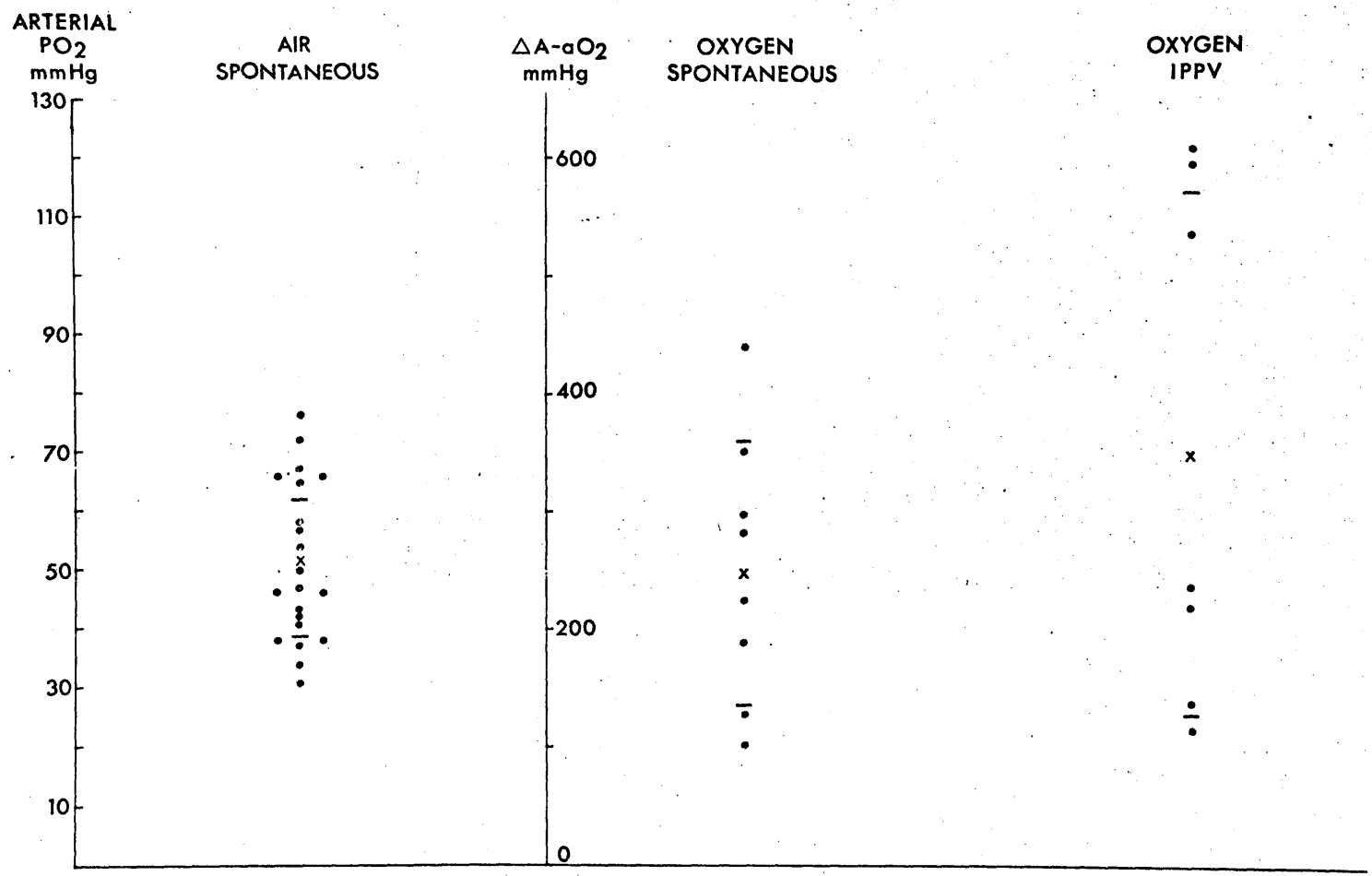


Figure 13.8. Arterial PO2 in spontaneously breathing (air) patients and alveolar/arterial PO2 difference in spontaneously breathing (oxygen) and ventilated patients at lowest temperature; cross indicates mean and bars one standard deviation.

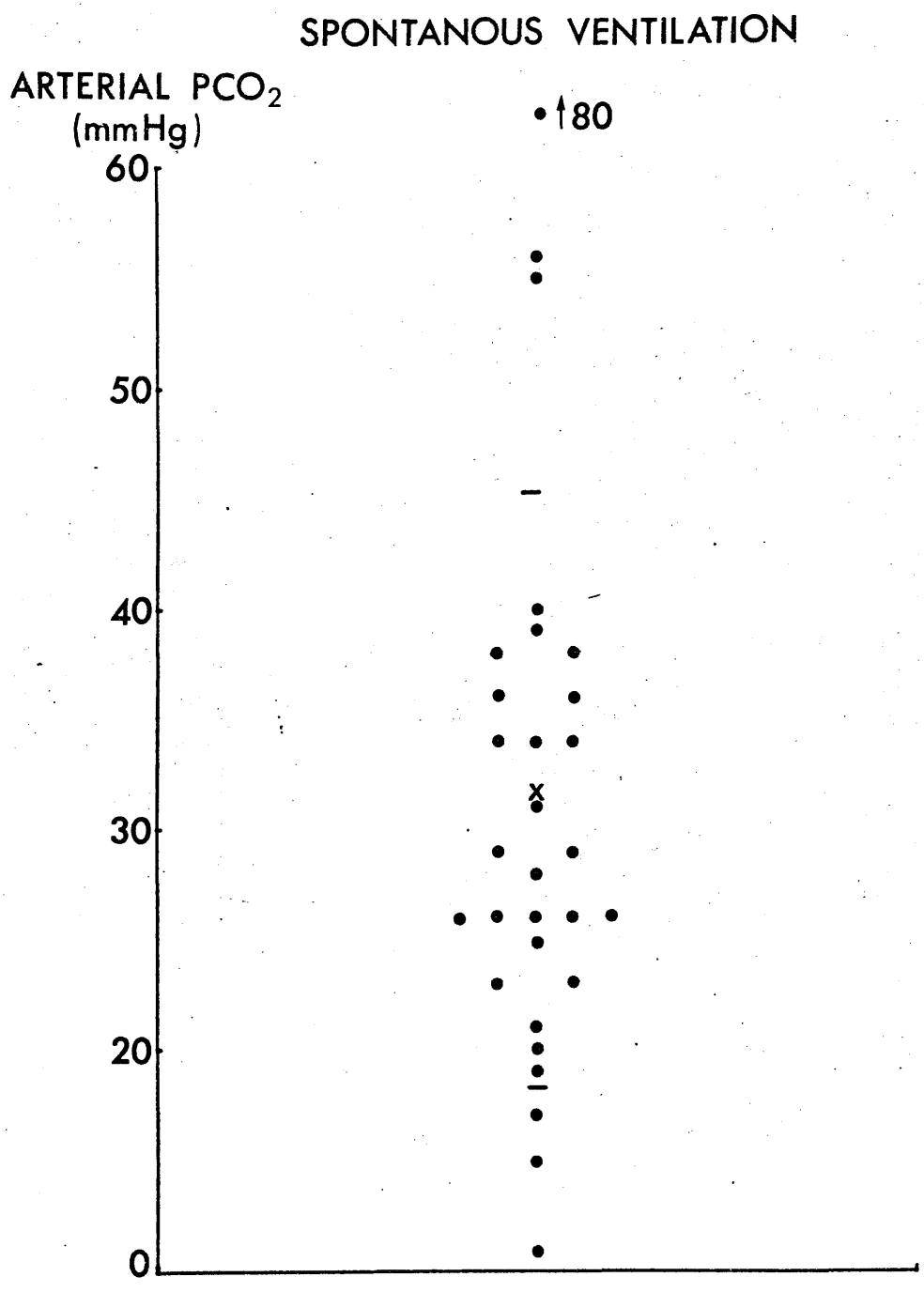


Figure 13.9a. Arterial PCO2 in spontaneously breathing patients. cross indicates mean and bars one standard deviation.

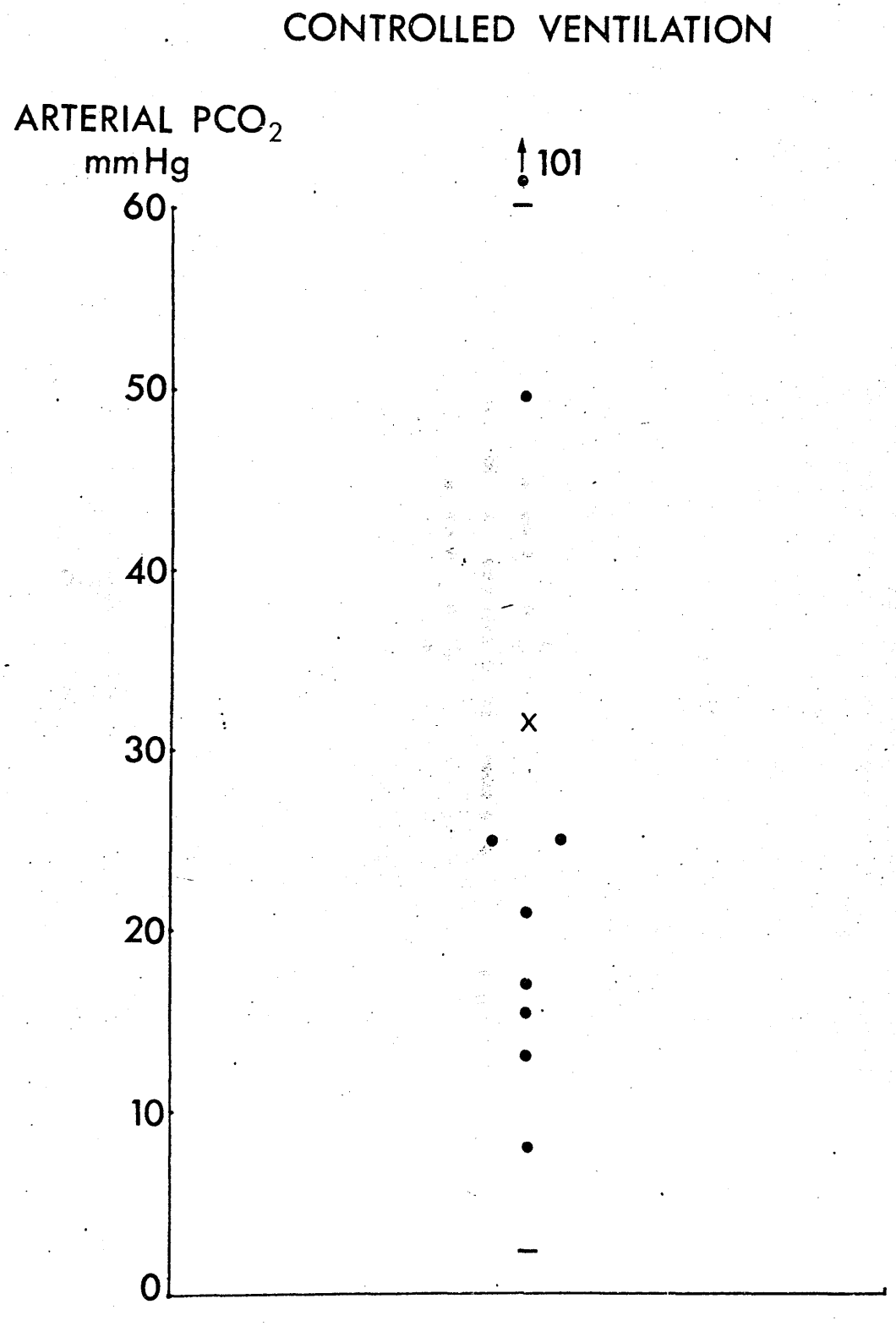


Figure 13.9b. Arterial PCO2 in ventilated patients at lowest temperature; cross indicates mean and bars one standard deviation.

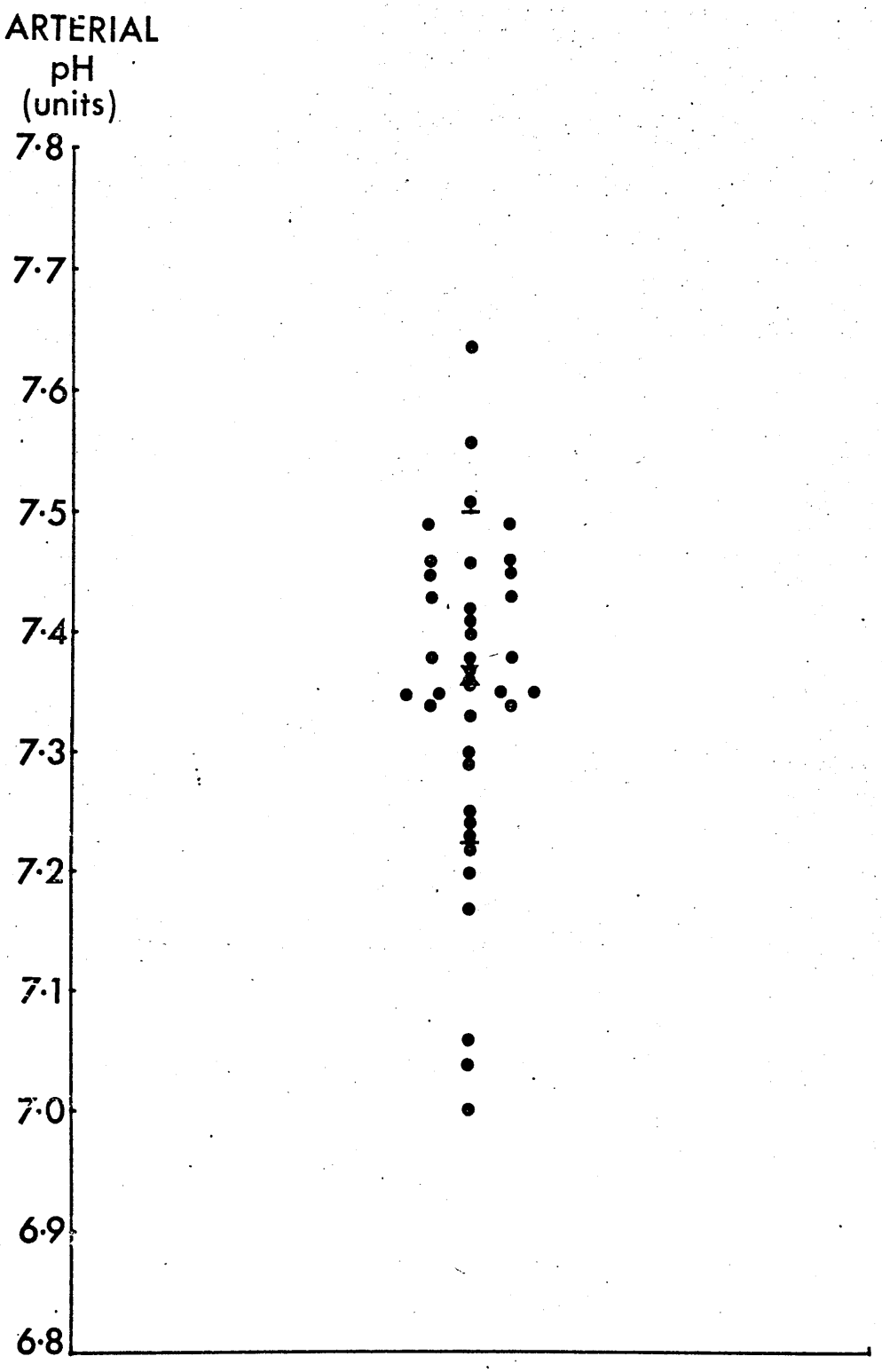


Figure 13.10. Arterial pH at lowest temperature.

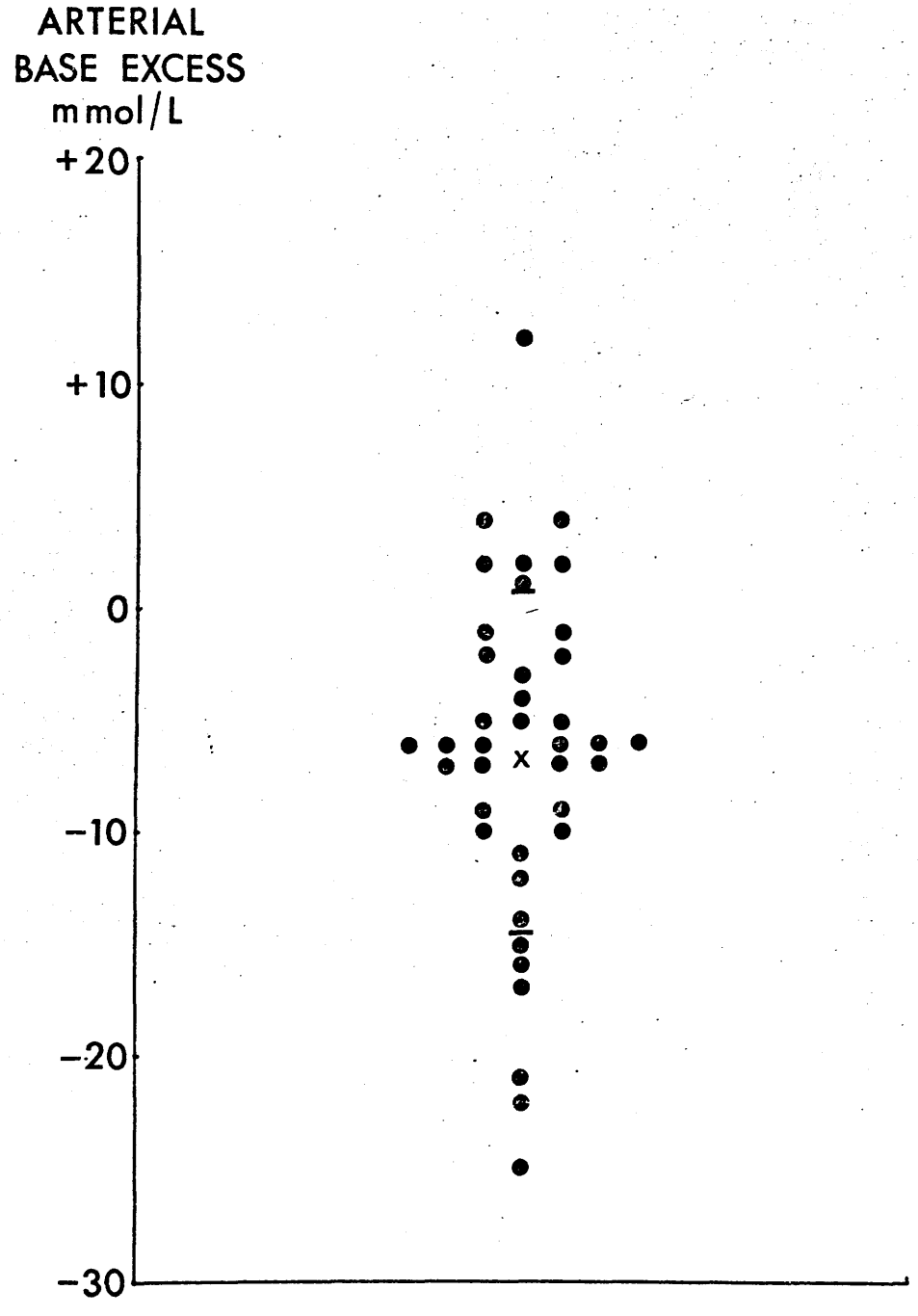


Figure 13.11. Arterial base excess at lowest temperature.

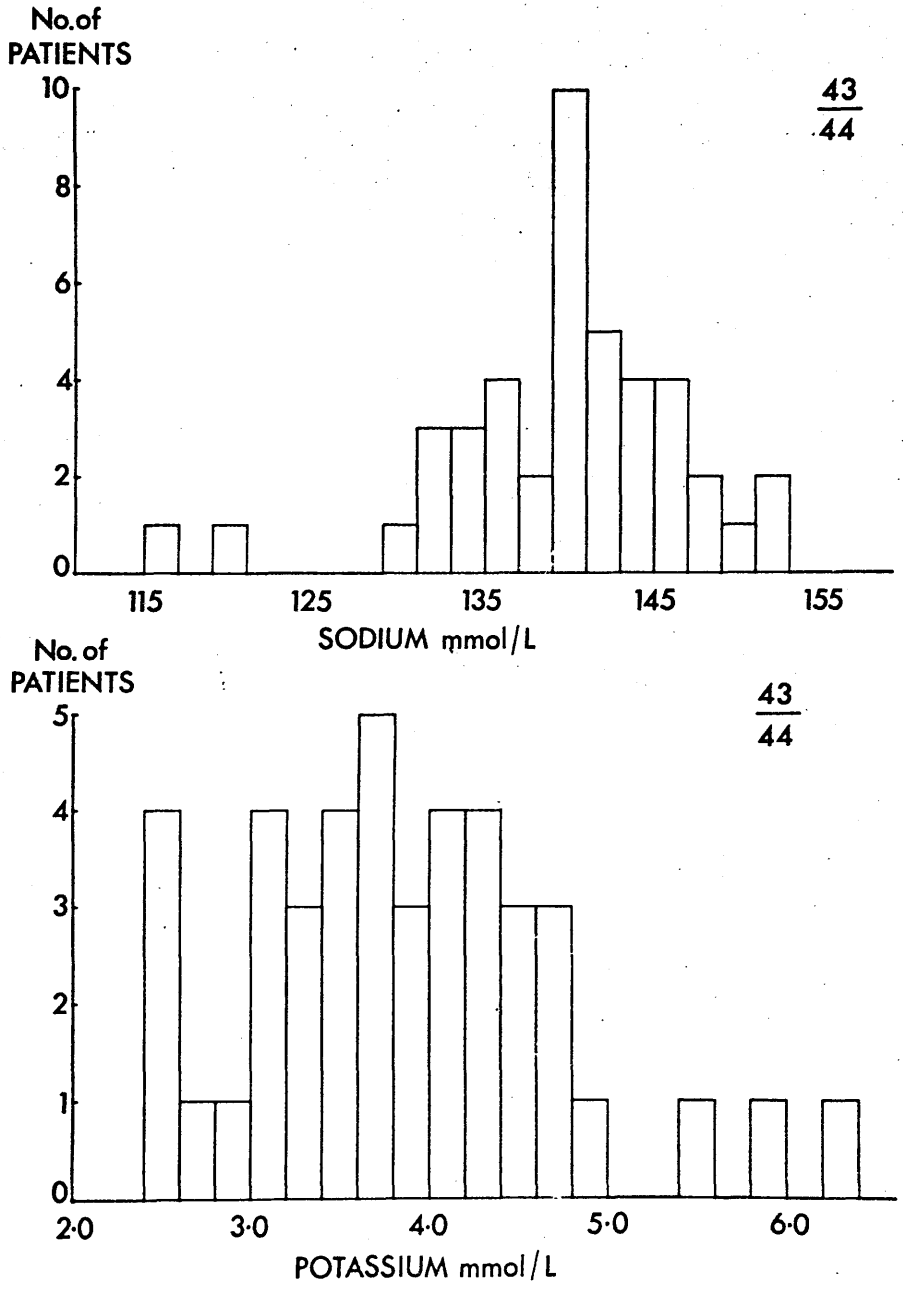


Figure 13.12. Serum sodium and potassium at lowest temperature.

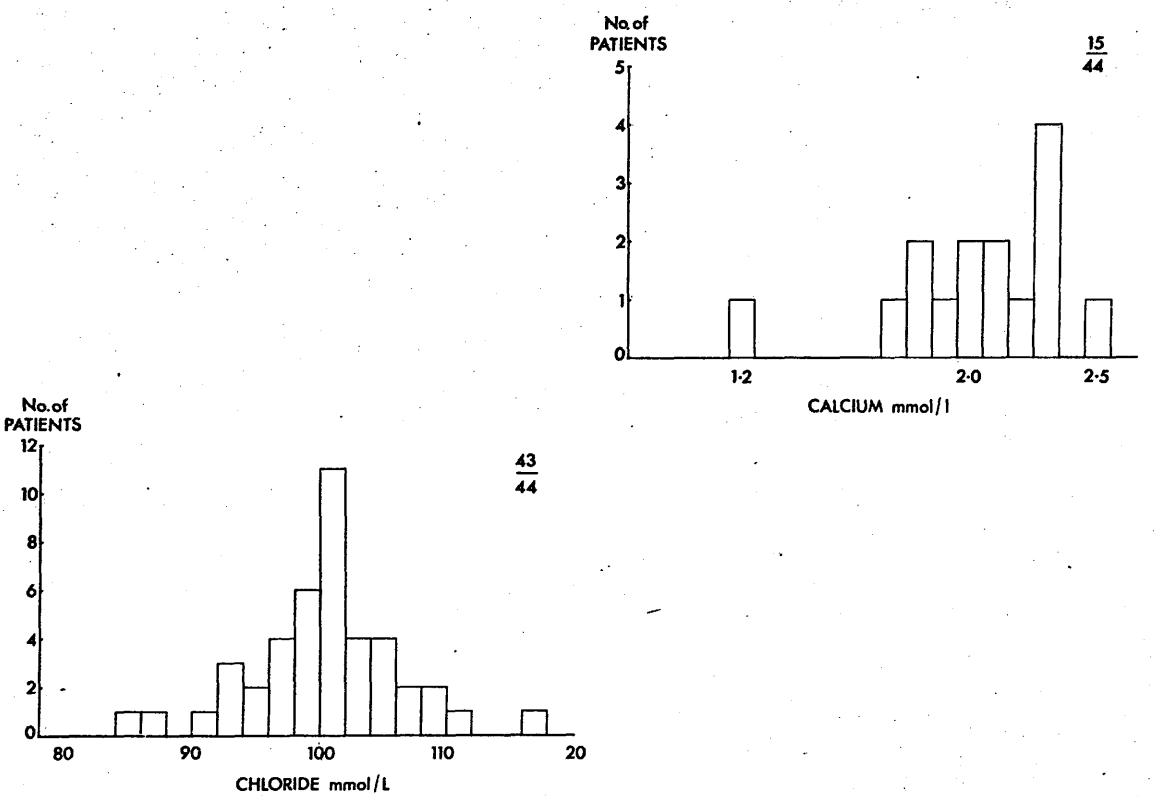


Figure 13.13. Serum chloride and calcium at lowest temperature.

volume (Fig. 13.15). Five patients had blood glucose levels below 3.3. mmol/l (60mg/100ml) (Fig. 13.14), for which appropriate treatment was given. Serum amylase was above 300 IU/100ml in 14 of 29 patients (48%) but in only two did the level exceed 2000 IU/100ml. Serum enzyme levels were slightly elevated but only a few results were available. Haematological analysis revealed the frequency of thrombocytopenia and leucocytosis (Fig. 13.15), although the latter generally became less marked once the circulating fluid volume had been restored. During fluid repletion four of 26 patients had hourly urine outputs of less than 30 ml (Fig. 13.16); one of these subsequently developed acute renal failure.

Treatment

No patient was adversely affected by any of the manoeuvres instituted for the purposes of monitoring or treatment. Neither reflex cardiac slowing nor induced arrhythmias was seen.

Rewarming was achieved at a mean rate of 1.13 $\pm$ 0.09 deg C per hour and the mean duration of rewarming was 8.03 $\pm$ 0.85 hours. The course of an uneventful active rewarming procedure is illustrated in Fig. 13.17; the patient breathed spontaneously throughout. Most patients received some intravenous fluids

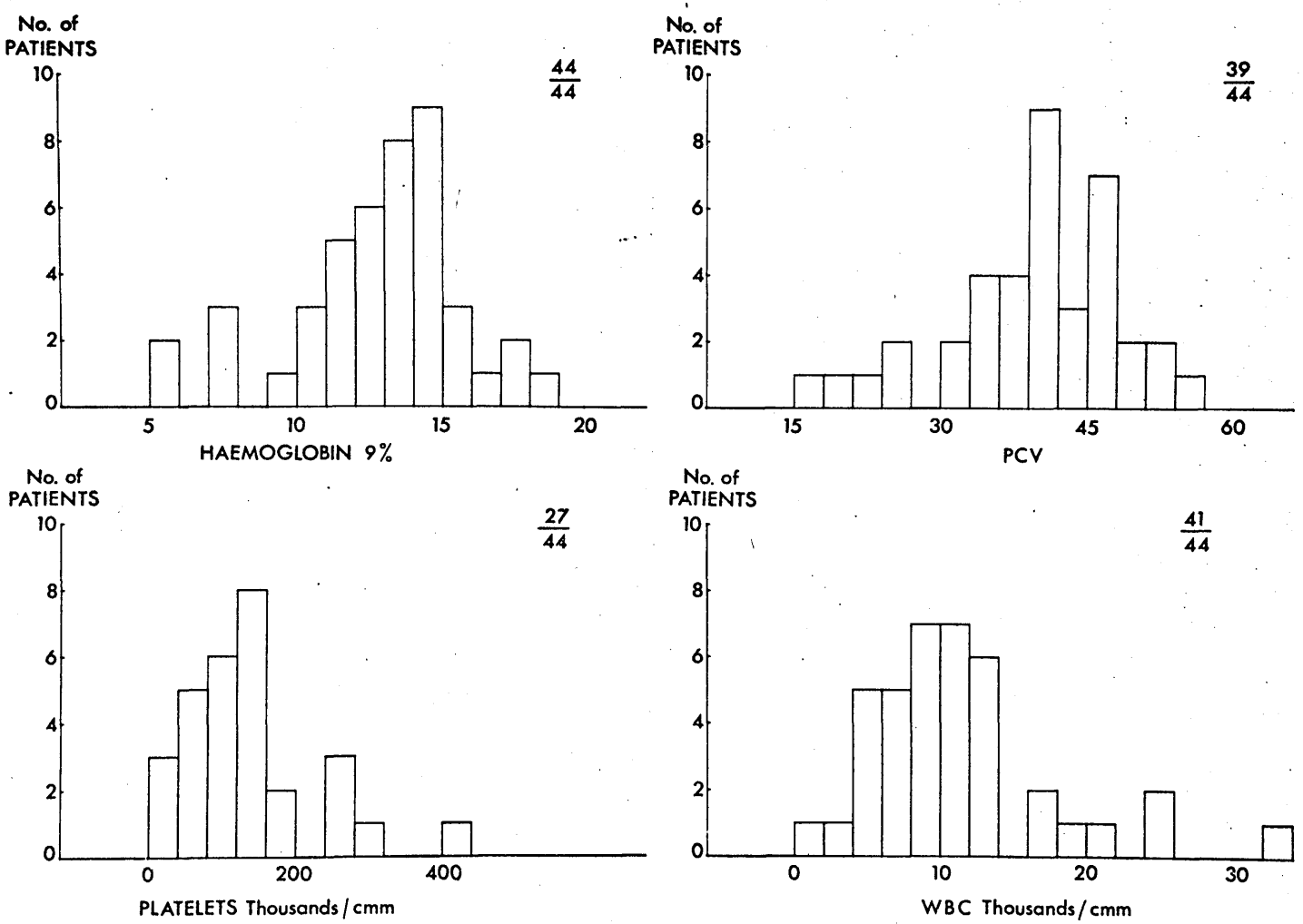


Figure 13.15. Haemoglobin packed cell volume, platelets and white blood count at lowest temperature.

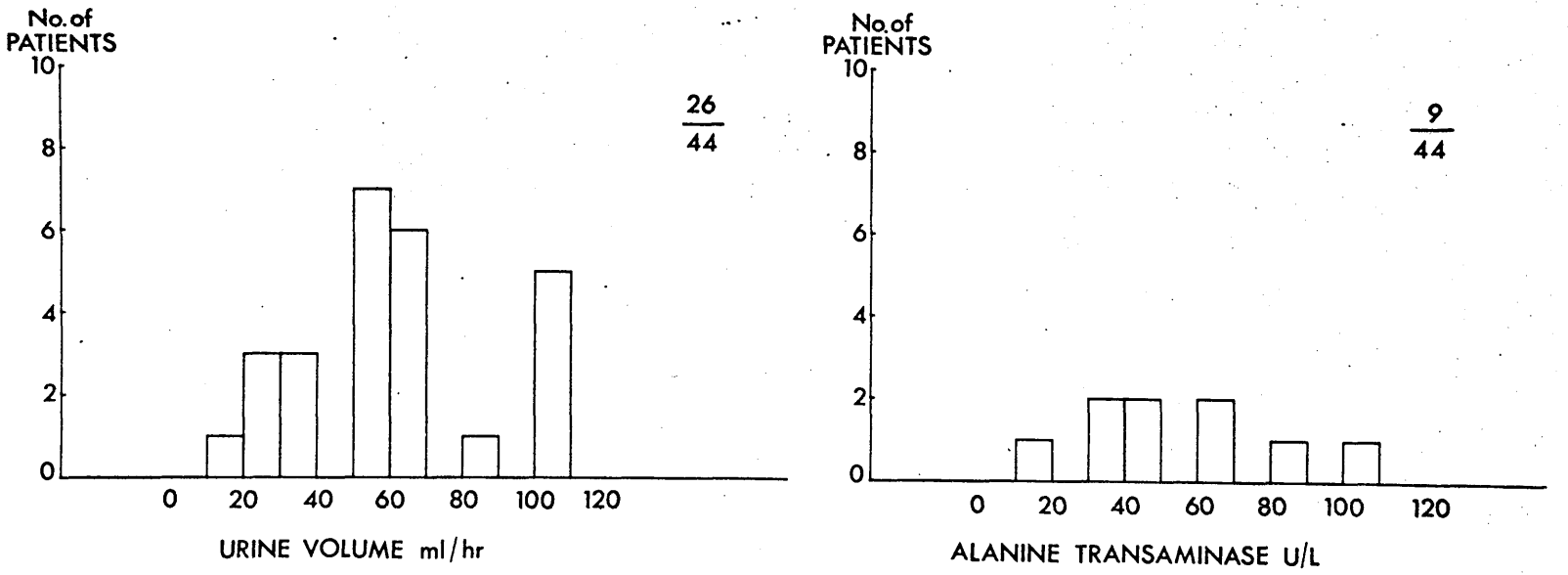


Figure 13.16. Urine output and alanine transaminase at lowest temperature.

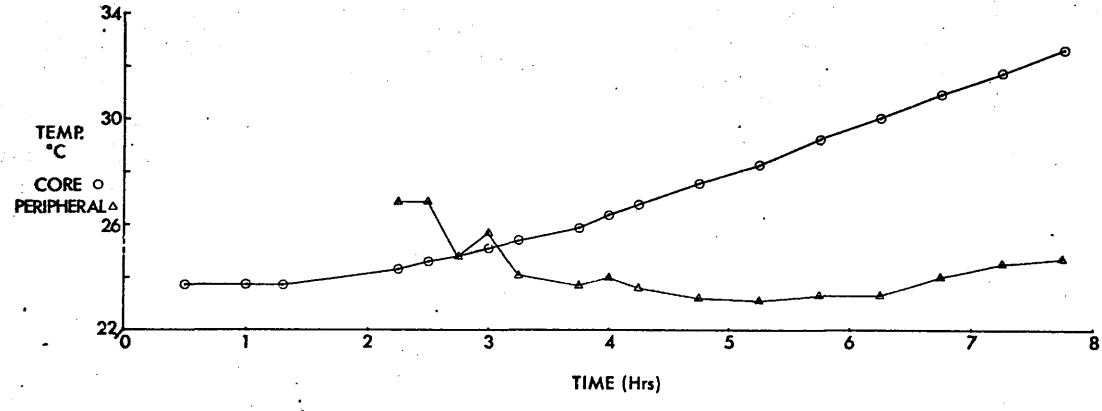


Figure 13.17a-d. Uneventful rewarming from 23.6°C in a 48 year old male who had taken some butobarbitone and alcohol and was found lying outside his caravan. Cardiac output fell during rewarming; oxygen availability was consistently adequate for tissue requirement and base excess returned to normal spontaneously; arterial PO2 was low prior to oxygen administration and PCO2 rose only marginally; (not shown) CVP varied between 10-15 cm saline and urine output between 25-50 ml/hr with a terminal diuresis after frusemide (20 mg).

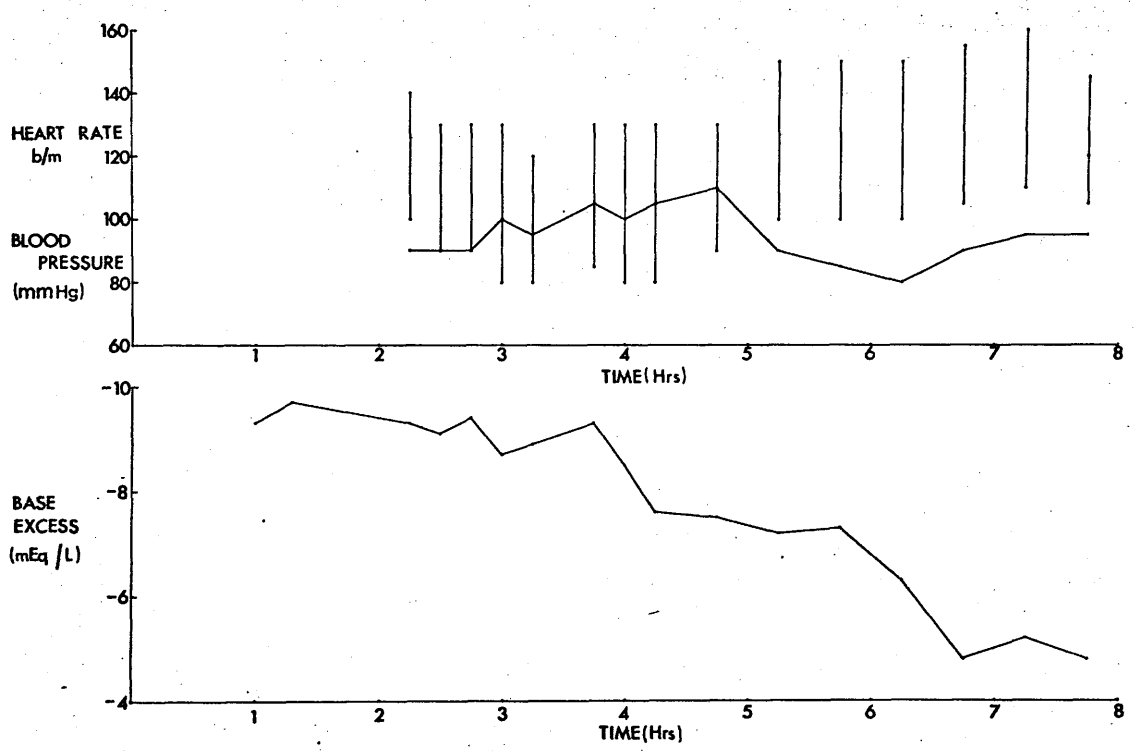


Figure 13.17b. See legend 13.17a.

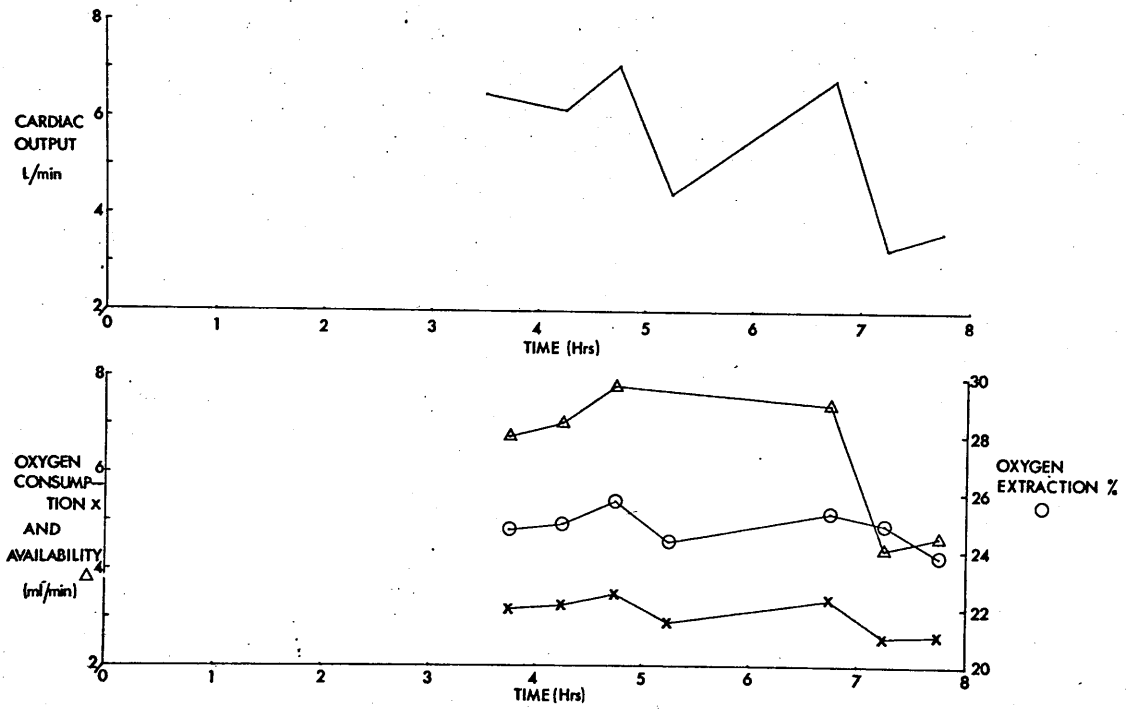


Figure 13.17c. See legend 13.17a.

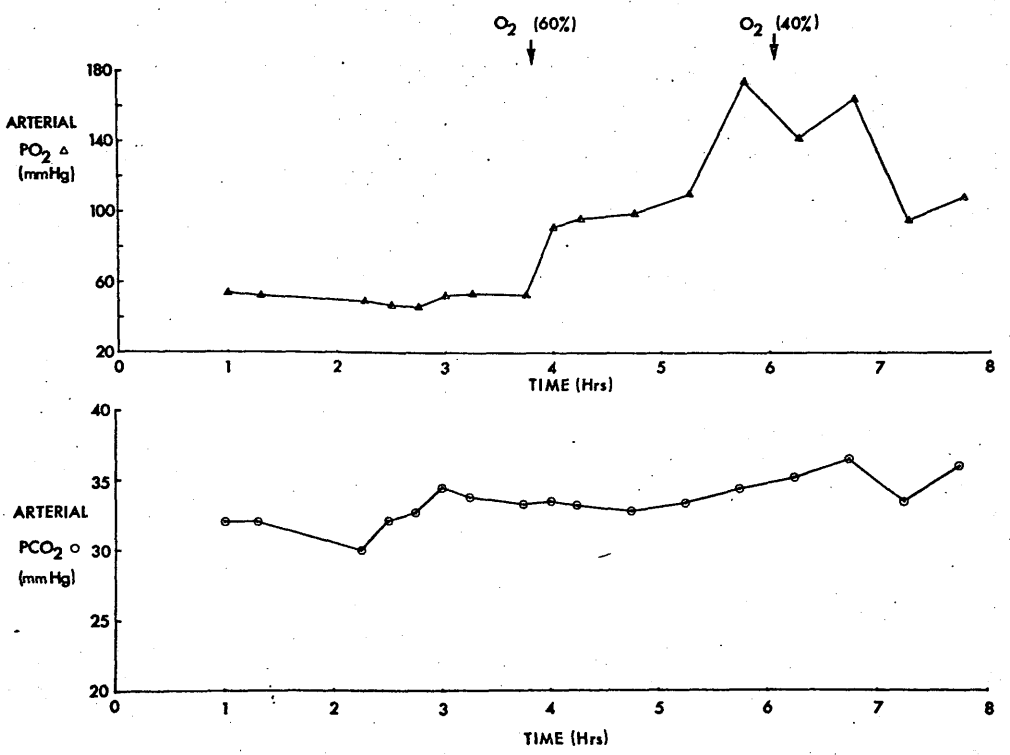


Figure 13.17d. See legend 13.17a.

during this period and the mean volume infused was 2.1 ± 0.2 litres (Table 13.5). Dextrose (5%) and saline were the fluids most frequently infused but on occasions plasma and blood were given; potassium was administered as indicated by sequential biochemical analyses; calcium was not normally given. Oxygen (in high concentration) was administered in all but four of the patients and intermittent positive pressure ventilation (IPPV) was instituted in 48% of the series (Fig. 13.18). At the end of rewarming the standard criteria for weaning from the ventilator were observed (Beach, Millen and Grenvik, 1973) and adequate spontaneous ventilation was usually achieved without difficulty.

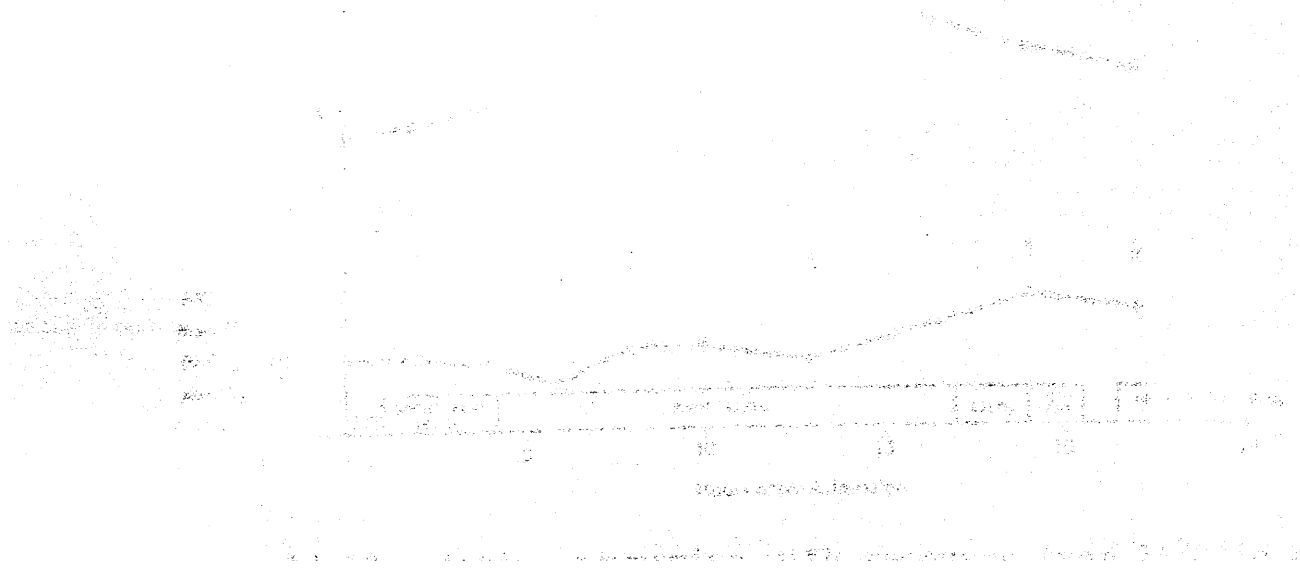
The most troublesome problem during rewarming was hypotension which was regarded as more than usual in 14 of the 44 patients (32%). Seven of these patients received drugs aimed at increasing blood pressure and thereby improving perfusion to vital organs. Four were given vasoconstrictors; one appeared to respond well, a second had a variable response (Fig. 13.19) and two showed no response (Fig. 13.20); (the clinical details of the first of these four patients were published as indicated in the following reprint).

Table 13.5

ACCIDENTAL HYPOTHERMIA

Summary of Treatment

Total no. patients		44
Active rewarming		44
Oxygen [mean max. concn.]		40 (65%)
IPPV/warm air humidifier		21
IV fluids (volume/litres)		2.1 ± 0.2
Drugs:	Antibiotics	24
	Steroids	7
	Vasoactive agents: aramine 4; dopamine 2; isoprenaline 1; thymoxamine 1	8



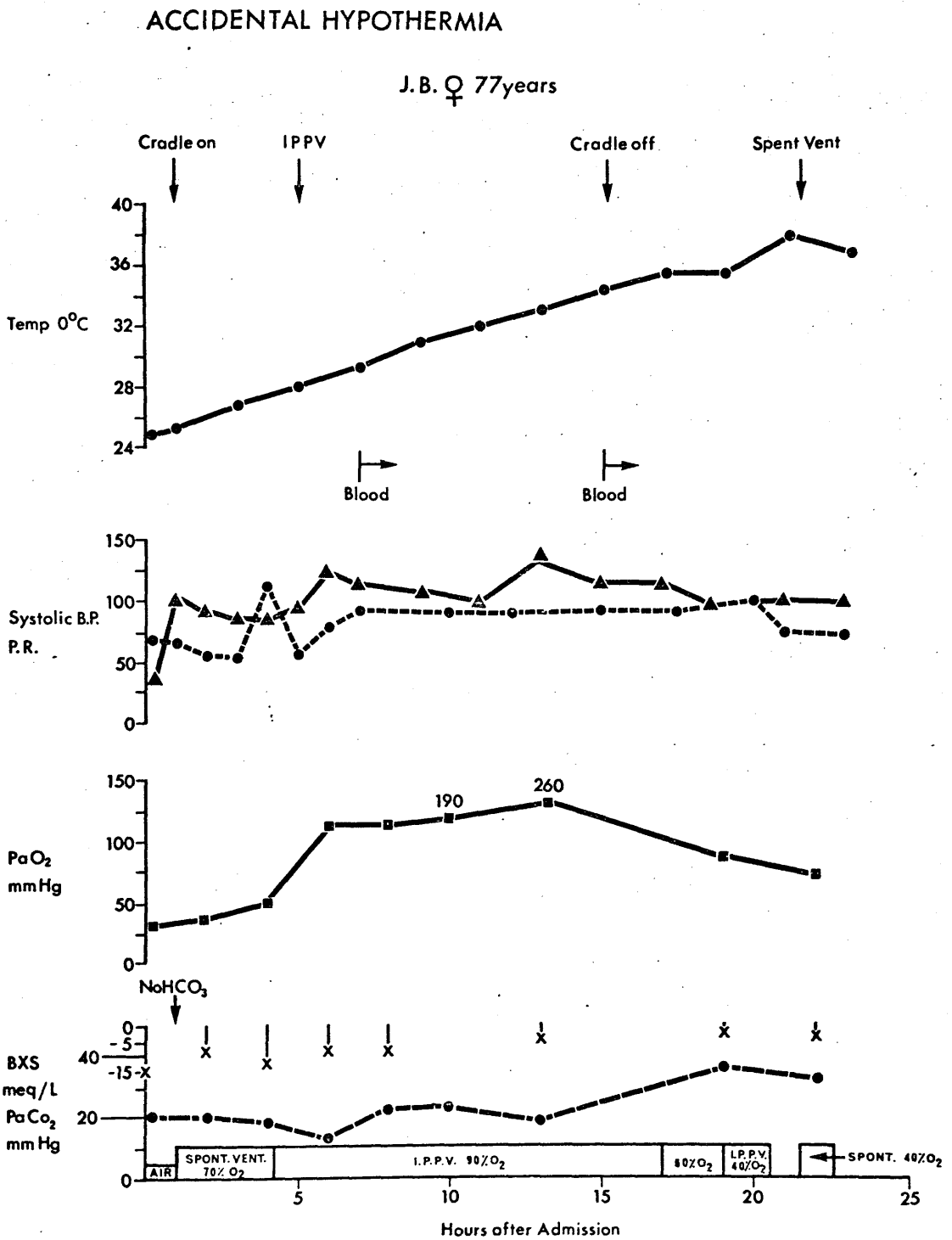


Figure 13.18. Active rewarming with recovery from 24°C in a 77 year old female found unconscious in an unheated bedroom; no cause for hypothermia was found. IPPV was commenced after earlier oxygen administration had failed to restore normal arterial PO2.

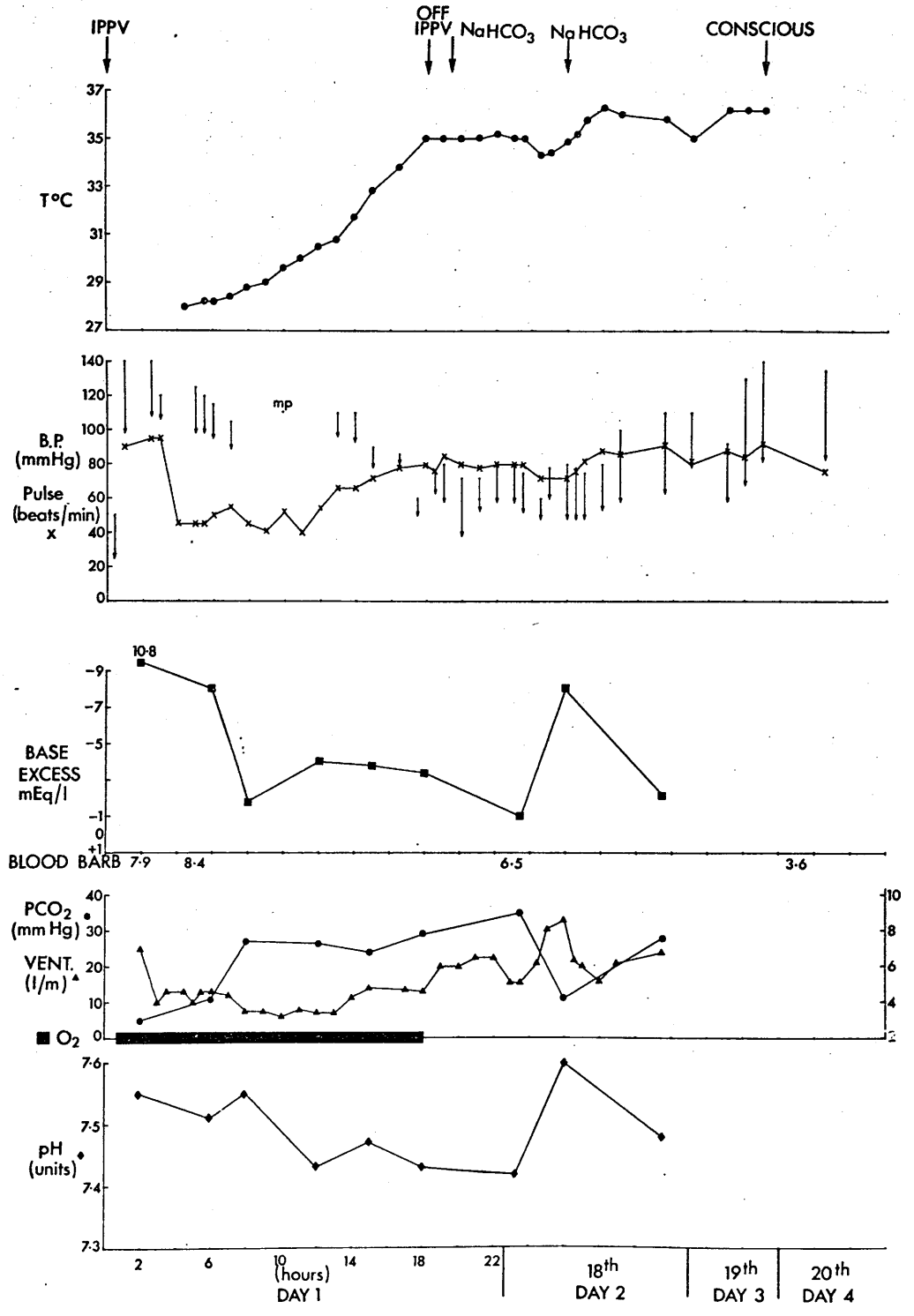


Figure 13.19. Active rewarming in a 55 year old female in whom hypothermia (28°C) occurred as a consequence of barbiturate overdose; blood pressure rose initially from 50/25 mm Hg in response to aramine but not later when hypotension recurred at 34°C: mp - mean intra-arterial pressure when blood pressure was unrecordable using a sphygmomanometer.

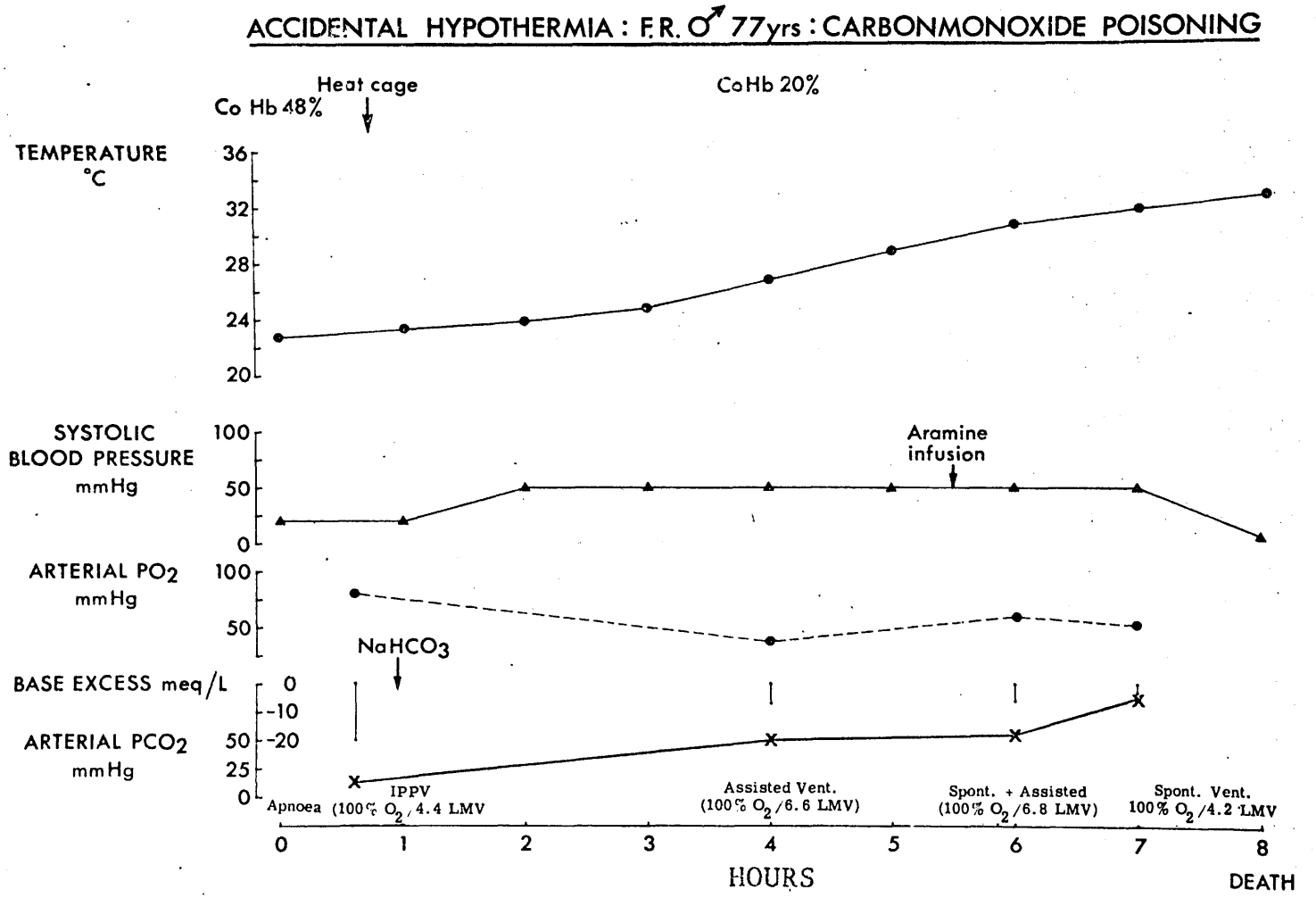


Figure 13.20. Active rewarming in a 77 year old male in whom hypothermia (23°C) occurred as a consequence of coal gas poisoning; death occurred shortly after IPPV was discontinued; aramine had no effect on persistent hypotension.

Treatment of intoxication with combinations of drugs and management of the associated shock

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SELF-POISONING with combinations of drugs is becoming increasingly common and such cases present considerable therapeutic problems.

The difficulty in measuring blood and urine levels of many new sedatives and tranquillizers has meant that no firm guide-lines for treatment have been laid down; in particular, little evidence exists as to the value of measures such as forced diuresis and haemodialysis in increasing the rate of removal of the drugs from the body. In addition, precise details of the multiple drugs ingested are seldom available, and treatment often resolves itself into the application of good respiratory care and the correction of shock. This latter problem is often difficult, and persistent hypotension commonly contributes to the patient's death. The present case is reported because of the success of the therapeutic methods used, and the initial failure of forced diuresis.

Case report

A female aged 27 was found unconscious and admitted to hospital at 11.00 hours on 18 September 1968. Comprehensive enquiry suggested that she had taken phenobarbitone and other drugs, including chlordiazepoxide and phenelzine.

On admission she was deeply unconscious, totally areflexic and had fixed, dilated pupils. Respiration was clinically adequate and systolic blood pressure 105 mmHg. Serum barbiturate level was reported as 9 mg/100 ml and on the basis of percentage hydrolysis the barbiturate was said to be of the long-acting group (Broughton, 1956). This apparently confirmed the suggestion that the patient had taken phenobarbitone, and that the barbiturate was not a major factor in the intoxication; a diagnosis of mixed sedative-tranquillizer intoxication was made. This conclusion was later found to be an error, for there is now no reasonable doubt that the barbiturate ingested was amylobarbitone, both on the evidence of the patient and subsequent identification of the drug in the blood by thin-layer chromatography. The patient had also taken large amounts of chlordiazepoxide and phenelzine.

On the erroneous assumption that phenobarbitone had been the drug ingested, forced diuresis was begun as described by Linton *et al.* (1964), with the object of maintaining the circulation and removing at least the barbiturate component of the intoxication. Serum urea and electrolytes were normal, and there was no clinical evidence of pre-existing cardiac or renal disease. At 14.00 hours (3 hr after admission), increasing respiratory depression necessitated transfer of the patient to the Intensive Therapy Unit; systolic blood pressure had fallen to 70 mmHg and blood gases were: Po_2 54 mmHg, Pco_2 80 mmHg, pH 7·2 (spontaneous respiration, on air).

An endotracheal tube was passed and assisted ventilation was begun using a Cape ventilator. Breathing 100% oxygen with a minute volume of 9·5 litres, blood gases (corrected for temperature) were: Po_2 405 mmHg, Pco_2 26·5 mmHg and pH 7·61, with a base deficit of 6 mEq. Systolic blood pressure remained 70 mmHg and progressive fall in rectal temperature to 34°C necessitated re-warming with a heat cage. The rectal temperature reached 37° C at 23.00 hours on the day of admission.

By 19.00 hours on 19 September 1968 the patient had received 3500 ml of fluid intravenously, but urine volume was only 1450 ml despite the administration of 80 mg of frusemide and 10 g of mannitol. Since there were no clinical signs of overhydration, it was thought that the relative failure of diuresis might be due to pre-existing dehydration. In addition, the hypotension of barbiturate intoxication has been attributed to a relative hypovolaemia from venous pooling of blood (Shubin & Weil, 1965), so it was

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decided to give 1000 ml of plasma and to continue with the forced diuresis in an attempt to raise the falling blood pressure. Over the next 8 hr, however, blood pressure became unrecordable by standard methods, and a further 160 mg of frusemide given intravenously produced only a small increase in urine flow rate. At 09.00 hours on 19 September 1968, 22 hr after admission, the patient was still deeply comatose with fixed, dilated pupils, the extremities were cold and the skin was pale, but there was no cyanosis. Direct recording of the arterial pressure using a transducer and ink-jet recorder (Elena-Schönander 'Minograf 34') showed the blood pressure to be 50/30, mean 35 mmHg, although no pulses could be felt nor any blood pressure recorded by sphygmomanometer. Intermittent positive-pressure ventilation continued with apparently good air entry to both lungs; the blood gases were: Po_2 110 mmHg, Pco_2 32 mmHg and pH 7·48. Standard bicarbonate was 25 mEq/l and base excess 1·8 mEq. The deterioration in Po_2 was thought to be due to venous admixture effect consequent upon hypotension and pulmonary oedema; the presence of pulmonary oedema was confirmed on chest X-ray. Serum barbiturate level was 9·8 mg/100 ml and central venous pressure recordings started at this time indicated a level of 24 cm H_2O. It was, therefore, obvious that forced diuresis had failed, and the patient now had considerable fluid overload. There was doubt whether vasopressor drugs would be of any value in view of the existing peripheral vasoconstriction; Shubin & Weil (1965) showed that the effect of such drugs in this situation may be to reduce urinary output and prevent satisfactory expansion in plasma volume, although the effect on cardiac output and peripheral vascular resistance appeared to vary with the dose of drug used. Equally, it was feared that attempts to improve tissue perfusion with a vasodilator drug would be likely to cause a further and probably fatal fall in blood pressure. A single dose of 100 mg of hydrocortisone was given to assess the effect of steroids, but at 11.30 hours the blood pressure had fallen to 45/25, mean 30 mmHg.

It was, therefore, decided to try the effect of mephentermine, and the patient was given 45 mg of this drug by slow intravenous injection. This immediately improved the mean blood pressure to 50 mmHg and increased urine flow rate from an average 75 ml/hr to 350 ml in the next hour. A continuous infusion of mephentermine was begun (150 mg in 500 ml of 5% dextrose), and given at a rate varying between 0·45 and 0·66 mg mephentermine/min; this maintained the mean blood pressure around 50 mmHg. Despite the fears that mephentermine would further reduce cardiac output and tissue perfusion, the increase in pressure was associated with a continued improvement in urine flow rate, this remaining around 250 ml/hr. The skin of the extremities also became noticeably pinker and warmer.

This regime was continued until 09.30 hours on 20 September 1968 (46 hr after admission). It now proved possible further to increase urine flow rate with frusemide (total of 560 mg given in 8 hr), and during the 24-hr period after the start of mephentermine therapy, some 5 litres of the retained fluid were excreted (2000 ml in, 7000 ml out). Fluid intake and output since admission were now almost equal, and the central venous pressure had fallen to 13·5 cm H_2O. Serum barbiturate level was 6·5 mg/100 ml. Blood pressure was 75/40, mean 53 mmHg and gradual reduction in rate of mephentermine infusion was possible. The infusion was stopped at 14.00 hours on 20 September 1968, and there was no subsequent fall in blood pressure. During the next 18 hr, the patient's condition improved steadily; blood pressure rose, and pupillary and cough reflexes returned. By 09.00 hours on 21 September 1968 (70 hr after admission) blood pressure was 117/62, mean 85 mmHg. Spontaneous ventilation was resumed and the endotracheal tube was removed later in the day. The patient was fully conscious on the morning of 22 September 1968, and suffered no ill-effects from her 90-hr period of unconsciousness other than a mild chest infection which responded quickly to antibiotics. There was no evidence of residual brain damage on clinical examination or on psychiatric assessment by a psychiatrist who had known her previously. Serum electrolytes and blood gas values were normal on 23 September 1968, and on 25 September 1968 she was transferred for psychiatric treatment.

Discussion

The drugs ingested by the patient described above were phenelzine, chlordiazepoxide and amylobarbitone. Pure phenelzine overdosage gives symptoms of massive catecholamine release (Solberg, 1961), which probably caused the widely dilated pupils and may have contributed to the peripheral vasoconstriction in this case. Chlordiazepoxide has been ingested in large doses without severe symptoms (Jenner & Parkin, 1961); deaths have occurred but only when the drug was taken together with other depressive agents (Cruz, Cramer & Parish, 1967). In retrospect, therefore, the amylobarbitone ingested was the major problem and the patient should probably have been treated by haemodialysis on the basis of our own previous criteria (Linton *et al.*, 1967b). Failure to institute haemodialysis was due to the erroneous clinical and biochemical information suggesting that the barbiturate ingested had been phenobarbitone. Further studies on the

identification of barbiturates as long or intermediate-acting suggest that percentage hydrolysis is unsatisfactory for differentiation, and where clinical decisions hinge on the result thin-layer chromatography should be used.

Extensive previous experience with forced diuresis in barbiturate intoxication has demonstrated its safety and effectiveness (Strickler, 1966; Linton, Luke & Briggs, 1967a). In this case, however, a second error of management was made in assuming that the failure to induce a diuresis quickly was due to pre-existing dehydration. It is probable that the low urine flow was due to poor renal perfusion with consequent low glomerular filtration rate. The resultant fluid overload should have been detected sooner by recording the central venous pressure earlier. It should, however, be emphasized that this is the first occasion in the experience of one of us (A.L.L.) in over 150 patients treated with forced diuresis that significant overhydration has occurred.

The principal therapeutic problem posed by this patient was the severe hypotension: no blood pressure or pulse were detectable by standard clinical methods for over 24 hr. The administration of fluids as suggested by Shubin & Weil (1965) failed to raise the blood pressure. The potential danger of treating shock with vasopressor agents is well documented (*Lancet*, 1967) and their use in hypovolaemic states with failure of the vasoconstrictor mechanisms is illogical (Bloch *et al.*, 1966). In order to improve tissue perfusion Lillehei *et al.* (1964) suggest the use of vasodilator drugs with replacement of blood volume as required. However, for the reasons already described, the patient was given mephentermine, with immediate effect on blood pressure, skin colour, temperature and urine volume. It seems probable that in hypotension of this severity mephentermine is beneficial by reason of its inotropic effect on the heart (Winsor, 1959; Li, Shimosato & Etsten, 1962) with a resultant increase in cardiac output; there was no increase in heart rate in this case. A paradoxical reduction in peripheral vascular resistance, as seen here, has been noted in severe hypotension with other vasoconstrictor agents, notably metaraminol and noradrenaline (Shubin & Weil, 1965). There is, however, no exact understanding of the mechanism of action, or indeed of the effect of vaso-active drugs under these conditions. Only by more frequent and intensive monitoring of haemodynamic changes in poison patients will empiricism be replaced by more logical therapy.

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Three of the patients received drugs having a major inotropic action on the heart; all responded well and the improvement in urine output was marked in the two patients given dopamine. One patient was given the ∝-adrenotropic blocking agent thymoxamine because of persistent vasoconstriction toward the end of rewarming; a moderate response was noted.

Steroids had been administered on seven occasions prior to referral; only small doses had been given and their effect was impossible to judge. Antibiotics were not administered on a prophylactic basis but 24 patients (55%) received a variety of antibiotics when clinically significant infection (usually of respiratory origin) was confirmed on bacteriological examination.

Mortality

Data relating to mortality are presented in Table 13.6 and Fig. 13.21. The overall mortality was 27%.

Only two patients died during rewarming; both deaths occurred in the early years of the study (1965 and 1968). One patient, who was 77 years of age and was found in a gas-filled room, died at a temperature of 34.5 deg C after IPPV had been discontinued

Table 13.6

ACCIDENTAL HYPOTHERMIA

Prospective Study

Mortality

Total no. patients	44
Mortality	
Rewarming	2 (5%)
Overall	12 (27%)

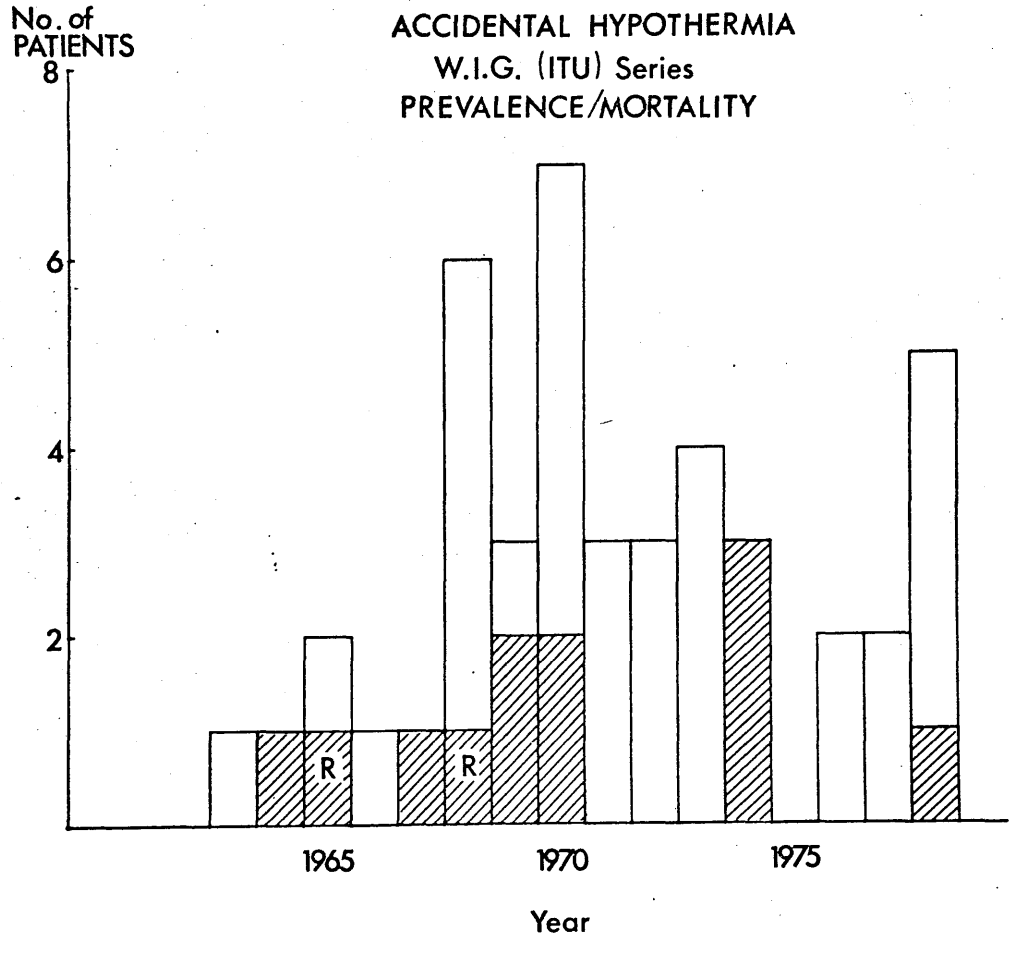

Figure 13.21. Mortality in patients suffering from accidental hypothermia.

and spontaneous ventilation proved inadequate for oxygen transport in the presence of severe hypotension (Fig. 13.20). The other patient, who was 65 years of age and a severe alcoholic, died, apparently from cardiac failure, at 29 deg C. On admission he had a central temperature of 20 deg C and was one of the two patients rewarmed by mediastinal irrigation via a thoracotomy. Laboratory data showed that this patient was extremely dehydrated and anaemic (haemoglobin - 7g/100ml); hypotension persisted throughout rewarming. On reflection, it is reasonable to assume that the main problem was a severe reduction in myocardial oxygen availability which, in the absence of adequate fluid repletion, became critical as oxygen consumption rose during rewarming.

The remaining 10 patients all died after regaining normal body temperature. The causes of death, confirmed at post-mortem examination in all but two, are listed in Table 13.7. Two deaths occurred on days 2 and 3 from acute cerebrovascular accidents, whether or not de novo could not be determined. Four more deaths occurred on day 4 - three from cardiovascular emergencies (one 'further' myocardial infarction, one subarachnoid haemorrhage and one cardiac arrest associated with a serum calcium of 1.2 mmol/l) and one from meningitis following surgery for pituitary

Table 13.7 Accidental Hypothermia

Details of Non-Surviving Patients (R - rewarming death)

Patient (year)	Age/ (yr) Sex	Precipitating/ associated factors	Day of death	Cause of Death
F.R. (1965)	77M	Coal gas poisoning	1 (R)	Respiratory failure during rewarming (No PM)
H.F. (1968)	65M	Alcoholism: anaemia	1 (R)	Cardiac failure during rewarming
A.F. (1970)	80M	Coal gas poisoning: cerebrovascular accident	2	Cerebrovascular accident (No PM)
R.McG. (1967)	84F	Cerebrovascular accident	3	Cerebrovascular accident (No PM)
A.E. (1970)	69F	Myocardial infarction	4	Further myocardial infarction
A.H. (1974)	66M	Hypertension	4	Subarachnoid haemorrhage: bronchopneumonia
F.A. (1974)	56M	Chronic respiratory disease: Diarrhoea/vomiting: Dehydration	4	Cardiac arrest (serum calcium -1.2 mmol/1)
P.D. (1969)	59M	Pituitary tumour	4	Meningitis
W.McD. (1978)	78M	Tuberculous bronchopneumonia: cerebrovascular accident	10	Acute renal failure cerebral softening
D.L. (1969)	60M	Reticulosis: anaemia	11	Reticulosis: bronchopneumonia
M.P. (1964)	69F	Myxoedema: rheumatoid arthritis: anaemia: myocardial infarction	12	Septic shock: perforated stercoral ulcer
J.N. (1974)	80F	Malaena: dehydration : inanition	19	Myocardial infarction

tumour. The remaining four deaths occurred on days 10, 11, 12 and 19. The first of these, a man of 78 years, developed acute renal failure and was discovered to have miliary tuberculosis - no treatment was instituted and at post-mortem recent cerebral softening was found. The other three patients had fully recovered from the hypothermic episode and were ambulant in the ward; one died from terminal complications of previously undiagnosed reticulosis, the second from a perforated stercoral ulcer and the third from an unheralded acute myocardial infarction.

Of the several factors which might have been expected to affect the ultimate outcome in patients suffering from hypothermia, three were considered in greater detail - age, temperature and nature of the principal precipitating condition. The mean age of non-survivors (71 $\pm$ 9 yr) was significantly greater ($p < 0.001$) than that of survivors (50 $\pm$ 17 yr) (Fig. 13.22) but there was no statistically significant difference in temperature between the two groups (Fig. 13.23). Patients whose principal precipitating factor was drugs appeared to have a considerably better prognosis (two of 25 died) than those in whom hypothermia was not due to drugs (10 of 19 died: $X^2 = 8.7$, $p < 0.005$). However, the difference in the mean age of the two groups was markedly different (44 $\pm$ 15 yr in the drug survivors and 64 $\pm$ 10 yr

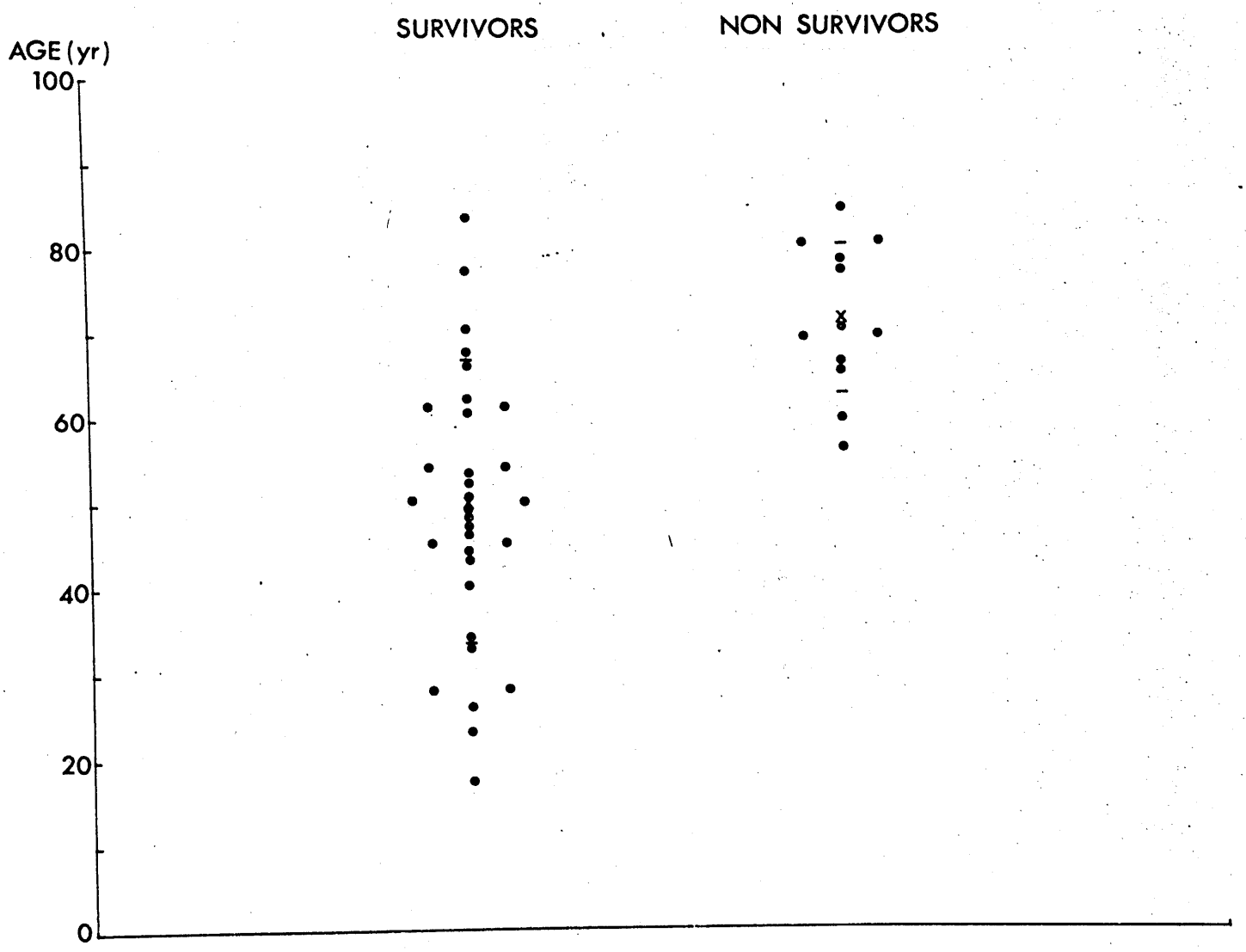

Figure 13.22. Age of survivors and non-survivors in total series.

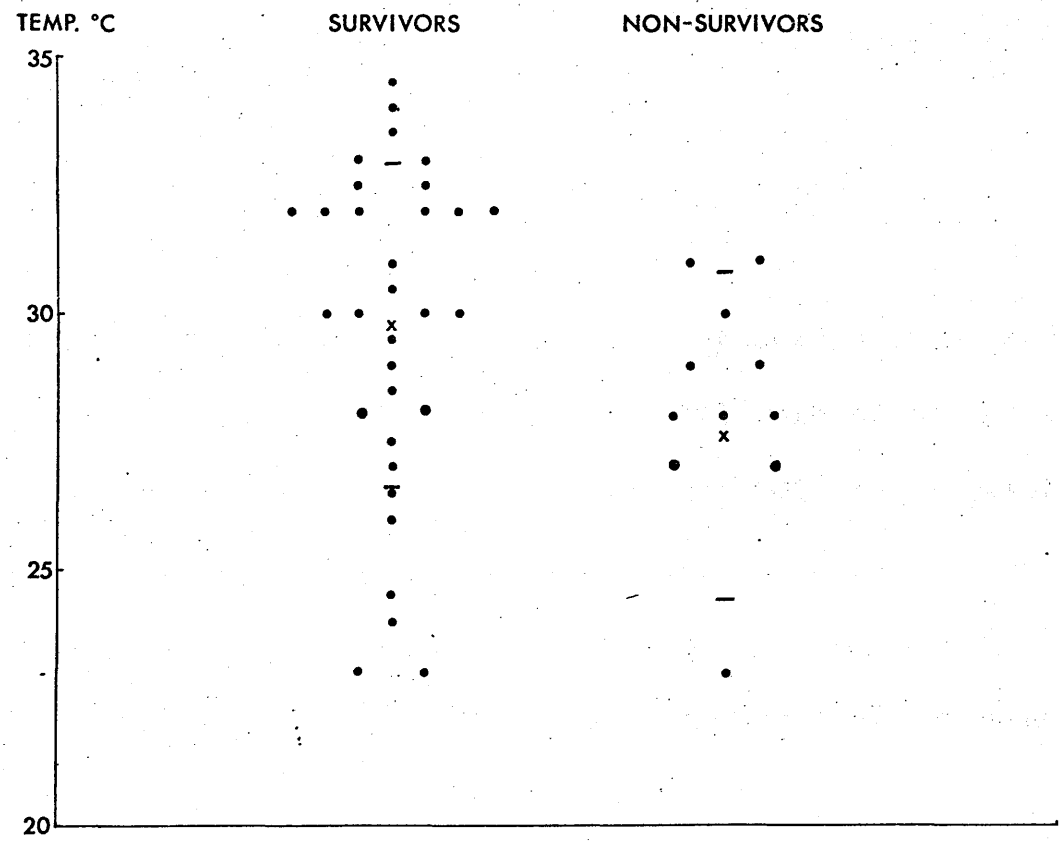

Figure 13.23. Lowest 'core' temperature in survivors and non-survivors.

in the non-drug survivors; $p < 0.001$): there was no significant difference between the mean ages of the non-survivors of the two groups (Fig. 13.24). Age did not significantly differentiate survivors and non-survivors in the non-drug group of patients.

Analysis of the data from the retrospective group of 77 patients (37M; 40F) revealed that the majority were in the seventh to ninth decades and the lowest individual recorded temperatures ranged from 20.0 to 34.7 deg C; 54 (71%) were below the level of 32.2 deg C. The overall mortality was 60%, the majority of patients (78%) dying during the first three days after admission (Table 13.8). The mean age of the non-survivors was 73 ± 2 yr and of the survivors was 67 ± 3 yr (the difference was not statistically significant); the mean central temperature of the non-survivors was 29.6 ± 0.5 deg C and of the survivors was 31.7 ± 0.4 deg C (the difference was statistically significant - $p < 0.005$). Nineteen of the 77 patients were hypothermic as a result of drug abuse, alcohol being the drug most frequently in question; six of these patients died (32%). The majority of the patients (58) had either some serious underlying illness or no obvious cause for hypothermia; 40 of these patients died (69%). The difference in mortality between the drug and the non-drug groups was significant ($X^2 = 6.8$; $p < 0.01$).

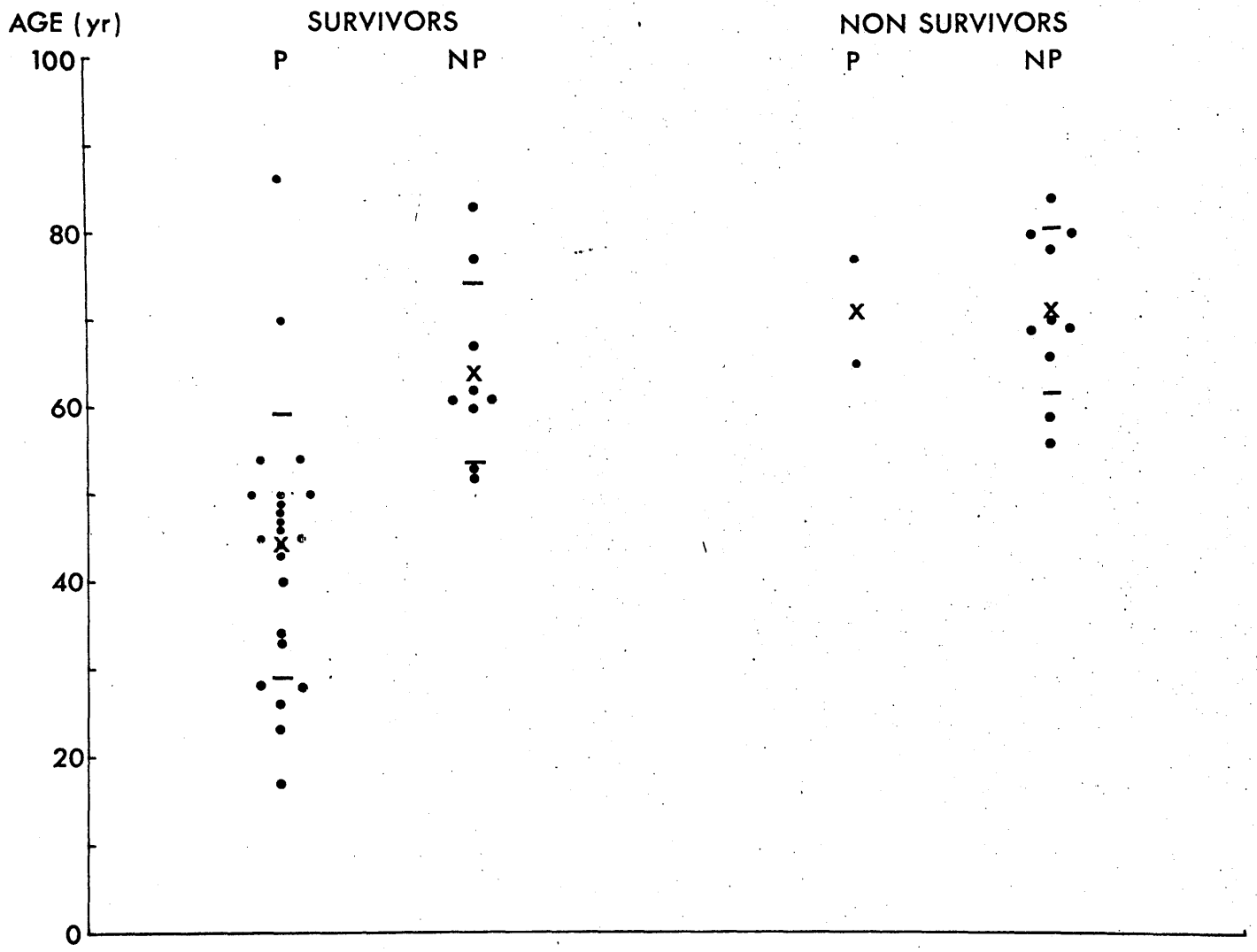

Figure 13.24. Age of survivors and non-survivors in the drug (P) and non-drug (NP) groups.

Table 13.8

ACCIDENTAL HYPOTHERMIA

Retrospective Study

Mortality

Total no. patients	77
Mortality	
Rewarming	36 (47%)
Overall	46 (60%)

DISCUSSION

Mortality

Mortality amongst patients suffering from accidental hypothermia is high. In a recent study (Tolman and Cohen, 1970) a mortality of 46% was claimed to be lower than 'in any previously published series'. As it happens this claim was not supported by fact since Paulley and his colleagues (1964) had previously reported a mortality of 41% but both studies compared favourably with other reports of mortality exceeding 80% (Emslie-Smith, 1958; Duguid, Simpson and Stowers, 1961; Rosin and Exton-Smith, 1964; McNicol and Smith, 1964). Comparison of mortality between different groups of patients is complicated, however, by the variability of such factors as age, severity and duration of hypothermia, and nature of precipitating condition, all of which may affect mortality. Accepting these constraints for the meantime, the overall mortality of 27% reported in the present prospective study is the lowest on record.

The value of treatment of accidental hypothermia as a medical emergency (British Medical Journal, 1964a) may be assessed in relation to the time and circumstances of death of non-survivors. Using conservative ward management MacLean and Emslie-Smith (1977b) record that in their series of 100

consecutive patients 41 died while still hypothermic, and others report similar experience (Duguid et al, 1961; Rosin and Exton-Smith, 1964; McNicol and Smith, 1964). Since restoration of normal body temperature using this technique may take 24 hours, or considerably longer if there are cardio-respiratory complications (Duguid et al, 1961; Exton-Smith, 1968), it may be assumed that the majority of the patients in the retrospective study also died during rewarming; hypothermia *per se* cannot, therefore, be excluded as a significant cause of death in these patients. Indeed it is notoriously difficult to make unequivocal diagnoses (particularly of cardiovascular, respiratory and neurological conditions) in the presence of hypothermia.

By contrast, in the prospective study no patient after 1968 failed to reach normal body temperature and most of the deaths occurred some time after rewarming and were readily explained on other grounds. It was not, of course, possible to exclude hypothermia as a contributing factor in the early acute cardiovascular deaths since vascular occlusions are believed to be a common post-mortem finding in hypo-thermia (Duguid et al, 1961; Mant, 1969 a and b). It may be concluded, however, that the treatment programme evolved in this centre has effectively eliminated deaths directly

attributable to hypothermia and, by decreasing the duration of recovery, has probably reduced the number of deaths indirectly attributable to this cause.

Rate of Rewarming

One of the more controversial aspects of treatment concerns the rate and technique of rewarming. Rapid rewarming may be achieved (1) by external means such as hot baths (Sheehan and Summers, 1952; British Medical Journal, 1964b; Pugh, 1966; Keatinge, 1969; Anderson, Herbring and Widman, 1970), heat cradles (Ledingham and Mone, 1972, 1978) or various forms of heated blankets (Fernandez, O'Rourke and Ewy, 1970), or (2) by internal means such as extracorporeal heat exchange circuits (Davies, Millar and Miller, 1967; Fell et al, 1968), peritoneal dialysis (Lee and Ames, 1965; Lash, Burdette and Ozdil, 1967; Soung et al, 1977), or irrigation of the pleural space (Blades and Pierpoint, 1954) or the mediastinum (Linton and Ledingham, 1966).

Rapid external rewarming has been used largely, although by no means exclusively, for younger patients suffering from hypothermia of relatively brief duration, while rapid internal rewarming has usually been reserved for patients with profound hypothermia whose resuscitation by simpler methods proved to be difficult or impossible. Rapid external rewarming, particularly in the elderly, fell into some disrepute following

the report of Rees (1958), and that of Duguid and her colleagues (1961) who stated that 'attempts at active rewarming were made in six of our earlier cases, all of whom promptly died'. The precise rewarming technique in the latter series was not described but the deaths were attributed to rapid release of intense vasoconstrictor tone resulting in hypotension and circulatory failure. Since then, with few exceptions, those concerned with management of the urban hypothermic patient have opted for the method known as passive external rewarming which consists of nursing the patient in an ambient temperature of 25 - 32 deg C, covered with a heat-conserving metallised 'space' blanket (MacLean and Emslie-Smith, 1977).

Comparison of the results of rapid and slow rewarming (Gregory and Doolittle, 1973) is a largely unrewarding exercise since no clinical study has been designed to examine the two techniques whilst other factors in treatment were maintained constant. The fact that no clearcut difference in efficacy between the two techniques has yet emerged is therefore not surprising. What is clearer is that before about 1970, and apparently for good reason, the general approach to treatment was 'conservative' with passive rewarming and minimal disturbance of the patient to lessen the risk of arrhythmias; during the

past few years a more 'aggressive' attitude has begun to emerge as understanding of the underlying pathophysiological mechanisms has increased. The conservative approach tends to be adopted in general medical wards while the aggressive approach, with continuous (and often invasive) monitoring and treatment techniques, is more frequently practised in intensive therapy units.

Invasive techniques and fluid replacement

Several facts have emerged from the newer, aggressive approach to treatment. Perhaps the most obvious from the present prospective study and from the work of others (Harari et al, 1974; Nicolas et al, 1974) is that invasive monitoring and treatment manoeuvres are not in themselves harmful. Much was made of the dangers of such techniques as gastric aspiration, intravenous and urethral catheterisation, and endotracheal intubation (Cooper and Sellick, 1960; Lee and Ames, 1965; Hockaday and Fell, 1969; Hockaday, 1972). It appears that if ventricular fibrillation was precipitated by these manoeuvres, factors other than hypothermia per se were responsible e.g., hypoxia (Lloyd, 1972), hypotension or acidosis (Jones et al, 1966). Awkward movement of a hypothermic patient may cause cardiac arrest or cerebral hypoxia (Freeman and Pugh, 1969) but the same is true when any critically ill patient is moved

in such a fashion; clearly the frequency of such movements will be less the shorter the period of rewarming.

The response to fluid repletion in the dehydrated hypothermic patient is not noticeably different from normal although a degree of left ventricular failure may be demonstrated in some patients which disappears when normal body temperature is attained (Harari et al, 1974). Significant and persistent left ventricular failure accompanied by hypotension is rare and suggests underlying acute myocardial ischaemia. Inadvertent fluid overload in the hypothermic patient can be adequately treated with diuretics; IPPV reduces the risk of this complication. Low molecular weight dextran has been used with the aim of counteracting the tendency to intravascular coagulation and improving tissue perfusion (Mohri et al, 1968; Tolman and Cohen, 1970) but the case for the use of this agent in hypothermia remains unproven.

Oxygenation

In earlier chapters of this thesis the matter of tissue oxygenation in hypothermia was discussed. The conclusion was reached that, under the controlled conditions of induced hypothermia, there was little evidence of significant tissue

hypoxia even at very low body temperatures. In the circumstances normally obtaining in accidental hypothermia the situation is different. Hypoxaemia is almost invariably present, and in many of the patients of the prospective study, was of marked degree. Since anaemia and low cardiac output (Nicolas et al, 1974) are also common features of accidental hypothermia it is obvious that tissue oxygen availability will be significantly reduced in most patients, and to a critical extent in some. Organs whose oxygen consumption falls less than others with reduced temperature e.g., the heart, will be particularly susceptible to hypoxic damage (Chapter 9, p 186). The presence of shivering aggravates the problem by increasing not only total body oxygen consumption (Michenfelder et al, 1965) but also e.g., cerebral oxygen consumption (Stone, Donnelly and Frobese, 1956).

McNicol and Smith (1964) were amongst the first to draw attention to the frequency of hypoxaemia amongst patients suffering from accidental hypothermia and these authors believed that 'anoxia was related to the high mortality' associated with this condition. They considered the possibility of 'cold injury' to the lungs as a cause of the increased alveolar/arterial PO_2 gradients found in all of their patients but in

a later study by Hedley-White et al (1965) on patients subjected to induced hypothermia, no evidence for such a mechanism could be demonstrated. It is probable that the only effect on the lungs of hypothermia per se is broncho-dilatation (Severinghaus, 1959). Carbon dioxide excretion is not impaired (Severinghaus et al, 1957), nor is oxygen uptake (Hedley-White et al, 1965) and pulmonary mechanics are not altered (Blair et al, 1964; Prakash et al, 1978). The main explanation for the hypoxaemia of accidental hypothermia (McNicol, 1967) is reduction in ventilation and depression of cough predisposing to collapse of alveolar units and larger segments of lung. Acidosis and infection may accelerate the deterioration in respiratory function.

Oxygen is clearly a logical component of treatment and previous concern about its use on the grounds that further respiratory depression might ensue (Duguid et al, 1961), has not been substantiated. The present study has shown that high concentrations of oxygen are required to restore arterial PO_2 to normal. IPPV was consideredto be justified in half the patients, most frequently in those with drug-induced hypothermia. In the critically ill patient the use of IPPV reduces the immediate anxiety about pulmonary gas exchange and allows

concentration on potentially life-threatening cardiovascular disturbances.

Drugs

The interaction between drugs and hypothermia is complex and variable (Blair, 1969). For this reason it has seemed appropriate to restrict the use of all drugs during the phase of rewarming. Adoption of such a policy in the present study has not been regretted although on occasions the temptation, for example, to resort to vasoactive agents in the face of persistent hypotension has been considerable. In the latter context two points are worth making. The first is that hypotension may be more apparent than real; this observation has been confirmed with the more frequent use of intra-arterial pressure monitoring. The second is that hypotension usually responds to fluid infusion and may only require pharmacological support when there is associated evidence of organ or tissue hypoperfusion.

Of the various vasoactive agents available, the most extensive experience has been with the vasoconstrictors but on the whole they have proved disappointing (Duguid, 1961; McNicol and Smith, 1964). Limited experience in the present study would

support these observations and suggest that greater benefit results from the use of agents with a major inotropic and peripheral vasodilator effect. Harari et al (1974) have been impressed with the effect of isoprenaline in patients showing hypothermic left ventricular failure. The use of digitalis preparations, on the other hand, is controversial. They were not used in this study because the ventricular rate was never rapid (Fruehan, 1960; Hockaday and Fell, 1969) and because short-acting inotropic agents could be given more safely by intravenous infusion. Nevertheless both ouabain (Motin et al, 1973) and digoxin (Nordqvist et al, 1960; MacLean et al, 1973) have been used, apparently with good effect, in combating cardiac failure although not in preventing dysrhythmias (Dundee and Clarke, 1964). Atropine undoubtedly increases heart rate in hypothermia although the increase may only be slight and delayed in onset. Certain antidysrhythmic agents, e.g., lignocaine, practolol and propranolol, are reported to be effective in controlling multiple ventricular extopic beats (Wollner and Spalding, 1973) but are rarely required in accidental hypothermia.

Other drugs have not been used in the present study. Steroids are not indicated on physiological ground since the plasma

II-OHCS levels are elevated in most patients with accidental hypothermia (MacLean and Emslie-Smith, 1977) and evidence of the value of steroids in pharmacological doses is lacking. Triiodothyronine has not been used during rewarming even in myxoedema coma and heparin has also been withheld. The evidence that prophylactic antibiotics are of value in accidental hypothermia is absent and, in the present study, respiratory infection was satisfactorily treated once bacteriological information became available.

CONCLUSIONS

Patients suffering from accidental hypothermia can be consistently and safely rewarmed to normal body temperature irrespective of the cause of hypothermia. Normothermia may be achieved as rapidly as is compatible with adequate tissue perfusion and oxygenation; surface rewarming of the torso is perhaps the simplest technique at present available but more efficient, non-invasive methods need to be developed. Evidence from the studies of others and from the retrospective analysis in this centre indicates that passive rewarming prolongs recovery and often does not achieve its aim of restoring normal body temperature. Much of the confusion that tends to surround treatment of the hypothermic patient once he has reached hospital would disappear if the programme described in this

chapter were more universally applied, preferably in an intensive care environment. Mortality would then be attributable to the underlying factor or disease and not to hypothermia.

APPENDIX

PERFUSION FIXATION OF THE BRAIN OF EXPERIMENTAL ANIMALS

1. Heparin is injected into the left ventricle.
2. The ascending aorta is cannulated via the left ventricle.
3. The descending aorta is clamped (unless spinal cord required).
4. The brain is perfused with physiological saline until venous return from incised right atrium is clear.
5. The brain is perfused with FAM (40 ml for the rat and 1000 ml for Rhesus monkey).

FAM	40% Formaldehyde A.R.	1 part
	Glacial Acetic Acid	1 part
	Absolute Methanol	8 part

Perfusion pressure not to exceed 40 mm Hg

FAM was developed by DAVID, G.B. (1955. Exc. med. Neurol. Amsterdam, 8, 777) in order to obtain undistorted sections and optimal staining for nucleo-proteins with cresyl violet.

6. The animal is covered with a damp cloth and the brain is left in situ for at least one hour but preferably 3-4 hours.
7. Carefully remove the brain and place into 25-50 vols. of fresh FAM.
8. Slice the brain into blocks of a convenient size and leave in FAM at room temperature for 24 hours.

DEHYDRATION

1. Wash blocks in 80% methanol (two changes)
2. Upgrade in methanol in increasing concentration in steps of 10%
3. Leave in absolute methanol for at least six hrs. (several changes).
4. Place in Benzene A.R. overnight.

EMBEDDING

1. Place in 50% 'PARAPLAST' (Shandon Scientific Co. Ltd.) in Benzene at 56 deg C for one hour.
2. Infiltrate with pure 'PARAPLAST' at 56 deg C for one hour.
3. Continue infiltration with pure 'PARAPLAST' at 56 deg C in vacuum embedding oven for two hours (two changes).
4. Cast the blocks, cooling them rapidly.

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