OBSERVATIONS ON CARDIOGENIC SHOCK

by

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INTRODUCTION

The mechanisms involved in the pathogenesis of shock following acute myocardial infarction in man are obscure and consequently treatment remains largely empirical and unsatisfactory.

The changing therapeutic emphasis over the years in the use of such measures as intra-arterial transfusion, digitalis compounds and vasopressor drugs reflect differing concepts of the underlying mechanism.

The use of the word "shock" may be criticised in that it lacks precise definition and objective measurement. Nevertheless a syndrome of systemic arterial hypotension in association with both the accepted clinical signs of vasoconstriction and evidence of clouding of consciousness does exist as a clinical entity complicating acute myocardial infarction and the use of the term cardiogenic shock to describe simply the presenting signs of such a patient would appear to be both valid and meaningful. The marked variation both in the incidence and the mortality rate of cardiogenic shock in the reported literature attest to boththis

lack of definition and lack of acceptance of uniform diagnostic criteria. Friedberg (1961) reviewed the incidence of shock in 2,955 cases of acute myocardial infarction in 10 reported series and noted this to be 14% with a mortality rate of 79% when 'strict' diagnostic criteria were used as compared to 52% with a mortality rate of 36% when less stringent criteria were employed. The adoption of inadequate diagnostic criteria and often the inclusion of cases merely exhibiting otherwise uncomplicated hypotension has lead to many unwarranted therapeutic claims. The reservation as expressed by Agress (1958) has received all too little attention from many authors, "In the future, any claim for efficacy of a new treatment must first fulfil the criteria for severe shock and second, must lower the mortality below the current rate of three out of five patients". This high mortality rate and our present therapeutic impotence can rightly be regarded as being related directly to our lack of knowledge and understanding of the basic pathophysiology of cardiogenic shock. The basis of rational therapy must surely lie in such knowledge.

The research worker, at an early stage, turned to animal experimentation in an attempt to evaluate the underlying circulatory changes. Although the dog's heart was subjected to extensive myocardial injury, either by multiple coronary artery ligation or direct chemical or traumatic injury, the reproduction of a syndrome of protracted arterial hypotension similar to that occurring in the human 'shocked' patient eluded the laboratory worker until the development of the technique of coronary artery embolisation. This latter technique has now been perfected to allow selective coronary artery embolisation and thus produce a picture more closely resembling that occurring in man (Jacobey, Taylor, Smith, Gorlin and Harken, 1962). Although the development of these techniques represented a significant advance for the laboratory worker, the relevance of much of the information derived from such studies on anaesthetised dogs to the treatment of the human patient must remain doubtful.

Although the serious nature of myocardial infarction has tended to discourage extensive

investigation of such patients, the precision and facility with which direct measurements of the blood pressure and cardiac output may now be made at the bedside have allowed their increasing application even to this grave clinical condition. Over the years each new development in the measurement of blood flow has been applied in an attempt to improve our knowledge of the haemodynamic changes following acute myocardial infarction. Cardiac output estimations were made in 1941 by Grishman and Master using the Wezler - Boeger technique of pulse wave analysis and in 1943 Starr and Wood reported the results of ballistocardiographic studies. The development by Hamilton et al. (1948) of the indicator dye dilution technique for the measurement of blood flow must be regarded as a most significant advance in the application of cardiovascular research to the patient's bedside. This provided a method for the more accurate determination of cardiac output with the minimum of inconvenience to the patient and lead to more active investigation of the circulatory changes following acute myocardial infarction. However the number of series reported of

patients studied haemodynamically following acute myocardial infarction remains small and experience of cardiogenic shock is obviously even more limited. Therefore, in spite of recent advances and the application of modern cardiovascular techniques, our knowledge of the pathogenesis of cardiogenic shock remains incomplete and there has been, as yet, no report of a definitive study in the evaluation of modern management.

Despite the knowledge gained from animal experimentation, from human studies in shock of varied aetiology, and more recently from experience of the metabolic consequences of the low flow state accompanying the use of the extracorporeal circulation there has been little attention paid to the possible metabolic complications of cardiogenic shock and the influence of any such changes on circulatory homeostasis and response to therapy.

The present investigation was designed in the belief that a definition and understanding of cardiogenic shock can be achieved only by direct studies and measurements on affected patients. The circulatory,

respiratory and metabolic consequences of acute myocardial infarction, with and without shock, have been studied serially in man. These studies have allowed not only a correlation of the circulatory and metabolic state but also a definitive evaluation of contemporary drug therapy and are in accord with a recent view expressed by Rushmer et al. (1962) that (by the application of modern technical progress) " ..... a fairly complete description of a few selected patients (in shock) could equal the incomplete study of hundreds of patients .....". These studies have further demonstrated that scientific measurement and clinical care of thecritically ill patient are not mutually exclusive but indeed are complementary to each other.

It is proposed to present the material in four sections. Section I will deal first with a historical review of the relevant literature, followed by a description of the organisation of and background to the present study. A detailed description and validation of the investigative methods and techniques will then be presented. Each of the remaining sections

will be devoted to the presentation of results with the relevant discussion and will be preceded by a short introduction. Section II will be further sub-divided into four chapters. The first of these will be devoted to a consideration of the underlying circulatory, respiratory and metabolic changes associated with the acute stage of myocardial infarction. The second chapter will report and discuss the results of oxygen administration in both the acute stage and during subsequent recovery follow-up studies. The third chapter will report and discuss the sequential changes to be found with both time and recovery. The final chapter of this section will be devoted to a discussion of the therapeutic considerations arising out of these findings. Sections III and IV will deal with the presentation of results and the relevant discussion in the evaluation of digoxin and noradrenaline vasopressor therapy respectively.

Summary tables and diagrams are presented throughout the text when they are felt to aid in the understanding of the results, arguments or discussions.

Individual detailed tables together with the detailed clinical features and findings relevant to each patient are included in the appendix.

SECTION I

Historical Review of Relevant Literature

STUDIES IN PATIENTS

Although the existence of myocardial infarction as a pathological entity was first demonstrated by Weigert in 1880, it was a further 16 years before Dock in 1896 described the first case in which the clinical diagnosis was made prior to death and was confirmed at post-mortem examination. The clinical features were, for the first time, described in detail in 1910 by Obrastzow and Straschesko. These authors, however, considered the disease to lead quickly and inevitably to death. Herrick however in 1912 drew attention to the fact that not only was myocardial infarction a recognisable clinical condition but also that it was not necessarily fatal. Levine and Brown reported the first large series of cases (145 patients) in 1929 when they analysed the clinical features in detail.

The word "shock" first appeared in the English medical literature in a translation of the works of a

French surgeon by the name of Le Dran in 1743 "..... and the Bullet, or whatever Body it is, thrown by Gun-powder, acquires fuch a rapid Force, that the whole animal Machine participates more or lefs in the Shock and Agitation .....". In 1795 James Latta an Edinburgh surgeon used the term to describe a moribund condition thought to be the result of inflammation. Gradually the word came to be descriptive of all forms of circulatory collapse and prostration occurring in a variety of traumatic and atraumatic disorders.

Atchley, in his review of medical shock in 1930, made no mention of myocardial infarction, as an aetiological factor and fostered the point of view that all cases of shock (whether due to trauma, toxaemia, haemorrhage or anhydraemia) could be attributed to a disproportion between the circulating blood volume and the size of the vascular bed. The physician had indeed become accustomed to the thought that all types of shock had a similar pathogenesis - namely, an insufficient effective circulating blood volume leading

to a diminished venous return and consequently an inadequate cardiac output. The origin of such a syndrome was obviously in the periphery and shock came to be regarded as synonomous with peripheral circulatory failure.

The introduction of the term, cardiogenic shock, by Harrison in 1935 to describe the shock syndrome arising primarily as a result of cardiac disease, could be regarded as unfortunate in that it led to a belief in the existence of two distinct different types of shock, i.e. central or cardiogenic and peripheral. Although the syndrome of cardiogenic shock is most frequently associated with acute myocardial infarction, other less common diseases may also precipitate the same clinical state viz. cardiac tamponade, extreme tachycardia, acute myocarditis etc. The clinical features described by Harrison were :- weakness, faintness, diminished mental acuity, pallor, cold moist skin, feeble thready rapid pulse and diminution of blood pressure. He stated that, in contrast to the clinical picture of peripheral circulatory failure, dyspnoea,

orthopnoea, pulmonary rales and distended neck veins may all be present.

The earlier clinical investigators therefore attempted to differentiate these two varieties of shock on the basis of the peripheral venous pressure.

In 1934 Fishberg, Hitzig and King carried out the first attempt at circulatory investigation in cases of acute myocardial infarction, with and without shock. Measurements were made of the peripheral venous pressure, circulation time and circulating blood volume. All measurements and injections were made in an antecubital vein. These workers concluded that the syndrome of shock accompanying acute myocardial infarction had its origin in the periphery and was due to a diminished venous return consequent upon peripheral pooling of blood. These conclusions were based on a demonstration of a normal to low venous pressure in the antecubital fossa, the finding of a reduced blood volume as estimated by the congo-red technique and only a slight prolongation of the arm to tongue circulation time using soluble gluside. However the

measurement of venous pressure in an antecubital vein can hardly be regarded as indicative of the state of venous return to the right atrium. The congo-red technique for blood volume estimation has been criticised in that a large error is introduced because of its diffusability (Agress et al. 1950) and indeed as originally suggested by Gross et al. (1937) only one case had in fact an unequivocably subnormal blood volume. There therefore appeared to be little justification for the conclusion of these authors that "the remarkable feature is that this exquisitely peripheral type of failure results from myocardial infarction, a cardiac lesion, par excellence" and in fact Fishberg in the second edition of his book (1940) had himself modified his views and considered a reduction in cardiac output to be the prime initiating factor in cardiogenic shock.

In 1942 Stead and Ebert reported the results of a study aimed at evaluating the separate individual roles of the heart and the peripheral vascular system in cardiogenic shock. Six patients were investigated.

The venous pressure was measured either in the femoral or external jugular vein, the plasma volume being estimated using T-1824 (Evans blue dye) and the arm to tongue circulation time measured using decholin. The venous pressure was either normal or only questionably elevated and the circulation time was prolonged in one of the three patients in which it was measured. The plasma volume tended to be somewhat decreased but never of a sufficient severity to account for the clinical picture. All six patients revealed evidence of pulmonary congestion on chest x-ray, and the authors suggested the possibility that the slight reduction in plasma volumes might have been due to the loss of fluid into the lungs. They further postulated that this pulmonary congestion might indicate an imbalance between the right and left ventricles and therefore the pulmonary venous pressure would be elevated in such patients. These findings and considerations lead to the conclusion that the clinical picture of cardiogenic shock which is suggestive of an inadequate peripheral blood flow resulted in fact from a failure of the left ventricle to maintain an adequate cardiac output.

The first attempt at actual measurement of the cardiac output in acute myocardial infarction was reported by Grishman and Master in 1941. The method used was that of Wezler and Boeger (1939) which is a physical method involving a computed result from the pulse pressure, pulse wave velocity and the estimated aortic diameter. Although a reduction in cardiac output was shown in four of the five patients (none of whom exhibited the features of shock) great doubt must remain as to the validity of the technique employed. Starr and Wood (1943) computed the cardiac output from ballistocardiographic studies in patients following acute myocardial infarction. These workers also reported a reduction in cardiac output and further suggested that the more severely ill patient did not necessarily have the lowest cardiac output. However, ballistocardiographic tracings may be influenced by many extraneous factors and these measurements still did not establish unequivocably the changes in cardiac output following myocardial infarction.

In 1950 Pritchard and Hellerstein reported the results of indirect Fick cardiac outputs with right atrial

catheterisation in 11 patients. None of these patients were shocked. The reported cardiac outputs again tended to be in the lower range of normal. Although the estimation of the cardiac output by the indirect Fick method may be suggestive, it can hardly be regarded as an absolute index. The oxygen content of blood in the right atrium varies widely according to which venous return stream is being sampled at any given moment. Further, during sampling, a catheter may well move from one "stream" to another. An isolated arterio-venous difference based on right atrial sampling is therefore quite unreliable and of doubtful value in the calculation of the cardiac output.

The development of the dye dilution technique for the estimation of blood flow by Hamilton et al. (1948) allowed the application of a safe and more reliable method for the determination of cardiac output at the patient's bedside and was increasingly applied over the next few years.

The first measurement of the cardiac output during cardiogenic shock in man was reported by Fries,

Schnaper, Johnson and Schreiner in 1952 when they also reported the first reliable estimates of the cardiac output in uncomplicated acute myocardial infarction. Haemodynamic studies were carried out in 11 patients and the results obtained were compared with those of similar studies in normal and hypertensive patients. Haemodynamic information is available in four cases of cardiogenic shock. The femoral arterial pressure was recorded intravascularly and thecardiac output was measured by the dye dilution technique employing Evans blue (T-1824) dye and intermittent sampling of the arterial blood according to the method of Werko and his associates (1949). An intravenous catheter having been advanced into the region of the great veins allowed not only the measurement of central venous pressure but also provided a central site for dye injection. The technical methods employed in this study have been outlined in some detail as they were the first attempt at detailed circulatory investigation in acute myocardial infarction and represented a significant advance. For the first time, the mean arterial pressure, central

venous pressure, cardiac output, and total circulating blood volume were measured more or less simultaneously in the same patient. The absolute accuracy of the cardiac output measurements must however be questioned in that there is an inherent error in the use of the intermittent arterial blood sampling technique and also that the quoted figures are based solely on one estimation. The mild cases of acute myocardial infarction failed to exhibit any significant abnormality. The cases of cardiogenic shock exhibited the most marked changes: a significant reduction in mean arterial pressure, cardiac output and stroke volume with elevation of the systemic vascular resistance and central venous pressure. The circulation time was prolonged in the severe and shocked cases but the central (cardiopulmonary) blood volume showed no significant change with increasing severity. The total blood volume tended to be slightly reduced in the severe and shocked cases. The moderately severe and severe cases occupied an intermediate position between the mild and shocked

cases. The conclusion reached was that the severity of the attack as judged by the clinical observations appeared to correlate directly with the degree of depression of the stroke volume and the authors therefore suggested that the primary event in cardiogenic shock was failure of the left ventricular stroke output. The consequent reduction in the systemic arterial pressure was held to result in the activation of neurogenic reflexes which produced an increase in systemic vascular resistance and tachycardia. The haemodynamic response was therefore considered to be similar to that occurring in the compensated phase of hypovolaemic shock except that the primary disturbance was to the pump itself and not due to blood loss. Indeed this opinion was in accord with the classical viewpoint as expressed by Wiggers (1945) "the similarity of the clinical syndromes following coronary occlusion and loss of blood or plasma is due to the fact that, in both cases the cardiac output is decreased, but for a different reason, hypovolaemia in the case of shock due to blood loss and failure of the contractile

capacity of the ventricle in the case of myocardial infarction". Wiggers (1947) in fact considered the heart to play a central role in all types of shock, either being involved initially as in myocardial infarction or latterly as the result of diminished coronary blood flow. This theme of the "central role of the heart" has recently been reviewed by Guyton and Crowell (1961) who consider that "irreversible shock" may well be due to myocardial failure.

Smith, Wikler and Fox reported the results of their circulatory investigations in acute myocardial infarction in 1954. These authors studied ten patients without shock, nine patients with shock and 12 patients during convalescence. Complete data of diagnostically acceptable "shocked" cases are available in six patients. The absolute validity of the cardiac output determinations may again be criticised in that the intermittent sampling method using Evans blue dye was similarly employed. A further criticism may be levelled in that the Evans blue dye was injected into either an antecubital or the femoral vein. The delay in

appearance time and possible "peripheral trapping" of dye which is particularly liable to occur during a forearm injection in the presence of shock may well lead to artificially low estimations of the cardiac output. Further, all results were based upon one isolated determination of the cardiac output. However, despite these criticisms of the techniques employed, the results obtained again represented a significant advance and were in general agreement with those reported by Fries et al. (1952). However one essential difference of opinion did emerge from these studies. Whereas Fries et al. were of the opinion that the degree of reduction of cardiac output alone determined the presence or otherwise of shock, Smith and his co-workers suggested that the cardiac output was often equally low in patients without evidence of shock, and that, therefore the reduction in cardiac output was only one of the features that determined the clinical appearance of the patient. Smith et al. further showed that whereas the cardiac output was always reduced in the presence of shock, the systemic vascular resistance was within the normal range in

three of their shocked patients. Blood volume studies revealed no significant deviation from normal. The studies carried out during convalescence indicated a gradual increase in cardiac output although not always back to normal values.

Gilbert, Goldberg and Griffin (1954) next reported the circulatory changes in 20 patients following acute myocardial infarction. The dye dilution technique of cardiac output estimation was identical to the previous studies and a peripheral (antecubital vein) dye injection site was used. Similar criticism can therefore be levelled at the results of this study, with a tendency to falsely low estimates of the cardiac output. The findings as reported by these authors were in general agreement with these reported by both Fries and Smith. Although the relationship was by no means an absolute one, the degree of cardiac output reduction following acute myocardial infarction was roughly proportional to the clinical severity of the attack. Again no significant change was found in total circulating blood volume. In the following year Gammil, Applegarth, Reed, Fernald and Antenucci (1955)

investigated 39 cases of acute myocardial infarction. An identical method of cardiac output estimation was used, with the same criticisms. The milder cases had the highest values for cardiac output and stroke volume and the lowest values for the appearance time of the dye. During hospitalisation a significant increase in both stroke volume and cardiac output occurred in the more severely ill patients, who had earlier exhibited an initial striking reduction in cardiac output. Despite the presence of a needle in the femoral artery for the purpose of "dye-sampling" the authors choose to measure the blood pressure in the arm by sphygmo-manometer, and derived the mean arterial pressure by choosing the mid-point between the systolic and diastolic pressures so recorded. The previous studies of both Fries et al. (1952) and Gilbert et al. (1954) had already demonstrated that the intravascular measurements of blood pressure often revealed surprisingly high mean arterial pressures in the presence of cardiogenic shock and consequently the validity of much of the calculations based on an

unreliable sphygmomanometer reading is open to question. The results reported therefore, other than the measurements of cardiac output, are not comparable with those of other workers.

Although the medical literature abounds with many reports of clinical impressions, particularly related to the therapy of cardiogenic shock, there are only 13 well documented diagnostically acceptable cases of shock in which detailed individual circulatory measurements are reported. These cases were reported by Fries et al. (1952), Smith et al. (1954) and Gilbert et al. (1954). Gammill et al. (1955) also reported incomplete results in two cases of cardiogenic shock but, as already stated the sphygmomanometric method of blood pressure recording in such an abnormal state is highly unreliable and these cases will not be further considered. The individual details of these 13 cases are summarised in Table 1. Two values for systemic vascular resistance (S.V.R.) are reported in this table: the authors own figures and a second group of figures in which the S.V.R. has

been recalculated by the formula as used in the present study. This table readily demonstrates the circulatory changes - there is a considerable reduction in both cardiac output and stroke volume although tachycardia is not an invariable accompaniment. The systemic arterial pressure is of course reduced and the central venous pressure tends to be elevated. Although the systemic vascular resistance is appreciably elevated in some cases, it could be regarded as being within the normal range, in at least four of the cases. Agress first stressed this point in 1958 when reviewing the literature and suggested that the defect in compensation involved was not actual vasodilatation but rather a failure of the total systemic vascular resistance to rise in the face of a falling cardiac output. These details in the circulatory changes of cardiogenic shock were further borne out by two illustrative cases. Fries et al. reported one case (case 1 in table 1) in which circulatory measurements had been carried out prior to shock. The development of shock was associated with a reduction in mean arterial pressure (120 -> 80 mm.Hg)

in cardiac output (3.4 - 2.41./min./sq.m.) in stroke volume (28 - 15 ml./sq.m.) and an increase in heart rate (112 - 160 beats per minute) and central venous pressure (6 - 9 mm.Hg). The systemic vascular resistance in fact fell from 1, 550 to 1, 300 dynes.sec. cm^{-5}. Smith reported one case in which circulatory measurements were again undertaken after recovery, (Case 10 in table I). Recovery from shock was associated with an increase in mean arterial pressure (70 - 76 mm.Hg) in cardiac output (1.3 - 2.8 1./min./ sq.m.) a fall in femoral venous pressure (11 - 4 mm.Hg) and on this occasion a reduction in systemic vascular resistance.

In 1957 Gunton, Paul and Woolf reported similar circulatory changes in cardiogenic shock. Nine cases of severe cardiogenic shock were studied using an ear oximeter and Evans blue dye for cardiac output estimation. No individual results were reported but the mean value for the cardiac output in shock was 1.5 1./min./sq.m. and this was accompanied by an elevated central (or cardiopulmonary) blood volume.

Following the first convincing demonstration, by a reliable technique of a slight reduction in the plasma volume in cardiogenic shock by Stead and Ebert in 1942, Agress, Rosenburg, Schneiderman and Brotman reported the first reliable total circulating blood volume studies in myocardial infarction and cardiogenic shock in 1950 using the Evans blue technique. They reported no significant change in the blood volume of patients without shock but approximately 16.0 per cent reduction in the presence of shock. As already discussed, many authors have since then reported measurements of the blood volume carried out simultaneously with other circulatory measurements. In general the total circulating blood volume has been shown to be within the normal range or slightly reduced. No author has reported a reduction in any patient of sufficient severity to have contributed appreciably to the production of the shock syndrome.

It has sometimes been stated that the cardiac output may not be significantly reduced in the presence

Evans blue dye and intermittent arterial blood sampling. An intravenous catheter was introduced centrally into the superior vena cava allowing both the monitoring of central venous pressure and providing a central site for dye injection. Cardiac output estimations are based on one isolated calculation. The most consistent finding was that of a raised central venous pressure. In addition both the cardiac output and the forearm blood flow were reduced. Again this study demonstrated that the degree of cardiac output reduction could be reasonably well correlated with the increasing clinical severity of the attack. Lee considered his findings to suggest left ventricular failure and further considered that the demonstration of a "square wave" response to the Valsalva manoeuvre in these patients supported this contention. This must be regarded as the first real evidence suggesting, although not proving, the existence of left ventricular failure in acute myocardial infarction. Lee was surprised that the degree of systemic vasoconstriction as measured by the decrease in forearm blood flow was

not greater. His forearm blood flow figures ranged from 1.5 to 2.6 ml./100 ml. tissue/min. (average 1.9 ml./100 ml. tissue/min.), whereas Brigden and Sharpey-Schafer (1950) had shown that intensive systemic vasoconstriction was the rule in left ventricular failure when the forearm blood flow rarely rose above 1.0 ml./100 ml. tissue/min. This led the author to postulate that the infarcted myocardium might lead to the production of vasodilator substances or reflexes which tend to counteract homeostatic vasoconstriction in the periphery.

In 1959 Broch, Humerfelt, Haarstad and Myhre reported measurements of the cardiac output in 35 patients during both the acute stage and following recovery from acute myocardial infarction. The cardiac output was measured using Evans blue dye and a photo-electric ear piece and a modified Coleman oximeter. The patients were given oxygen to breath throughout the study to avoid possible fluctuations of the arterial blood oxygen saturation. It may therefore be argued that the patients were not completely basal

and were in fact receiving oxygen drug therapy. No measurement of the blood pressure was carried out. These authors again found the lowest values for cardiac output and stroke volume were to be found in the most severely ill patients. In agreement with other workers, they also showed a gradual increase in cardiac output values with increasing recovery.

Murphy, Glick, Schreiner and Yu in 1963 reported serial determinations of the cardiac output in both the acute phase and during recovery. The cardiac output was measured by precordial detection of indicator dilution curves following the rapid injection of I^{131} labelled human serum albumin. This is the first study reported in which some but not all measurements of cardiac output were carried out in duplicate. The authors, on the basis of previous experimentation suggested that their method of cardiac output determination would yield results within approximately $\pm$ 10 per cent of the Fick procedure. No patients exhibited the features of cardiogenic shock during the study and no measurements of blood

pressure were undertaken. These workers agreed with Smith et al. (1954) that the cardiac output can often be extremely low even in the absence of shock. Broch et al. (1959) had again raised doubts as to this possibility. Murphy and his co-workers showed that a consistently normal cardiac output or a gradual increase from a low to a normal value was observed only in surviving patients. Serial stroke volume estimations provided equally interesting information. A persistently subnormal stroke volume was seen only in fatal cases and was not necessarily associated with a rapid heart rate. Conversely the nine survivors tended to maintain a normal stroke volume or to show an increase to a normal level if the initial determinations were low.

Malmcrona and Varnauskas (1964) particularly commented on the effects of temperature elevation on the haemodynamic changes in acute myocardial infarction. The cardiac output was measured by a dye dilution technique employing intermittent sampling of the arterial blood. Bromsulphthalein was used as the

indicator and was injected centrally into the subclavian vein. The quoted cardiac outputs for each patient are based on one isolated determination. None of the patients studied exhibited the features of cardiogenic shock. During the first few days after myocardial infarction the cardiac output and arterial pressure were shown to decrease. In patients with significant pyrexia there was a fall in peripheral resistance but not in output, similarly leading to lower arterial pressures. After recovery and before discharge from hospital these haemodynamic parameters had returned to normal levels. These authors therefore rightly stressed the importance of the temperature in the regulation of the peripheral resistance in these patients and considered this to be haemodynamically important in the course of the disease.

STUDIES IN DOGS

Since Orias in 1932 first ligated the anterior descending branch of the left coronary artery and noted the effects on the circulation by means of

strategically placed sensitive manometers, many other workers have likewise studied the haemodynamic changes following this procedure in an attempt to evaluate the circulatory changes in acute coronary occlusion, (Gross et al., 1937; Manning et al., 1939; Wegria et al., 1954, and many others). Taylor, Davis, Vawter and Hass, when reviewing the literature in 1951 pointed out that the production of myocardial destruction by chemical, traumatic, hyperthermic or hypothermic methods did not result in protracted arterial hypotension. None of these methods in fact produced a state of profound hypotension analogous to cardiogenic shock. Indeed the profound circulatory changes resulting from the obligatory anaesthesia and thoracotomy make an evaluation of the effects due to the induced myocardial infarction per se virtually impossible. It must surely be apparent that an open chest approach in the dog does not provide a satisfactory method for the study of acute coronary occlusion as it occurs in man.

Occlusion of the coronary arteries by the introduction of emboli (lycopodium spores) was first

attempted in 1926 by Hamburger, Priest and Bettman. In 1952 Agress et al. reported the application of this method to the production of protracted arterial hypotension in the closed chest dog. The development of this technique, therefore, for the first time provided the laboratory worker with the capability of reproducing in the dog a situation closely resembling that occurring in human cardiogenic shock. The method developed by these workers produced myocardial injury by the injection of plastic microspheres into the coronary arteries through a special aortic catheter. A further study by Agress, Glassner, Binder and Fields, 1957, showed that the same degree of myocardial injury, as judged by the reduction in cardiac output and also subsequent post-mortem examination, was associated with a variable degree of systemic arterial hypotension. In fact, the identical degree of myocardial injury produced no change in blood pressure in nine dogs whereas a further 12 dogs exhibited profound and protracted arterial hypotension. These authors postulated that the failure of the peripheral

vascular resistance to rise in the 'shocked' dogs might be due to a reflex arising from the injured myocardium interfering with normal homeostasis. These workers further showed prior bilateral cervical vagotomy did not prevent the production of the shocked state and that therefore the hypotension could not be explained on the basis of the Jarisch - Bezold reflex as was suggested by Lee (1957) in his human studies when he likewise postulated such a reflex mechanism. Agress and his co-workers therefore suggested that since shock occurs after vagotomy, the afferent pathway from the injured myocardium must be by way of the upper dorsal posterior sympathetic roots. The afferent cardiac sympathetic fibres were therefore blocked in the dog by section of the posterior roots of T_1 - T_5 with a prompt rise in peripheral resistance in the previously hypotensive animal. These workers also reported the application of this method of treatment to three patients, intractable to all other known therapeutic measures. Epidural block of the upper dorsal roots was carried out with a resultant

pressor effect, although ultimate survival occurred in only one patient. These findings although not conclusive, did suggest that cardiogenic shock was not due entirely to the reduction in cardiac output but that an inadequate elevation of the systemic vascular resistance may well be contributing to the hypotension. These animal experimental studies are in line with the haemodynamic observations in human shocked patients.

However, as pointed out by Guzman, Swenson and Mitchell (1962) the embolisation technique as described initially be Agress lacks selective distribution of the embolising particles in the coronary vascular bed, and in fact a considerable "spill over" of the emboli into the systemic circulation occurs. These "spill over" emboli may well reach the medullary cardiovascular centres and raise problems in the final interpretation of the experimental results. Guzman et al. circumvented these difficulties by carrying out selective embolisation of specific coronary vascular beds, and as a result of their dog experiments suggested that the hypotension was caused in fact by a decrease in

cardiac output but that the latter appeared to be out of proportion to the amount of coronary vascular bed selectively blocked. They suggested that either myocardial contractility was inhibited or more likely that some reflex coronary vasoconstriction had occurred.

At the same time Guzman, Swenson and Jones (1962) reported that coronary angiographic studies suggested that embolisation of one branch of a coronary artery does in fact produce at least temporary narrowing of other non-embolised coronary vascular beds. This reflex was prevented to a great extent by the prior injection of atropine, but not by cervical vagotomy. The authors considered this evidence to suggest the existence of a local axone or intercoronary reflex. The haemodynamic changes found by these workers to follow coronary embolisation were, in addition to the immediate and marked decrease in cardiac output, hypotension to a shock level, elevation of the pulmonary arterial and left atrial pressures and a marked increase in systemic vascular resistance.

These haemodynamic changes were likewise partially blocked by prior administration of atropine. West, Kobayashi and Anderson (1962) on the other hand using the same techniques found no evidence to suggest the occurrence of reflex coronary spasm and in fact came to the conclusion that the same type of embolisation caused reflex vasodilatation in the uninjected parts of the coronary circulation. It may at first sight appear strange that similar experiments produce opposite conclusions. Whatever are the reasons (and these were minor variations in technique, such as variation in the size of occluding emboli, differing anaesthetic agents and differing radio-opaque material) it must be remembered that angiography is essentially a morphological technique and great caution must always be exercised in the interpretation of functional conclusions from morphological evidence.

Jacobey, Taylor, Smith, Gorlin and Harken (1962) have recently re-evaluated the technique of coronary arterial embolisation and have further developed this technique to allow the reproducible

creation of coronary occlusion with predictable and varied degrees of myocardial infarction in the closed chest dog. The severity of the occlusion can be adjusted to the purpose of the investigator.

Rushmer et al. (1963) carried out some very elegant studies in ventricular performance in intact unanaesthetised dogs and showed a reduced stroke volume with a reduction in both peak ejection velocity and peak acceleration of blood in the aorta after abrupt coronary artery occlusion. In 1963 Costantin reported his results of coronary arterial ligation in open chested anaesthetised cats and dogs and suggested the existence of a reflex originating in the heart which significantly diminishes the sympathetic activity to both the peripheral circulation and the heart itself in spite of the lowered systemic arterial pressure. These experiments were carried out during anaesthesia, following extensive surgical procedures and were associated with the perfusion of the isolated hind limb by a partial arterial bypass at a constant flow rate. Results were then based on changes in the femoral

arterial perfusion pressure resulting from various experimental manoeuvres. However convincing the evidence for a reflexly induced influence towards vasodilatation in these experiments it would indeed be hazardous to accept the existence of such a reflex in man on the basis of these findings.

The evidence from animal experimentation is therefore in general agreement with the studies in the human patients. Cardiogenic shock is associated with left ventricular failure, a fall in cardiac output and stroke volume with elevation of the left atrial and pulmonary arterial pressures and with variable changes in the systemic vascular resistance.

Methods

ORGANISATION AND BACKGROUND

It may be argued that investigations of this nature should not be performed on patients, often critically ill during the acute stage of their disease. The compelling arguments in favour of such an investigation have already been advanced. The design of the present study was such that the investigative procedures were carried out simultaneously with, without hindrance to, and in support of the routine clinical care and treatment. The technical procedures were carried out without discomfort to the patient and were, at no time, associated with any resulting clinical complication. The precision and ease with which continuous measurement of the blood pressure and cardiac output could be undertaken without disturbance to the patient and without the need of their co-operation has not only proved to be a useful aid in their clinical assessment and management but has further added a considerable safety factor in the

care of such patients. The undoubted value of "intensive care units" in the management of acute myocardial infarction has recently been established (Brown et al., 1963; Robinson et al., 1964; and Julian et al., 1964). The patients, in the present study were subjected to similar intensive care and observation. However, in these selected patients, the circulatory status as well as the electrocardiogram was monitored continuously during the period of study. There were obvious difficulties to be overcome in the establishment, organisation and running of such an acute investigation. A method of study had to be designed which would reveal the maximum amount of information with the minimum of inconvenience to the patient and which would neither delay nor interfere with routine clinical care. These demands were met and the inherent difficulties overcome in the following way -

I. <u>The Organisation of a Team</u>

It will be readily appreciated that such a study requires the work of a team. A team was

therefore organised and consisted of two doctors, including the author, one nurse and three technicians. The duties of these three technicians were pr e dominantly 1. cardiological 2. biochemical, and 3. stenography etc.

During the agreed hours of a "stand-by" arrangement, this team was immediately available, thus ensuring immediate attention to the patient on arrival in hospital. This team of workers had all acquired prior training in a routine cardiopulmonary investigative laboratory.

II. <u>The Availability of an "intensive care" ward</u>

The Board of Management of the Royal Infirmary of Edinburgh kindly agreed to the use of a side ward attached to the male professorial medical ward as an intensive care and investigative area. The possible use of this room for such a purpose had been anticipated during major ward reconstruction in the preceding year. This area had therefore been fitted with additional electrical

output points, had adequate facilities for "washing-up" and had a direct piped supply of oxygen. This two-bedded side ward was consequently removed from the routine bed establishment and remained available at all hours, for the purpose of this study. The exclusive use of this room allowed not only the permanent siting of all the necessary monitoring apparatus but also the immediate availability of a bed for any patient admitted to the study. This room was "set up" each day to allow the direct monitoring of any patient with the minimum of delay following his admission to the resuscitation ward. This "setting up" was carried out under sterile conditions and involved -

(1) the provision of a trolley containing the necessary sterile surgical gowns, squares and instruments for the insertion of both an arterial and a venous catheter.

(2) the assembly of the system of taps, manometers and the cuvette oximeter

required for the measurement of blood pressure and flow. This combined system was of course assembled under sterile conditions and all parts were then filled with a heparinised saline solution and the two remaining "open ends" were occluded by sterile plastic or stainless steel caps. This prior sterile assembly of the monitoring apparatus ensured its being immediately ready for use at all times. Measurements could be carried out as soon as the arterial and venous catheters from the patient were connected to the two "open ends" of the system (see figure 3).

(3) the assembly of the dye injection syringe and manually operated injector pump. Each day the syringe and its related nylon connecting lines were filled with a dye solvent solution which could then rapidly be discarded and replaced by the prepared solution of dye in solvent

when an investigation commenced. The initial priming of the system with solvent had the advantage of maintaining sterility and allowing initial testing of the system each day to check on possible leaks at the various connections.

Figure 1 shows a general view of the resuscitation ward and the recording apparatus which included -

(i) a multichannel ultra-violet light recorder (New Electronic Products Ltd. Type 1185) for the measurement of arterial and venous pressures, cardiac output and the electrocardiogram,

(ii) one dye cuvette densitometer control unit,

(iii) one four-channel oscilloscope for display of arterial and venous pressures, electrocardiogram and cardiac output, and

(iv) one mobile trolley designed for the purposes of this study to ensure the facility of bedside application of modern cardiovascular techniques.

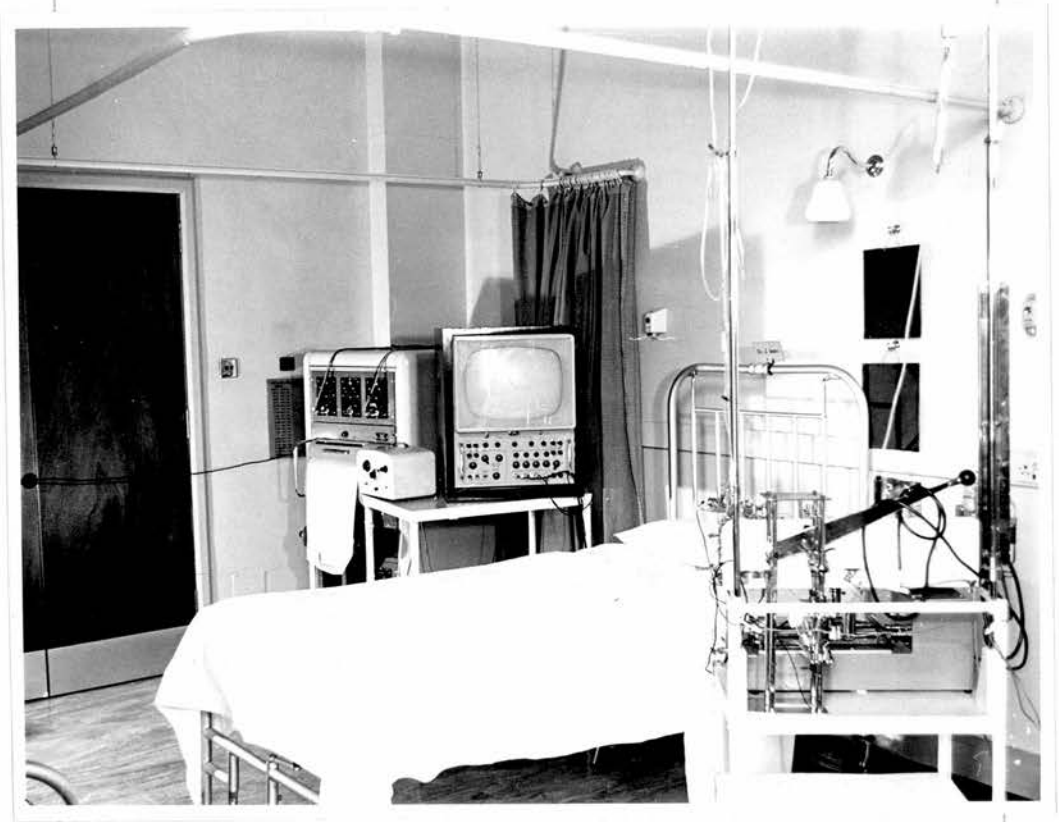


Fig. 1

General view of the resuscitative ward area

This picture shows the ultra-violet light recorder, the dye cuvette densitometer control unit, the four channel oscilloscope and the specially constructed mobile trolley.

The room for the purposes of this study, was converted into a one-bedded area. The removal of the second bed allowed ample room for movement of personnel in addition to accommodating the monitoring apparatus.

III. The Bed-side Application of Modern Cardiovascular Techniques

Two pieces of apparatus were designed in the work-shop of the Department of Medicine, the Royal Infirmary of Edinburgh, to facilitate the study and treatment of these patients.

A. A mobile trolley was designed as shown in Figs. 2 and 3. This design allowed the mounting of all equipment necessary to the measurement of blood flow and pressure in one mobile unit which could then be operated by one individual and could be approximated to the patient's bedside with ease. The electrical output from the manometers and cuvette oximeter were then led from this trolley to the amplifiers in the recording unit and to the oscilloscope.

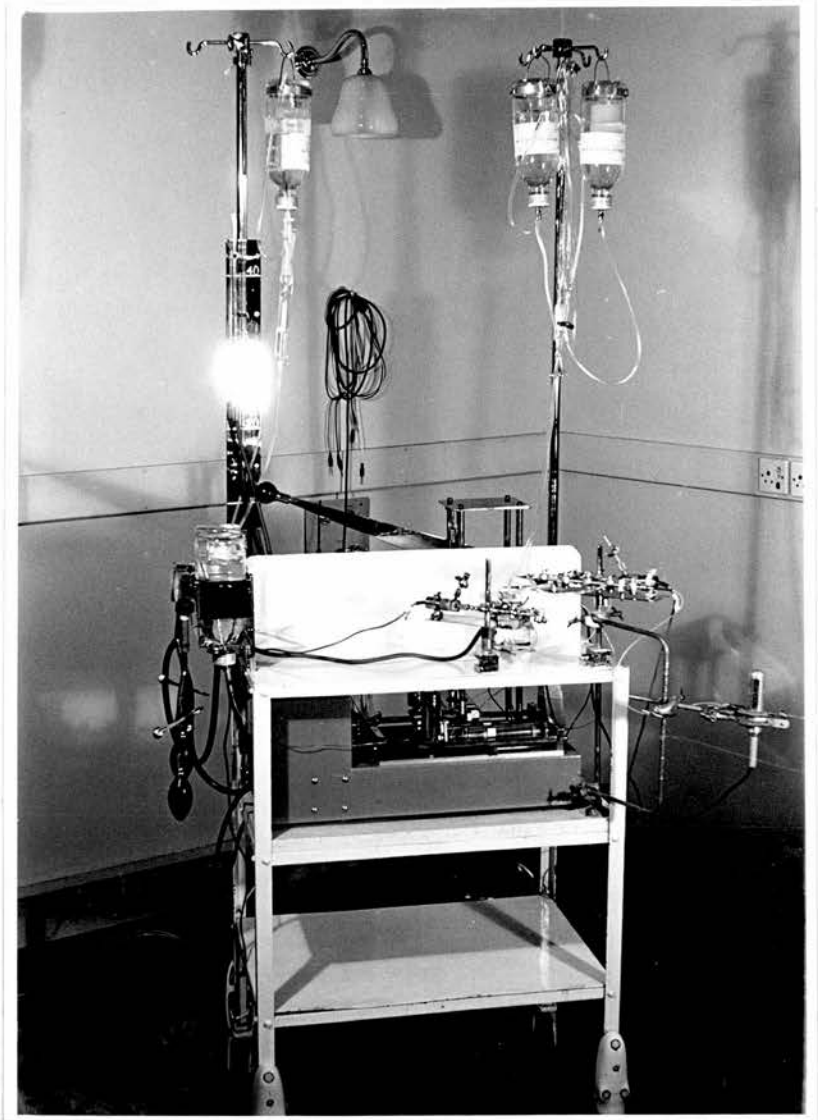


Fig. 2

The mobile trolley

This picture shows - the dye cuvette; two plates on which are mounted the arterial and venous pressure transducers and the associated taps; pressurised saline bottles for arterial calibration; open saline column for venous calibration; three heparinised saline drips to allow free flushing of arterial and venous tap and catheter systems; Harvard infusion/ withdrawal pump; the handle of the manually-operated dye injector pump can be seen at the back of the trolley.

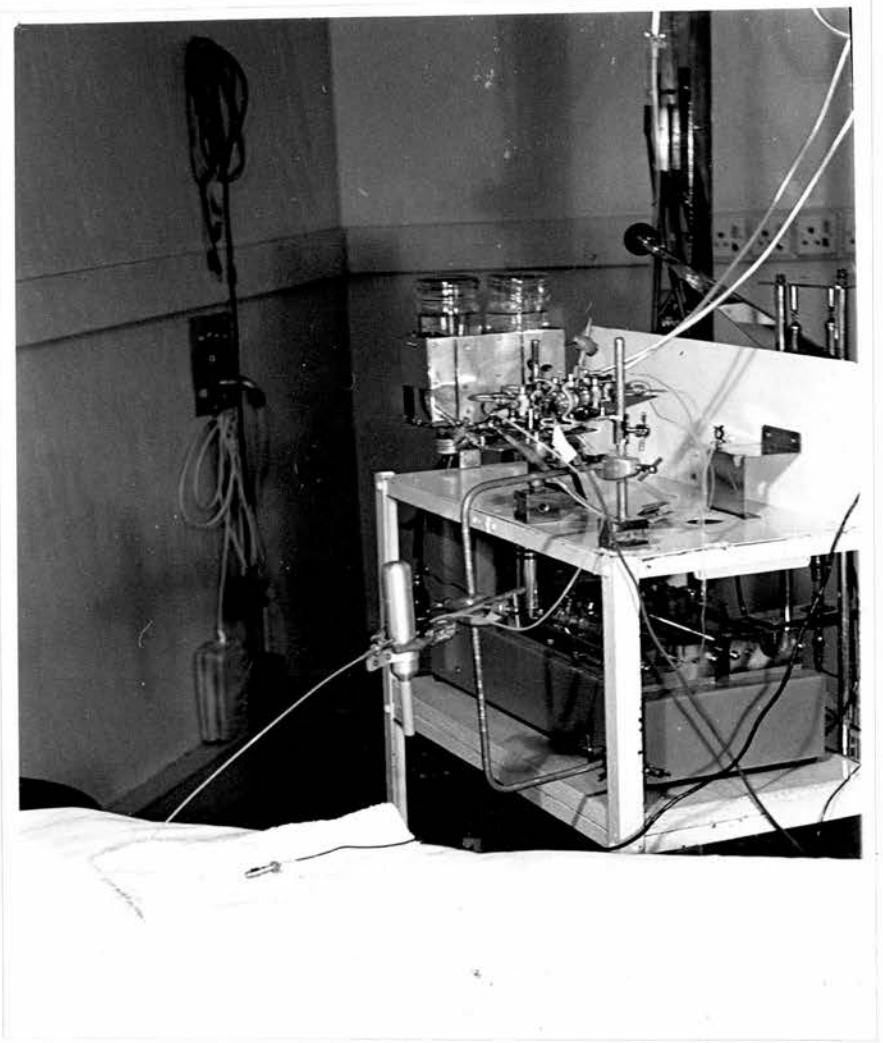


Fig. 3

Close-up view of the trolley "merely awaiting connection to the patient". An arterial catheter has been attached to the dye cuvette and the remaining connection - i.e. the catheter from the dye injection syringe - is shown.

The overall design of the trolley is shown in fig. 2. A "close-up" view of the trolley at the bedside is shown in fig. 3 in which the two connecting lines to the patient are shown. The dye injection nylon line is connected to one lumen of a cardiac catheter and a second nylon line connects one further lumen of this catheter to the venous transducer. The arterial catheter from the patient's brachial artery is then connected to the cuvette oximeter as shown. This cuvette is attached to a bracket which allows considerable freedom of movement in the siting of the actual cuvette. The latter can in fact, in a restless patient, be strapped to the forearm. A nylon catheter leads from this cuvette through a system of taps which allows either the direct suction of arterial blood into the syringe withdrawal pump for the estimation of cardiac output or alternatively, by re-arrangement of the taps, allows the

monitoring of systemic arterial pressure. The arterial and venous calibration systems are also mounted on this trolley, as are the necessary drips, containing heparinised saline (1,000 I.U. per 600 ml. fluid) for the prevention of clotting and maintaining the patency of both the arterial and venous catheter systems.

B. A second piece of apparatus was designed to ensure the administration of oxygen to a patient is as high an inspired concentration as possible (the aim was to achieve virtually 100% oxygen administration). It was realised that this was best done by the "high flow" principle and the apparatus was designed accordingly and is shown in fig. 4. By the use of two large rotameters a vacuum cleaner and a piped oxygen supply, fairly accurate predetermined mixtures of air and oxygen can be delivered. The delivery of as high a concentration of pure

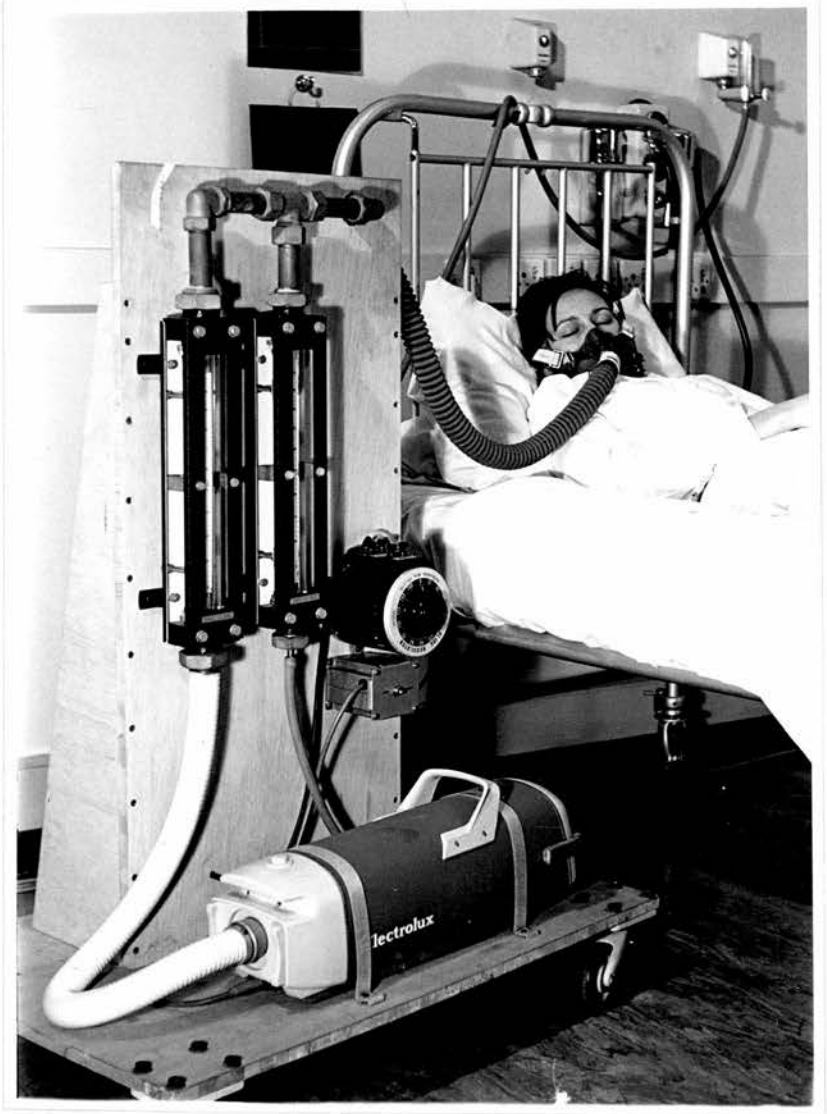


Fig. 4

The apparatus and method of administering "high" oxygen is shown. The oxygen was taken from a direct piped supply and was "blown" at the patient at a flow rate of 50 litres per minute using the face mask as shown. The inspired gas was also passed through a humidifier which is mounted at the back of the illustrated apparatus.

oxygen as possible was achieved by blowing pure oxygen through this apparatus at 50 litres per minute and administering it to the patient through a close-fitting airman's face mask with the outlet valves removed as shown in fig. 4. This gas mixture was also passed through a humidifier before inhalation by the patient. Direct sampling from the mask showed that the inspired oxygen concentration was between 82 and 96% (mean value 87%) in the patients to whom it was administered in this way. Air or various other gas mixtures could of course be delivered at the same high flow rate by this apparatus.

LABORATORY TECHNIQUES

Systemic arterial pressure was taken through a small bore nylon catheter, (O.D. o.80 mm., length 55 cm.), introduced percutaneously into the brachial artery by a modified Seldinger technique and advanced into the aortic root. Pressures were transduced by a Statham

P23Db strain gauge manometer. The catheter-manometer system was critically damped to give a virtually flat frequency response to 20 cycles per second. The square wave response of the system was 95 per cent within 0.03 seconds, with less than 5 per cent overshoot. The electrical output from the manometer was arranged to allow synchronous recording of both pulsatile and mean aortic pressures. The systemic arterial calibration was arranged to extend approximately 10 mm.Hg on either side of the aortic pulse pressure to allow maximum recording precision with the least electro-mechanical distortion. The saline-filled calibration pressure heads for the system were maintained by specially calibrated Reckla anaeroid manometers.

Right atrial or central venous pressure was either taken through one lumen of a triple lumen cardiac catheter (No. 9) as used in the acute studies or through the small bore nylon catheter (O.D. 0.80 mm., length 55 cm.) introduced percutaneously into an antecubital vein and subsequently advanced into the region of the right atrium, as used in subsequent follow-up studies.

Phasic and mean pressures were transduced by a Statham P23Db strain gauge manometer and calibrated against an open saline column.

Zero reference level of all manometers was 10 cm. below the level of the manubrium sterni.

Cardiac output was determined by an indicator dilution technique employing indocyanine green. Precisely known amounts of the dye, approximately 2 mg. in 1.5 ml. volume were injected into the region of the right atrium by a rapid action manually operated syringe pump, each injection being completed in 0.3 seconds. In the acute studies this central dye injection was made through the middle lumen of the triple lumen catheter. In the "follow-up" studies, as only one lumen was available, the venous tap assembly was so arranged as to allow the temporary interruption of the ve nous pressure recording for intermittent central dye injection. The dye dilution curves were taken from the aortic root through the arterial catheter (the recording of systemic arterial pressure was temporarily interrupted during the

inscription of the dye curve) at a constant sampling speed by a syringe type withdrawal Harvard pump and transcribed by a Waters X-250 cuvette densitometer. (Vide infra).

The electrocardiogram was recorded continuously .

All analogue tracings were recorded on a multi-channel ultra-violet light recorder (New Electronic Products Ltd., Type 1185) using galvanometers of 35 cm. focal length and a distortion-free deflection of 10 cm. The frequency response of the galvanometers used for recording the intravascular pressure was 90 cycles per second at 95 per cent of true fidelity.

Total circulating blood volume was determined by means of the plasma volume corrected for the haematocrit. The plasma volume was estimated by means of a standardised radio-iodinated albumin technique. 5 to 10 micro curies of radio-iodinated human serum albumin diluted in 20 ml. of freshly constituted human plasma were injected through the venous catheter. Samples of blood were subsequently taken from the aorta at intervals of 5, 10 and 15 minutes and centrifuged. The radio-activity of exactly 2 ml. of the resulting plasma was measured in a well scintillation

counter coupled to an automatic timer over a period of 400 seconds. Duplicate counts were required to check to less than 1 per cent. The standard solution prepared from the original dilution of radio-albumin was corrected for dropped counts. Extrapolation of the three points to zero time was judged to give the circulating plasma volume at this time. The haematocrit was measured by the Hawksley micro-centrifuge method.

Measurement of Arterial Blood Gas Tensions

Arterial blood oxygen tension was measured by means of a Clark polarographic cell (Bishop and Pincock, 1959). The electrode was calibrated with air after every 3 - 4 determinations. Nitrogen gas produced a zero current. Prior experimentation had revealed that the recordings on this electrode with blood tonometered with air was 0.95 times the reading obtained with air alone. This correction factor of x 0.95 was therefore applied to all readings. Each measurement was carried out in duplicate and had to agree to within 2 mm.Hg.

Arterial blood carbon dioxide tension was measured by means of a Severinghaus electrode, (1958). This electrode was calibrated with two standard carbon dioxide mixtures prior to each study and when practical was also repeated at the end of the study. The carbon dioxide tension was thereby obtained to the nearest 1 mm.Hg.

Arterial blood pH was measured by means of a capillary electrode system (Electronic Instruments Ltd.). The glass electrode was calibrated before each blood sample with a 7.416 phosphate buffer and in turn this buffer was daily calibrated against Radiometer Co. precision buffers. The pH was expressed to the nearest 0.01 pH units, as the precision buffers are only accurate to $\pm$ 0.005 units. Duplicate readings on blood were within 0.004 pH units.

All measurements of arterial blood gas tensions were carried out immediately. The temperature of the water bath surrounding these electrodes was maintained at 38°C.

Measurement of arterial blood lactate, pyruvate and glucose levels

All three measurements were made from one 6 ml.

blood sample. The arterial blood was sampled from the patient into a cold heparinised syringe. The blood was immediately transferred into a chilled plain tube and from this 4 ml. was pipetted, using a chilled pipette, into a test tube containing 4 ml. 5% perchloric acid. The tube was then stoppered and shaken vigorously. At some convenient time this perchloric-blood mixture was centrifuged and the resulting supernatant was separated into another tube to be centrifuged once again. This supernatant fluid could then be refrigerated for analysis at leisure. The fluid could then be used for the analysis of the lactate and pyruvate levels by the respective Boehringer methods (1962).

Analysis of blood lactate (Boehringer Method)

The blood had been deproteinised by the perchloric acid and the protein-free supernatant after centrifugation was now buffered with Glycine buffer (pH 9.0). On the addition of lactic dehydrogenase and Diphosphopyridine Nucleotide (DPN +), the following reaction takes place -

$$\text{Lactate} + \text{DPN}^{+} \rightleftharpoons \text{pyruvate} + \text{DPN-H} + \text{H}^{+}$$

The reduced diphosphopyridine nucleotide, (DPN - H), thus formed is measured in an ultra-violet spectrophotometer at 340 mμ. The normal range of values by this method was found to be 0.48 - 1.74 m.M./l.

Analysis of blood pyruvate (Boehringer Method)

The supernatant fluid is treated with potassium phosphate, forming a preciptitate of potassium perchlorate leaving an almost neutral supernatant. By adding DPN - H and lactic dehydrogenase, the equation as quoted above is reversed and the resulting conversion of DPN - H is again measured in an ultra-violet light spectrophotometer. The normal range of values by this method was found to be 0.055 - 0.085 m.M./l.

Analysis of blood glucose (Huggett and Nixon, 1957)

The glucose in the protein-free filtrate of blood is oxidised by the addition of glucose oxidase. The resulting hydrogen peroxide, in the presence of peroxidase oxidises the colourless O - Dianisidine to a reddish brown dye. The intensity of this colour is proportional to the glucose concentration and is again

measured in the spectrophotometer. The normal range of values by this method was found to be 60 - 97 mg./100 ml.

Measurement of Serum Electrolytes

All the undermentioned measurements were made on a 10 ml. sample of arterial blood, withdrawn into a dry syringe and allowed to clot. The sample was then centrifuged, the serum separated and the following estimations carried out -

Serum phosphate 1 ml. of serum was used for the estimation carried out by Ammonium Molybdate method of Gomorri (1942). (Normal range 1.5 to 2.45 m.eq./l.)

Serum potassium 1 ml. of serum was diluted to 50 ml. with distilled water for estimation by the Flame Photometer. (Normal range 3.6 to 5.1 m.eq./l.)

Serum sodium A further dilution of the above solution (to 1 - 500) was made for the estimation by the Flame Photometer. (Normal range 132 to 148 m.eq./l.)

Serum chloride The method used was an ultramicro adaptation of the mercuric nitrate method of Schales and Schales (1941) using the Beckman Spinco Microtitrator; 10 microlitres of serum were used in the estimation. (Normal range 95 to 106 m.eq./l.)

TECHNIQUE OF CARDIAC OUTPUT DETERMINATION

The dye dilution method of cardiac output estimation as used in the present study was developed in the Department of Medicine, the University of Edinburgh, during the previous two years and as part of a separate study was subjected to critical analysis and comparison with the standardised Fick method of cardiac output determination (Taylor, Kennelly, Mackenzie, Sutherland, Hutchison, Staunton and Donald 1965). Indeed the once popular Fick method is being increasingly superseded by the less cumbersome indicator dilution method in most cardiovascular laboratories and this transition has been greatly

accelerated by the development of the more accurate and reliable continuously recording photoelectric densitometers.

1. Methods used in the Dye Dilution Technique

The essential feature of the method used in the present study was the acute rapid injection of a small accurately known volume of indocyanine green dye into the great veins or right atrium in association with constant speed high velocity arterial blood sampling through a continuously recording cuvette densitometer linked to an ultra-violet light recorder.

A. Method of dye injection

Small precisely known amounts of dye (approximately 2.0 mg. dissolved in 1.5 ml. of solvent solution) were injected by a rapid action manually operated pump closing the plunger of a metal supported glass syringe, which was automatically reloaded on release

of pressure from a central dye reservoir. Each injection from this syringe pump was completed in 0.3 second. The stroke of the pump was arranged to activate an electronic time marker on the recorded dye base-line, the time of injection being thus precisely marked as a square wave. The metal support of the syringe allowed the setting of a fixed syringe stroke volume and thus ensured constancy of the volume of injectate. The actual injectate volume was determined after each study by injecting separate boluses of dye in four accurately weighed flasks and re-weighing. The injection volume varied between 1.055 and 1.569 in different studies (average 1.450 ml.) but in any one study the difference between the weighed separate injections was always less than 0.01 ml. The average amount of dye contained in the injectate was 2.024 mg. varying between

1.548 and 2.986 mg. The actual concentration of dye can be easily calculated by a series of weighing experiments. Initially the bottle containing dye (as marketed) is weighed; Solvent is added and the flask reweighed; finally the bottle itself is re-weighed after removal of the contents to a central dye reservoir. By a simple process of subtraction the actual weight and concentration of dye can be derived. Although the absolute amount of dye injected was determined in each of the present studies, the method of calibration is independent of a knowledge of the actual amount of dye injected (vide infra). The injection was performed by volume displacement in a dye-filled catheter. The injector system incorporated a series of one-way valves so that operation of the manual plunger opened the syringe to the catheter. Completion of the syringe stroke likewise synchronously closed this valve and opened the syringe to the central

dye reservoir which lead to reloading of the syringe. This system allows the catheter to be continuously full of dye. The dye injected was withdrawn from a light screened central reservoir containing sufficient dye for the whole study and calibration.

B. Method of Arterial Blood Sampling

As the spectral transmission of whole blood passing through a cuvette varies with the rate of flow, it is obviously essential to keep the blood flow through the cuvette completely constant, not only during the transcription of a single dye curve but also between different dye curves and during calibration of the instrument. These considerations lead to the use of a constant rate infusion-withdrawal pump employing a 1500 r.p.m. motor (Harvard Apparatus Co. Inc.) and using 50 ml. Luer-Lock syringes. This pump allowed not only

the use of absolutely constant rates but also provided the choice of a wide range of individual flow rates.

The design of an adequate arterial blood sampling system was further complicated by a number of practical and technical factors. The high linear velocity attained in the catheter-cuvette system (of the order of 150 cm./sec.) by the usual rate of sampling required was necessarily associated with the production of high negative pressures in the system. The majority of tap connector assemblies initially used were found to admit air. This resulted not only in a fluctuation of the withdrawal rate due to expansion of the air bubbles but also precluded an essential design requirement that all blood withdrawn should be immediately re-infused into the patient. The incorporation of an adequate "flushing" system to prevent blood clotting was also an essential requirement. The

final requirement was that the system should also be capable of transmitting arterial pressure wave forms with minimal distortion. These stringent requirements were finally met by a system which is illustrated in Fig. 5. The entire tap system was precision machined as one assembly, (Ole Dich, Denmark). After transcription of a dye curve, the blood was returned immediately to the patient, by reversing the pump. The catheter-cuvette system and the pump were then immediately flushed with heparinised saline solution from the drip bottles. The systemic arterial pressure was then monitored through the same tap system until the next dye curve was due to be carried out.

C. Method of dye curve transcription

The dye curves were transduced by a Waters X-250 cuvette densitometer

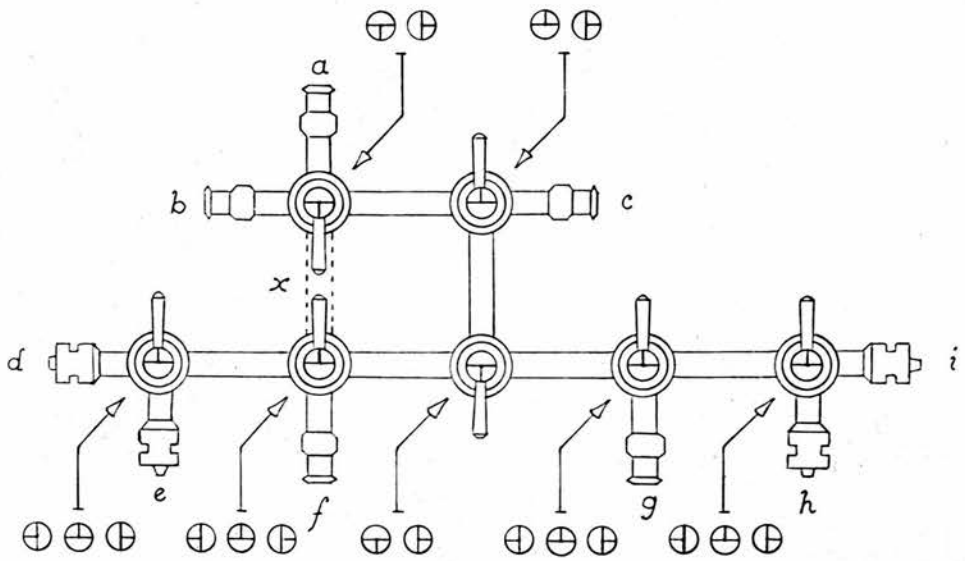


Fig. 5

The combined arterial tap assembly

a. systolic pressure calibration standard

b. diastolic pressure calibration standard

c. pressure transducer

d. syringe pump

e. spare syringe or waste

f. fast drip

g. slow drip

h. arterial blood sampling

i. dye cuvette

x mechanical strut only

in conjunction with an ultra-violet light recorder and display oscilloscope. The Waters X-250 cuvette consists of a single cadmium selenide photocell with a single filter which has its maximum sensitivity at 800 mμ, the wavelength of indocyanine green dye. The dye curve was written by an ultra-violet light recorder. An automatic time marker, operating a rotating mirror in the path of the ultra-violet light beam, inscribed vertical lines on the paper trace at pre-arranged intervals of 0.1, 0.25, 0.5, 1.0 or 2.5 secs. as required. A representative dye curve is shown in fig. 6.

D. Linearity of the system

For the normal routine manual method of dye curve mensuration, it is essential that the relationship between the dye concentration in the blood and the deflection of the writing galvanometer should be

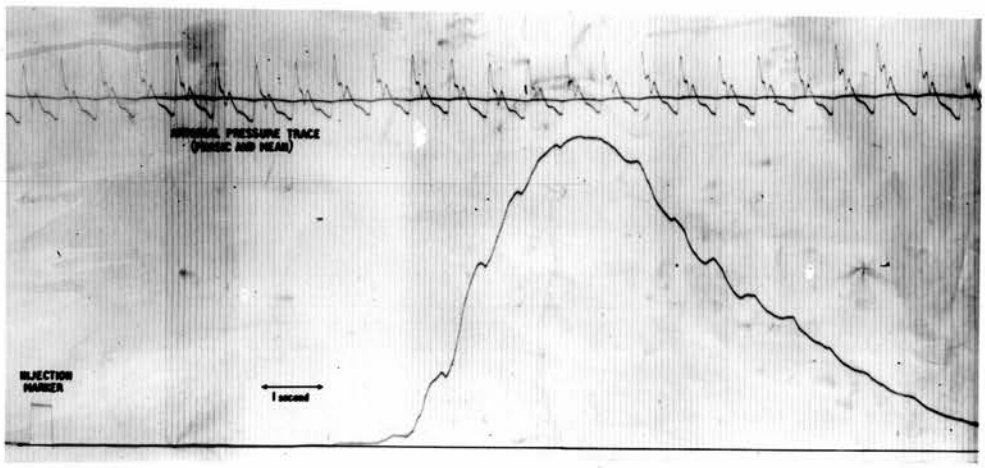


Fig. 6

A typical dye curve

This figure also shows the simultaneous recording of both phasic and mean systemic arterial pressure.

absolutely linear, if accurate measurements are to be made. The response of the system described was absolutely linear in the ranges of dye concentration employed in the present studies.

E. Method of calibration

The dye cuvette densitometer assembly was calibrated by a whole blood technique. Before the start of the study, 85 ml. of blood were removed from the patient with dry syringes and run into a siliconed flask (containing 1 ml. of 25,000 units/ml. heparin), with constant agitation and rotation to assist mixing and prevent clotting. The flask was then stored at body temperature and the calibration carried out at the end of the study. The actual method used was as follows -

1 ml. of dye from the central reservoir of dye, as used in the study, was accurately pipetted into a 25 ml. flask which was then made up with "undyed"

whole blood. This flask was rotated to ensure complete mixing of dye and blood and from this "base" flask samples of 1 ml. and 2 ml. were then pipetted into two additional 25 ml. flasks. These latter two flasks were then made up again to their full volume from the stored undyed blood. The remaining 10 ml. of blood were used for base-line control. The blood from these flasks was then withdrawn through the cuvette at the same suction rate as that obtaining during the study, in an ascending order of concentration. A typical calibration trace is shown in Fig. 7. The average value of the two steps was taken as the calibration factor. This calibration method as described was used for the initial acute study on day 1 of the illness. When a subsequent follow up study was carried out on the same patient, either again during the same day or during

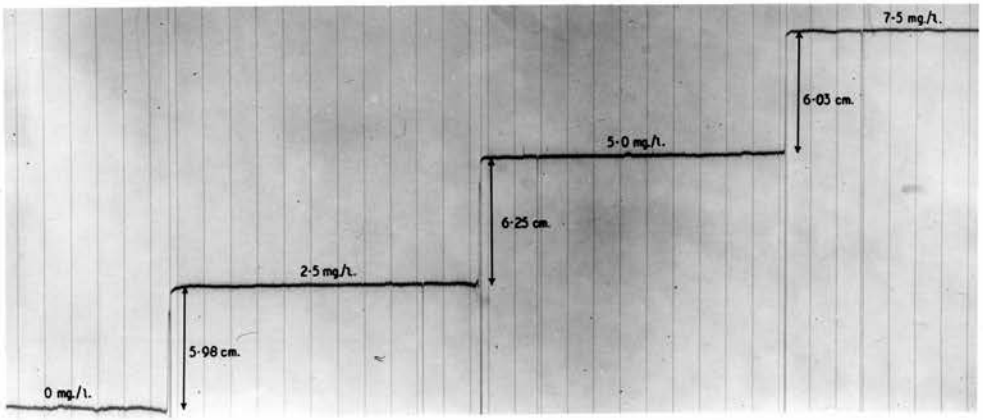


Fig. 7

A typical calibration tracing.

day 2, the calibration factor as measured in the initial study was again used. This procedure was adopted in an attempt to reduce the amount of blood letting and provided the identical measuring apparatus from cuvette to galvanometer was used, would appear to be valid. During subsequent follow up studies 110 ml. of blood were removed prior to the onset of the study for calibration purposes. This allowed the preparation of three flasks with increasing concentration of dye and permitted the calibration factor to be derived from three instead of two steps.

F. Method of dye curve measurement

Prior to each injection of indocyanine green dye into the patient, "undyed" whole blood was routinely withdrawn through the cuvette to establish a base line. This was followed by the time marker of injection and finally the transcription of

the arterial dye curve. The initial step in measurement was the drawing in and extension of this base-line under the dye curve; unusually pulsatile curves were meaned freehand. Readings of the height of the dye curve to the nearest tenth of a millimetre were taken at half-second intervals with a set square laid along the base-line of the dye curve. The presence of vertical time marker lines on the trace at intervals of 0.5 sec. greatly facilitated this process. Values were replotted on semi-logarithmic paper. Recirculation was excluded by extrapolation of the downslope to zero by eye-fitting, the minimum number of points being 5 and usually greater. Readings taken from the replotted curve to the lowest reading of 1 mm. on the extrapolated portion were then summed.

The cardiac output in litres per minute was then calculated from the formula -

$$\text{Cardiac output l./min.} = \frac{60 \times I}{\frac{\leq c}{2} \times F}$$

where I = injectate in ml.

$\frac{\leq c}{2}$ = Sum of the heights of the dye curve at half second intervals in cms.

F = Calibration factor in ml./cm.

or alternatively,

$$\text{Cardiac Index l./min./sq.m.} = \frac{\text{Cardiac output l./min.}}{\text{Surface area sq.m.}}$$

The appearance time was measured from the mid-point of the square wave recording dye injection, to the initial upstroke of the dye curve from the base-line. The appearance time was corrected for a time delay of 0.8 second in the catheter cuvette sampling system.

The mean transit time was calculated using the standard formula -

$$\text{M.T.T. secs.} = \frac{C_1 t_1 + C_2 t_2 + \quad + C_n t_n \text{(mg.sec.)}}{C_1 + C_2 \quad + \quad + C_n \text{ (mg.)}} + \text{A.T. secs.}$$

The mean transit was corrected for a time delay of 0.8 second in the catheter cuvette sampling system.

Cardiopulmonary blood volume

This represents an estimation of the blood contained between the site of injection (great veins or right atrium) and the sampling site (aortic root)

$$\text{C.B.V. (ml.)} = \text{CO ml./sec.} \times \text{M.T.T. sec.}$$

or alternatively,

$$\text{C.B.V. ml./sq.m.} = \text{C. Index ml./sec./sq.m.} \times \text{M.T.T. sec.}$$

2. Validity of Dye Dilution Technique

As already stated the estimation of cardiac output by the technique described has been subjected to extensive analysis and comparison with the standardised Fick procedure, as a distinct and separate study to the work of this thesis (Taylor et al., 1965).

A. Clinical details of the patients studied in this Dye Fick comparison

Serial and repeated observations were made on 40 patients. The groups studied were chosen in anticipation that their resting and exercising cardiac output range would

cover all but the most extreme values encountered in clinical and physiological practice. In addition the groups of patients were chosen so that the effect of some commonly encountered pathophysiological states on the validity of the dye method could be accurately assessed. For this purpose, hypertensive patients with left ventricular dilatation were chosen to exemplify the effect of volume increase without valvular disease. Patients with atrial fibrillation due to ischaemic heart disease were chosen for their isolated rhythm abnormality. Patients with mitral and aortic valvular disease were chosen to exemplify the effects of these commonly found lesions on the validity of the dye method. Patients with myxoedema and anaemia were chosen for their low and high resting cardiac outputs in the absence of valvular heart disease.

B. Plan of investigation

Repeated standardised 4-minute Fick estimations of cardiac output were carried out in each patient after central cardiac catheterisation. The initial estimation was carried out at rest and then during moderate and finally during heavy exercise. The measurement during the exercising period was confined to the final two minutes of a six minute period. Thereafter the patient was allowed to recover for the next 30 minutes following which a minimum of seven Fick estimations of cardiac output were undertaken.

Dye dilution curves were recorded at one minute intervals during each period, allowing five individual determinations of cardiac output in each Fick period. The duration of the dye curve was prolonged in some cases necessitating an alteration in protocol in that the cardiac output could only be determined during alternate minutes,

allowing three individual determinations of cardiac output in each Fick period.

C. Results and validity of the method

The mean value of cardiac output as measured by the dye dilution method in each period has been compared with the Fick determination. The following conclusions have emerged from this study. The dye dilution technique operates over the entire range of cardiac outputs, from normal to abnormal - viz. from 2.5 to 25 l./min. Within this range and in the absence of regurgitant mitral valve disease nearly all dye values fall within 10% of the median line with a correlation coefficient of 0.993 as shown in Fig. 8. 70% of all values, in fact, were within 5% of the median line. There is no systematic error.

However in the presence of gross mitral regurgitation there does appear to be a systematic deviation such that the dye

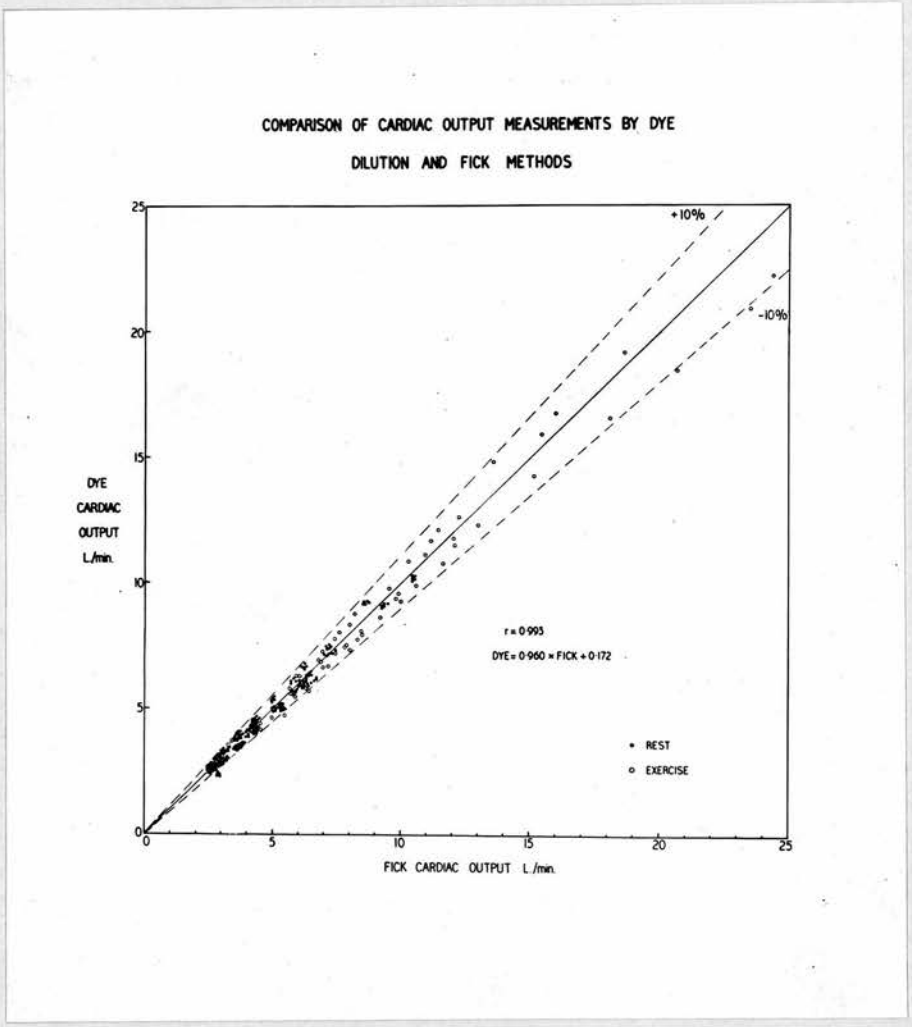

COMPARISON OF CARDIAC OUTPUT MEASUREMENTS BY DYE
DILUTION AND FICK METHODS
+10%
-10%
DYE
CARDIAC
OUTPUT
L./min.
r = 0·993
DYE = 0·960 × FICK + 0·172
• REST
○ EXERCISE
0
5
10
15
20
25
FICK CARDIAC OUTPUT L./min.

Fig. 8

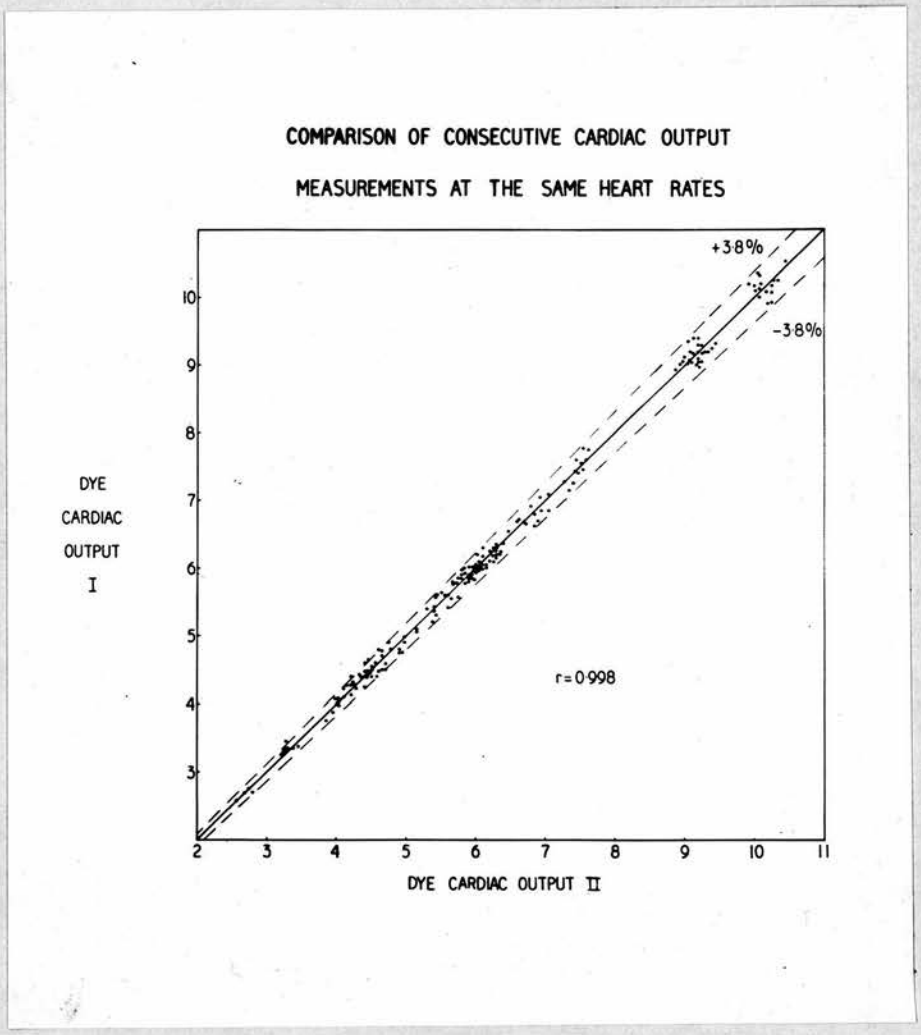

COMPARISON OF CONSECUTIVE CARDIAC OUTPUT
MEASUREMENTS AT THE SAME HEART RATES
+3.8%
-3.8%
r=0.998
DYE
CARDIAC
OUTPUT
I
DYE CARDIAC OUTPUT II
2
3
4
5
6
7
8
9
10
11

Fig. 9

invariably reads lower than the Fick estimation. The reproducibility of the technique is such that duplicate dye curves measured at a constant heart rate showed a maximum difference of 8% while 95% of all observations differed by 7% and 70% of all observations differed, in fact, by less than 4% as shown in Fig. 9.

CLINICAL MATERIAL

The patients represent a selected population. Seventeen patients who had had an acute myocardial infarction were selected for treatment and investigation. Sixteen of these patients had suffered their acute episode of infarction within the preceding 24 hours. One patient (A.C.) was not investigated until the development of cardiogenic shock 36 hours after his initial episode of chest pain. The evidence of myocardial infarction was based on unequivocal electrocardiographic proof of recent transmural myocardial infarction. Serum transaminase, hydroxybutyric dehyrogenase, white cell counts, sedimentation rate and temperature chart as well as the clinical

history, were used as confirmatory evidence. Patients who either had a history or electrocardiographic signs suggestive of previous myocardial infarction were excluded unless they were shocked.

Criteria used to define cardiogenic shock The diagnostic criteria employed in this study were a systolic blood pressure on auscultation of less than 100 mm.Hg in the presence of cold, clammy, sweating and cyanosed extremities with associated clouding of consciousness usually manifested as mental apathy or restlessness. Six patients fulfilled this criteria.

Nine patients had had an acute myocardial infarction uncomplicated by either shock or manifest left ventricular failure. Two patients had manifest left ventricular failure but without evidence of shock. The clinical details of each patient are summarised in table 2 and more detailed information relating to each patient is given in the appendix.

The patients were admitted direct to the intensive care resuscitation room in the ward area, in which the apparatus essential for their continuous

TABLE 2 - CLINICAL DETAILS AT TIME OF ACUTE STUDY - DAY 1

SUBJECT SEX AGE yr.	HT. m. WT. kg. S.A. sq.m.	APPROXIMATE TIME AFTER FIRST SYMPTOMS Hours	APPROX. DURATION OF SHOCK Hours	J.V.P.	LUNGS CREPS.	TRIPLE RHYTHM	TREATMENT BEFORE STUDY	E.C.G.	OUTCOME
				CARDIOGENIC SHOCK					
A.S. F 74	1.57 56.0 1.55	6	6	+	+	+	Morphine 15mg. IM. 5 hours before	Posterior myocardial infarction	Recovery from shock Died on day 4 P.M. confirmed infarction
A.F. F 58	1.57 70.5 1.71	5	5	0	0	+	Morphine 15mg. IM. 30 min. before	Antero-septal myocardial infarction	No recovery from shock Died on day 2 P.M. not obtained
J.F. M 75	1.77 80.0 1.96	6	6	0	0	+	Nil	Antero-septal myocardial infarction	No recovery from shock Died 4 hours after admission P.M. confirmed infarction
A.C. M 52	1.70 56.0 1.63	36	4	0	0	+	Morphine 10mg. IM. 8 hours before	Anterior myocardial infarction	Recovery from shock Died suddenly on day 12 P.M. not obtained
M.R. F 68	1.55 60.0 1.57	6	6	0	0	+	Morphine 15mg. IM. 4 hours before	Antero-septal myocardial infarction	No recovery from shock Died 12 hours after admission P.M. confirmed infarction
W.M. M 52	1.73 84.0 1.97	12	1	0	0	+	Morphine 15mg. IM. 30 minutes before	Anterior myocardial infarction	No recovery from shock Died 2 hours after admission P.M. confirmed infarction
				WITHOUT SHOCK					
M.L. F 49	1.58 63.6 1.64	18	-	+	+	-	Nil	Anterior myocardial infarction	Recovered Had associated chronic obstructive airways disease
G.B. F 72	1.52 58.5 1.54	12	-	+	+	-	Morphine 15mg. IM. 7 hours before	Anterior myocardial infarction	Recovered but delayed intractable congestive cardiac failure
B.G. F 54	1.61 79.0 1.83	12	-	0	0	-	Nil	Posterior myocardial infarction	Recovered
A.S. F 74	1.52 44.5 1.37	4	-	+	+	-	Nil	Posterior myocardial infarction	Recovered
I.H. F 61	1.60 44.5 1.37	12	-	0	0	+	Morphine 15mg. IM. 2 hours before	Anterior myocardial infarction	Recovered
L.L. M 64	1.71 65.0 1.75	6	-	+	0	-	Morphine 15mg. IM. 5 hours before	Posterior myocardial infarction	Recovered
V.H. F 68	1.55 54.0 1.50	18	-	0	0	+	Morphine 15mg. IM. 3 hours before	Antero-septal myocardial infarction	Died suddenly on day 4 P.M. confirmed old and recent myocardial infarction
J.M. M 51	1.71 54.5 1.62	20	-	0	0	-	Pethidine 100mg. IM. 2 hours before	Anterior myocardial infarction	Recovered
G.D. M 64	1.74 54.5 1.62	4	-	+	0	-	Morphine 15mg. IM. 4 hours before	Posterior myocardial infarction	Recovered Had associated chronic obstructive airways disease
				ACUTE LEFT VENTRICULAR FAILURE WITHOUT SHOCK					
I.S. F 59	1.55 80.5 1.79	14	-	+	+	+	Nil	Anterior myocardial infarction	Died suddenly on day 4
V.B. F 58	1.56 51.0 1.48	12	-	+	+	+	Nil	Anterior myocardial infarction	Recovered

monitoring was already assembled, sterile and merely awaiting "connection" to the patient.

DESIGN OF INVESTIGATION

The aim of the investigation was to carry out detailed and serial circulatory, respiratory and metabolic measurements on the day of onset of acute myocardial infarction (Day 1) and to evaluate contemporary therapy by assessing the changes which are thereby induced by such treatment. When possible follow-up studies were similarly undertaken on day 2 of the illness and subsequently at variable times during the recovery period of one month.

Acute Study - Day 1

Immediately after admission to the resuscitation unit the following steps were undertaken. A routine electrocardiogram (E.C.G.) was recorded and thereafter continuous monitoring with oscilloscopic display of the E.C.G. was instituted. After local anaesthesia and a small cut-down procedure a No. 9 triple lumen cardiac catheter was inserted into an antecubital vein and passed centrally into the region

of the great veins or right atrium. A subsequent chest x-ray at the completion of the study was used to confirm the position of the catheter. This triple lumen catheter allowed the measurement of right atrial pressure, a central site for dye injection and also a third remaining lumen was available for the administration of drug therapy. A small bore nylon catheter (O.D. 0.8 mm., length 55 cm.) was introduced percutaneously into the brachial artery by a modified Seldinger technique. The average time taken to place these catheters in situ was approximately 10 - 15 minutes. The ends of these catheters were then immediately connected to the monitoring apparatus and both investigation and treatment could proceed forthwith.

Control Observations were made initially in each patient over a period of 15 minutes while breathing warmed humidified room air from a close fitting face mask at a flow rate of 50 litres per minute. Vascular pressures and the electrocardiogram were monitored continuously and cardiac output determinations were made at intervals of 5 minutes. Arterial blood pH,

oxygen and carbon dioxide tensions were measured at the beginning and end of the 15 minute control period. Arterial blood lactate, pyruvate, glucose, phosphate, sodium, potassium and chloride levels were also measured at either the beginning or end of this period. An illustrate example of the protocol is shown in Fig. 10.

Evaluation of oxygen therapy

On the completion of the control period, pure oxygen was administered by the same apparatus at an identical flow rate for the following 30 minutes, the patient being unaware of the change in inspired gas concentration. Direct sampling from the mask showed that the inspired oxygen concentration was between 82 and 96% (mean value 87%). This concentration will later be referred to as "high" for the purposes of results and discussion. Vascular pressures and cardiac output determinations were carried out as during the previous control period. The arterial blood oxygen tension levels were measured following 5, 15 and 30 minutes of breathing this high oxygen

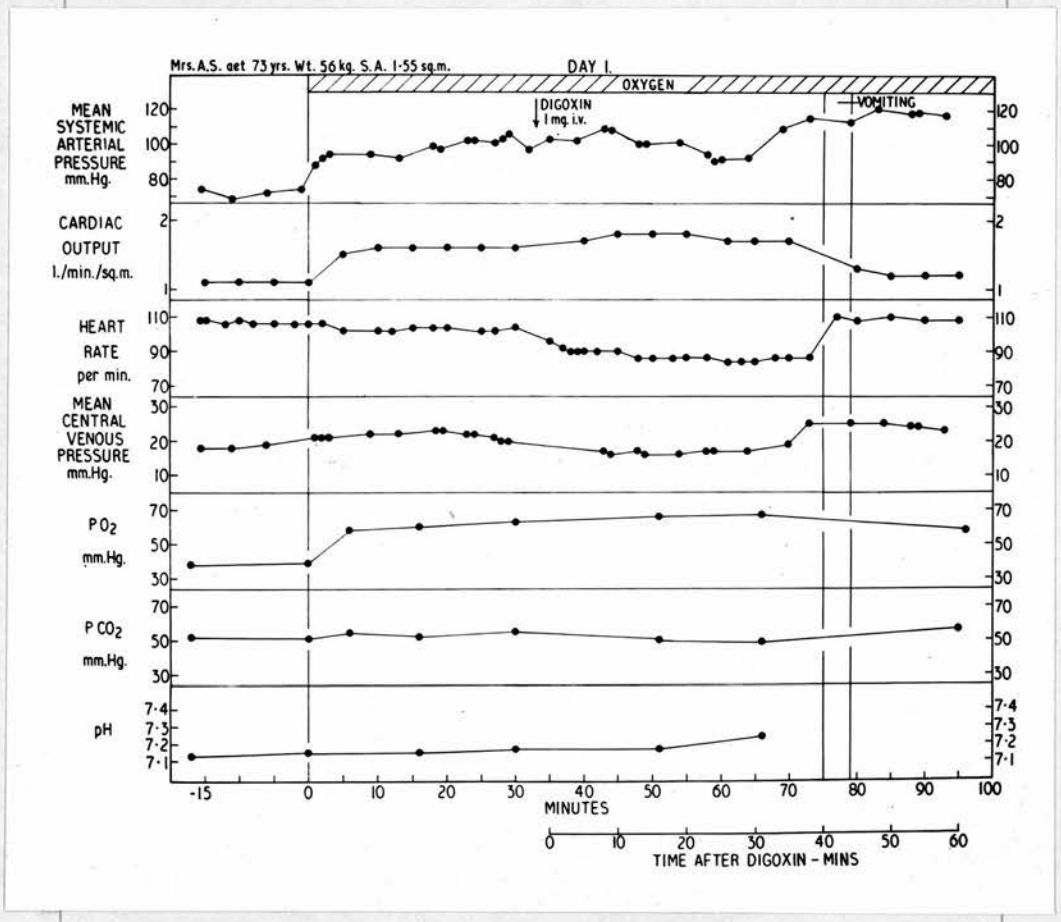


Fig. 10

An illustrate example of the experimental protocol.

concentration. The arterial blood pH and carbon dioxide tension was also measured after 15 and 30 minutes. The lactate, pyruvate, glucose, phosphate, sodium, potassium and chloride levels were measured after 30 minutes of oxygen breathing. An illustrate example of most of these details is again shown in Fig. 10.

In some patients with myocardial infarction uncomplicated by shock the concentration of inspired oxygen was then reduced for a further 20 minutes and the effects of such subsequent variations in the arterial blood oxygen tension on the circulatory state was assessed.

At the completion of the oxygen study per se, the administration of oxygen was continued at an unaltered concentration during the subsequent evaluation of the effects of either intravenous digoxin or noradrenaline infusion therapy. The final 15 to 20 minutes of oxygen therapy was thus used as the control period in the drug evaluation.

Evaluation of Digoxin Therapy

The period of oxygen therapy alone was followed by the administration of intravenous digoxin to four of the patients with cardiogenic shock and six of the patients with myocardial infarction uncomplicated by shock.

Intravenous digoxin (0.75 - 1.0 mg.) was given, diluted in 10 ml. of distilled water, over a period of 2 minutes. The slight variation in dose was conditioned by a clinical assessment of the weight of the patient. Continuous recording of the vascular pressures and the electrocardiogram and cardiac output determinations at 5 minute intervals were undertaken for the following 60 minutes - as illustrated in Fig. 11. Arterial blood pH, oxygen and carbon dioxide tensions were measured at 15, 30 and 60 minutes following injection. Blood lactate, pyruvate, glucose, phosphate, sodium, potassium and chloride levels were also measured after 60 minutes.

Evaluation of noradrenaline infusion therapy

The effect of noradrenaline infusion therapy was studied in five patients. Two of these patients

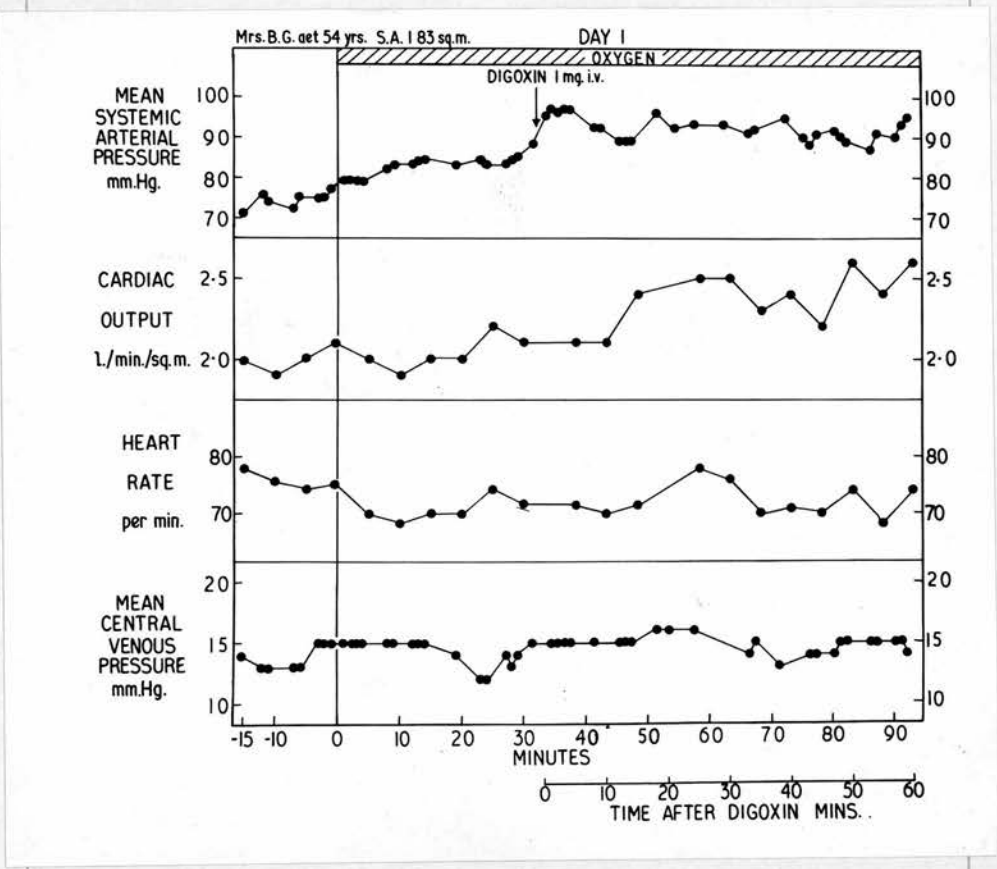


Fig. 11

An illustrate example of the experimental protocol in the evaluation of digoxin therapy.

suffered from cardiogenic shock and three had had a myocardial infarction with subsequent systemic arterial hypotension but without other features of shock. The concentration of noradrenaline infusion was varied according to blood pressure response. The vascular pressures and E.C.G. were recorded continuously. The cardiac output determinations were carried out at 5 minute intervals during the duration of infusion which varied between 15 and 30 minutes. The circulatory effects were further monitored after cessation of the drug as shown in each case. The arterial blood pH, oxygen and carbon dioxide tensions and serum electrolyte determinations were carried out before, during and after the infusion.

Although the preceding plan of the detail relating to an evaluation of contemporary therapy was faithfully adhered to in most cases, it will be appreciated that in some instances the protocol required to undergo slight alteration depending on clinical circumstances. These variations were of a minor degree and largely involved some alteration in the timing of arterial blood samples or cardiac output

determinations as detailed in the tables in the appendix.

At the completion of the study on day 1 the arterial catheter was filled with heparin (1000 I.U. per ml.), stoppered and left in situ. The triple lumen cardiac catheter was removed and replaced by a 55 cm. nylon catheter similar to that used for arterial catheterisation. This was also filled with heparin, stoppered and left in situ. These catheters being left in situ and bandaged to the arm, allowed free access to arterial or venous blood and ensured that further circulatory measurements could be immediately undertaken again if necessary. The bandaging of these catheters to the forearm also allowed the patient the free use of his limb.

Continuous oxygen therapy was given for the following 24 hours.

Follow-up Study - Day 2

Whenever possible the patients were restudied on the second day of their illness. As both arterial and venous catheters were already in situ, the necessary

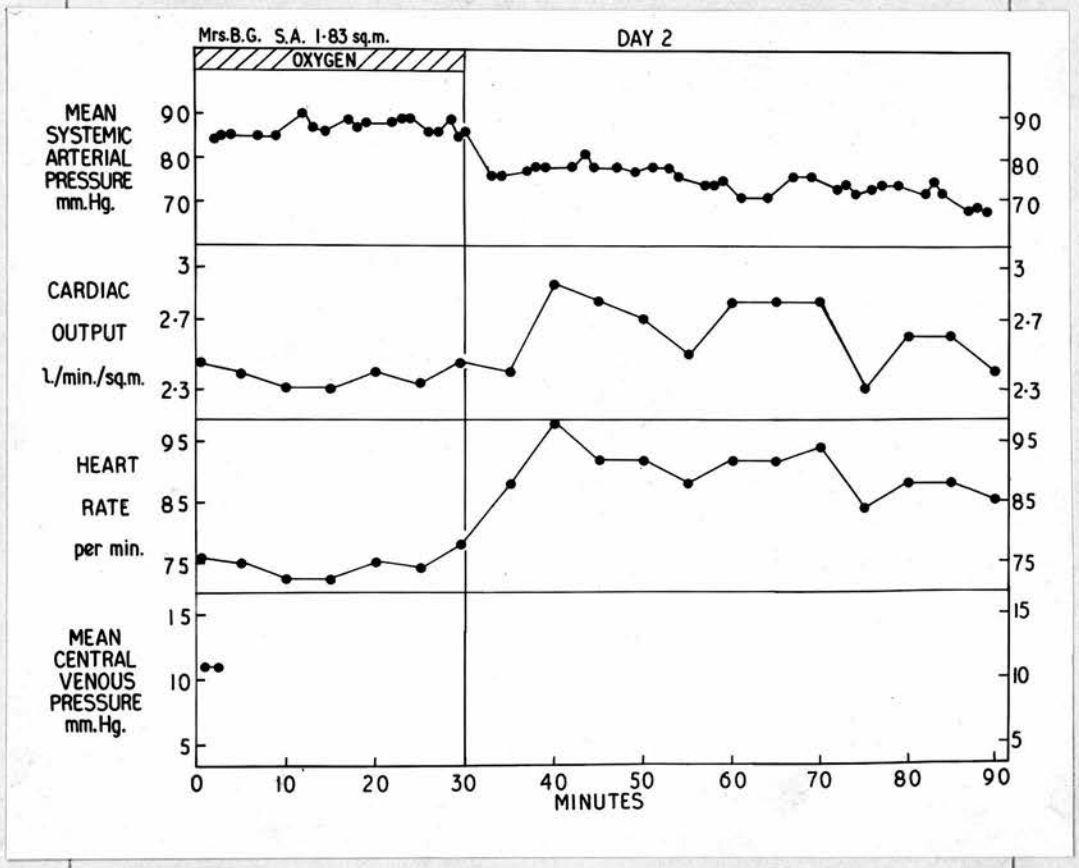


Fig. 12

An illustrate example of the study undertaken on Day 2.

measurements could be undertaken with ease. As oxygen therapy in a "high" concentration had been continued since the previous study, the initial measurements were undertaken for a period of 30 minutes whilst continuing this treatment. Measurements were therafter continued for a following 30 minutes (or 60 minutes in some cases) whilst breathing room air, (as shown in an illustratedexample in Fig. 12). Arterial blood lactate, pyruvate, and remaining electrolyte levels were measured at the beginning and end of the study.

Subsequent Days

Similar haemodynamic, respiratory and metabolic measurements were undertaken in some patients at varying times during the recovery phase of their illness. The details relating to each patient are contained in the appendix. These subsequent studies were carried out breathing room air and in some patients, a 30 minute control period while breathing room air was followed by a 30 minute period of "high" oxygen breathing. In three patients the final follow-up

study which was undertaken about one month after the onset of their illness was performed in the cardiac catheterisation laboratory. A double lumen cardiac catheter was passed into the right atrium under fluoroscopic control. These patients were then studied whilst breathing room air for 20 minutes followed by "high" oxygen for 30 minutes and finally again air for further 20 minutes. During these periods, the haemodynamic, respiratory and metabolic measurements were undertaken as outlined in the previous studies.

MEASUREMENTS AND CALCULATIONS

Intravascular pressures and heart rate were measured as the average of the 15 second values falling about the definitive point. Cardiac outputs were measured by conventional techniques, with replotting of the downslope according to the Hamilton semi-logarithmic extrapolation method as previously described. The appearance time, mean transit time and cardiopulmonary blood volume, corrected for surface area were measured according to the Hamilton

formula as previously described under dye dilution technique. The systemic vascular resistance was calculated according to the formula -

$$\text{Systemic vascular resistance (dyne. sec. cm}^{-5}\text{. sq. m.)} = \frac{\text{Mean aortic blood pressure - mean right atrial pressure in mm. Hg} \times 1332 \times 60}{\text{Cardiac output (ml. per min. per sq. m.)}}$$

Normally the unmeasured mean capillary or venous pressure is ignored in the calculation of the systemic vascular resistance owing to its relatively insignificant value compared to the magnitude of the central systemic arterial pressure. In the present studies, however, the central venous pressure was significantly raised and for this reason it was taken into account in calculating systemic vascular resistance. It is standard practice to use a correction factor for body surface area when expressing the results of cardiac output determination. The argument in favour of such a correction must surely also be applied to other derived parameters such as cardiopulmonary blood volume and systemic vascular resistance.

Pulse wave analysis and measurements of myocardial performance

A representative pulse wave for analysis of the various features is shown in Fig. 13. The maximum rate of blood pressure rise in the aorta (M.R.P.R.A.) was measured by tangential extrapolation of the upstroke of the aortic pressure pulse with the recording trace run at 135.4 mm. per sec.; it is expressed in mm.Hg per sec. The mean systemic arterial pressure was determined by electronic integration of the whole cycle wave form. The mean systolic ejection pressure (M.S.E.P.) and the mean diastolic aortic pressure (M.A.D.P.) were measured by conventional planimetric techniques

In the calculations pertaining to the measurement of left ventricular work, the measured mean left ventricular systolic ejection pressure (M.S.E.P.) should normally be corrected by a subtraction of the left atrial pressure. The latter was, of course, not measured in these patients. However myocardial infarction predominantly affects the left ventricle and animal experiments have shown a rise in left atrial

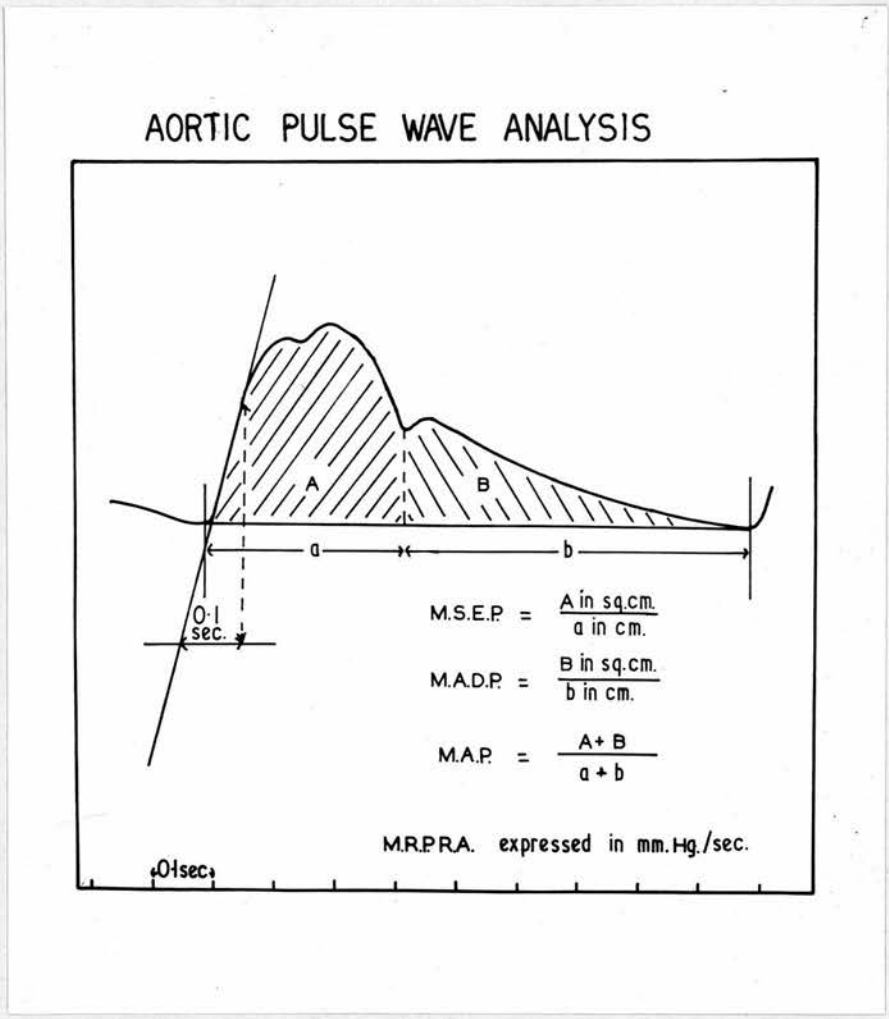


Fig. 13

Diagrammatic representation of pulse wave analysis

M.S.E.P.	=	mean systolic ejection pressure
M.A.D.P.	=	mean aortic diastolic pressure
M.A.P.	=	mean aortic pressure
M.R.P.R.A.	=	maximum rate of pressure rise in the aorta

pressure following experimental myocardial infarction in dogs. It, therefore, seems not unreasonable to suggest that the left atrial pressure is similarly elevated in the human patient. Furthermore, the elevation in left atrial pressure would probably be of the same order, if not higher, as the demonstrable increase in right atrial pressure. In the present calculations, therefore the value for left ventricular systolic ejection pressure was corrected by subtraction of the measured right atrial pressure. The error introduced by this method would be expected to give an artificially high value as presumably the left atrial pressure was in fact much higher. Furthermore, the error is consistent in that all cases, both shocked and not shocked, were treated in a similar manner as regards calculation. The systolic stroke pressure time index was determined as the product of the mean systolic ejection pressure minus the right atrial pressure and the duration of systole per stroke. The minute systolic pressure time index was calculated as the product of the stroke pressure time index and the heart rate. The diastolic pressure time

indices were similarly calculated. Diastolic minute duration is the total time per minute devoted to diastole; it was calculated as the product of the heart rate and the diastolic duration per cycle and expressed in seconds per minute. The mean ejection flow index was calculated by the division of the stroke volume by the systolic duration in seconds.

Left ventricular work has been calculated as the product of the cardiac index and the mean left ventricular systolic ejection pressure, the latter pressure again being corrected by subtraction of the right atrial pressure. In this calculation no account has been taken of the specific gravity of blood, 1.005. Since its introduction by Dexter et al. (1953), many authors have used the specific weight of blood (1.055) in the equation for the calculation of ventricular work. However, work represents the product of force and distance. In haemodynamic calculations, pressure represents the force while volume actually represents distance, given a constant cross sectional area of ventricular outlet. It is therefore incongruous to be

concerned with the weight of the distance. In the present study therefore the calculation of left ventricular work is 5.5% less than that calculated by the method of Dexter et al. (1953). Left ventricular stroke work index (S.W.I.) was obtained by division of the total minute left ventricular work by the heart rate. The left ventricular mean ejection power index was calculated by dividing the stroke work index by the duration of systole.

SECTION II

The Pathophysiology of Acute Myocardial Infarction and Cardiogenic Shock and an Evaluation of Oxygen Therapy

INTRODUCTION

The development of a metabolic acidosis as a complication of hypovolaemic shock in dogs is well known (Levenson Einheber and Malm, 1961). This has been considered to be due largely to the tissue hypoxia resulting from the persistent and prolonged deficiency in blood flow. It is also well known that the inadequate perfusion of blood during cardiopulmonary bypass operations will inevitably lead to a metabolic acidosis, which has been described as one of the "dreaded" complications of open heart surgery (Kolff, et al., 1960). In contrast, there is surprisingly little published information about the metabolic state in the human shocked patient. Cournand et al. (1943) reported the development of a metabolic acidosis in a number of patients with haemorrhagic and traumatic shock. In 1961 Thrower, Darby and Aldinger likewise reported the occurrence of metabolic acidosis in ten

patients suffering from the terminal stages of shock of varied aetiology. More recently Weil and Broder (1963) reported, in abstract form, the results of their metabolic measurements in 36 patients with shock of varied aetiology. They reported that increasing arterial blood lactate levels and metabolic acidosis in shock due to overwhelming infection, myocardial infarction or blood loss were invariably indicative of a poor prognosis. In 1964 Broder, Weil and Cramer reported, again in abstract form, that the measurement of excess lactate, as defined by Huckabee (1958) was the most reliable index of the degree of circulatory failure in shock, again of varied aetiology. Shubin and Weil (1964) when reporting an abstract of their findings in ten patients with cardiogenic shock, noted the development of a metabolic acidosis in three of these patients. The data, presented in these recent abstracts, is indeed interesting but must, of course, be viewed with reserve, at this stage. The reporting of evidence in an abstract form does not allow of a critical assessment

of methods and techniques employed. Further, no details are given of the diagnostic criteria employed and of course no detailed tabular information is available. It will be readily apparent, that there is as yet no detailed report of the metabolic state associated with either uncomplicated myocardial infarction or cardiogenic shock.

Although oxygen therapy is widely employed in the treatment of shock following acute myocardial infarction, surprisingly little information is available concerning the nature of the arterial blood gas tensions in this type of shock. In 1952 Borden, Ebert and Wilson reported their findings of the arterial blood gas changes in 17 patients with uncomplicated acute myocardial infarction, four patients with pulmonary oedema, and two patients with cardiogenic shock. The oxygen saturation showed a slight reduction in the uncomplicated group (average value 94.1 %, range 88.0 - 96.8% with a quoted normal value of 97.5%). The patients with pulmonary oedema or shock were considered together as a group

and were noted to have a greater degree of reduction in their arterial oxygen saturation (average value 80.8 , range 61.4 - 92.4). The arterial blood pH and carbon dioxide tensions were normal in both groups. Since this report there have been numerous studies of the changes in arterial blood gas tensions in patients with pulmonary oedema or left ventricular failure due to a variety of causes, but there has been no further study reported of these measurements in uncomplicated myocardial infarction or cardiogenic shock. The administration of oxygen, even in uncomplicated myocardial infarction, has been advocated in the belief that it may help to relieve pain (Barach, 1931; Boland, 1940) and also increase the tissue oxygen tension in the marginal ischaemic areas surrounding a myocardial infarct (Sayen et al., 1951). Although oxygen breathing produced a slight increase in systemic arterial pressure accompanied by a fall in heart rate and cardiac output in normal man at rest (Daly and Bondurant, 1962; Eggers et al., 1962) the circulatory effects after myocardial infarction are unknown. The basis of rational oxygen therapy in myocardial infarction and

cardiogenic shock must obviously depend on a knowledge of the underlying circulatory and arterial blood gas tension changes and their response to oxygen administration.

Chapter I

The underlying pathophysiology of the acute stage

Results

The detailed results, relevant to each patient are shown in the appendix. The mean values with the standard error of the mean and the standard deviation of the observations are shown in table 3. The results are also expressed in diagrammatic form in figures 14, 15 and 16.

CARDIOGENIC SHOCK (6 cases)

Circulatory changes breathing room air The mean systemic arterial pressure was severely reduced in all six patients (mean value 75, range 71 - 80 mm.Hg). The cardiac stroke volume was likewise consistently reduced (mean value 16, range 10 - 26 ml. per sq.m.), and despite a relative tachycardia (mean value 108, range 83 - 140 per minute) the cardiac output was

TABLE 3 - THE CIRCULATORY BLOOD GAS AND METABOLIC CHANGES IN ACUTE MYOCARDIAL INFARCTION - DAY 1

PATIENT	SYSTEMIC ARTERIAL PRESSURE mm.Hg						CARDIAC OUTPUT l./min./sq.m.		HEART RATE per min.		STROKE VOLUME ml./sq.m.		M.R.A.P. mm.Hg		SYST. VASC. RESIST. dyne.sec.cm^{-5}.sq.m.		C.P.B.V. ml./sq.m.		ARTERIAL BLOOD CHANGES											
	SYSTOLIC		DIASTOLIC		MEAN														pH		PO_2 mm.Hg		PCO_2 mm.Hg		O_2 Sat. %		LACTATE m.M./l.		PYRUVATE m.M./l.		GLUCOSE mg./100ml.	
	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2
CARDIOGENIC SHOCK																																
A.S.	90	120	59	87	72 ±1.4 (2.8)	101 ±1.5 (4.3)	1.08 ±0.031 (0.063)	1.59 ±0.005 (0.011)	107 ±0.6 (1.2)	104 ±0.4 (1.1)	10 ±0	15 ±0.28 (0.57)	18	22	3996 ±85 (171)	3971 ±178 (356)	1066 ±7.9 (14)	943 ±7.0 (14.0)	7.14	7.24	39	67	52	54	59	88	6.40	4.18	0.090	0.245	332	248
A.F.	91	110	61	80	73 ±0.7 (2.5)	95 ±0.4 (0.8)	2.16 ±0.080 (0.182)	1.64 ±0.015 (0.032)	83 ±0.8 (1.8)	85 ±0.8 (1.6)	26 ±0.8 (1.8)	19 ±0	19	18	1998 ±70 (157)	3752 ±44 (87)	1181 ±40 (89)	1005 ±40 (79)	7.30	7.30	66	230	44	45	89	99	4.33	3.63	0.168	0.164	376	356
J.F.	85	87	64	65	71 ±1.2 (3.0)	73 ±0.9 (2.8)	1.11 ±0.058 (0.118)	1.10 ±0.053 (0.105)	107 ±1.8 (3.6)	112 ±0.05 (1.0)	10 ±1.8 (3.6)	10 ±0.5 (0.96)	16	16	3960 ±379 (659)	4141 ±136 (271)	845 ±26 (52)	841 ±25 (49)	7.27	7.27	48	68	31	32	77	89	6.05	5.98	0.291	0.304	194	162
A.C.	94	95	71	82	80 ±0.3 (1.1)	82 ±0.2 (0.7)	1.97 ±0.015 (0.031)	1.87 ±0.037 (0.075)	140 ±0	138 ±0	14 ±0	14 ±0.29 (0.57)	20	19	2434 ±8 (16)	2692 ±146 (291)	1040 ±2.8 (6)	1036 ±21.6 (43.8)	7.42	7.43	40	112	28	32	76	98	3.38	2.95	0.227	0.218	166	175
M.R.	100	96	64	64	77 ±1.0 (2.9)	76 ±0.5 (1.4)	1.85 ±0.159 (0.318)	1.59 ±0.077 (0.155)	105 ±0.8 (1.4)	103 ±0.6 (1.2)	18 ±1.4 (2.9)	15 ±0.7 (1.29)	12	13	2808 ±17 (34)	3167 ±184 (369)	1309 ±57 (113)	1344 ±184 (369)	7.30	7.29	53	120	46	44	82	98	2.81	3.58	0.162	0.201	204	196
W.M.	83		63		76		1.87		108		17		8		2906		1185		7.10		37		57		53		10.7		0.415		314	
WITHOUT SHOCK																																
M.L.	129	130	63	63	88 ±0.3 (1.0)	89 ±0.6 (1.2)	2.53 ±0.022 (0.044)	2.50 ±0.128 (0.221)	62 ±0	61 ±0	41 ±1.6 (3.9)	41 ±0.8 (0.78)	5	6	2622 ±41 (81)	2653 ±98 (170)	553 ±29 (55)	555 ±30 (52)	7.43	7.40	47	360	47	44	83	99	0.85	0.73	0.063	0.065	67	74
G.B.	133	145	76	83	99 ±0.8 (2.3)	107 ±0.4 (1.2)	1.88 ±0.042 (0.082)	1.50 ±0.020 (0.040)	80 ±0.5 (1.0)	72 ±0.5 (1.0)	24 ±0.8 (1.5)	21 ±0.2 (0.50)	8	8	3868 ±67 (135)	5275 ±98 (196)	593 ±54 (104)	563 ±17 (33)	7.42	7.43	67	335	41	37	93	99	0.82	0.70	0.072	0.074	116	112
B.G.	91	102	62	69	74 ±0.7 (2.0)	84 ±0.4 (1.0)	2.00 ±0.050 (0.100)	2.08 ±0.046 (0.090)	76 ±0.9 (1.7)	72 ±1.0 (1.9)	26 ±0.5 (0.96)	29 ±0.4 (0.82)	14	14	2398 ±59 (119)	2690 ±37 (73)	501 ±8 (15)	509 ±8 (16)	7.46	7.38	70	465	32	39	94	99	0.95	0.95	0.088	0.102	116	120
A.S.	129	139	56	70	87 ±1.6 (4.9)	102 ±1.4 (3.2)	2.20 ±0.137 (0.274)	2.17 ±0.070 (0.139)	52 ±0.6 (1.2)	58 ±4.0 (8.0)	42 ±2.1 (4.1)	37 ±1.4 (2.75)	8	9	2870 ±257 (514)	3425 ±103 (205)	960 ±16 (31)	970 ±18 (35)	7.41	7.40	74	401	38	39	94	99	0.81	0.78	0.088	0.079	114	104
I.H.	180	189	96	105	136 ±1.0 (3.0)	145 ±0.7 (2.3)	3.10 ±0.042 (0.085)	2.75 ±0.066 (0.133)	84 ±1.3 (2.5)	81 ±1.9 (3.8)	37 ±0.4 (0.82)	34 ±1.1 (2.20)	7	7	3326 ±193 (386)	4011 ±133 (267)	609 ±29 (58)	656 ±8 (15)	7.35	7.35	77	335	46	46	94	99	1.61	1.41	0.082	0.091	116	114
L.L.	109	112	86	67	84 ±0.72 (2.4)	86 ±0.6 (2.2)	2.07 ±0.090 (0.170)	1.58 ±0.020 (0.040)	68 ±1.4 (2.8)	63 ±0.7 (1.7)	30 ±1.1 (2.24)	25 ±0.10 (1.0)	10	9	2857 ±140 (287)	3895 ±57 (125)	1052 ±56 (112)	952 ±57 (125)	7.39	7.40	62	424	36	37	90	99	1.66	1.66	0.132	0.134	150	158
V.H.	141	145	94	99	113 ±0.4 (1.1)	119 ±0.3 (1.1)	2.61 ±0.033 (0.066)	2.28 ±0.046 (0.093)	118 ±1.2 (2.3)	112 ±0.5 (1.0)	22 ±0.4 (0.81)	20 ±0.5 (0.96)	7	7	3246 ±50 (100)	3926 ±67 (135)	726 ±29 (59)	741 ±67 (135)	7.42	7.41	62	440	42	44	91	99	0.61	0.66	0.096	0.096	101	102
J.M.	118	118	69	76	89 ±0.4 (1.5)	96 ±0.5 (1.3)	4.04 ±0.110 (0.221)	3.82 ±0.047 (0.093)	87 ±1.0 (2.0)	88 ±1.3 (2.5)	44 ±0.9 (1.7)	41 ±0.5 (0.92)	8	8	1982 ±39 (79)	1921 ±30 (59)	823 ±20 (41)	829 ±18 (35)	7.45	7.43	70	432	36	38	94	99	0.80	0.78	0.104	0.084	92	86
G.D.	133	146	64	70	91 ±1.2 (3.9)	98 ±0.7 (1.8)	3.42 ±0.242 (0.479)	3.08 ±0.065 (0.130)	66 ±1.2 (2.3)	64 ±0.5 (1.0)	52 ±4.2 (8.4)	48 ±1.0 (2.1)	9	8	1916 ±126 (252)	2335 ±84 (167)	1203 ±84 (167)	1069 ±30 (60)	7.40	7.37	73	328	44	47	94	99	1.44	0.88	0.077	0.078	88	102
ACUTE LEFT VENTRICULAR FAILURE																																
WITHOUT SHOCK																																
I.S.	103	123	70	77	84	94	1.64	1.43	100	103	16	14	17	17	3267	4300	830	798	7.41	7.38	48	382	37	42	83	99	1.70	1.62	0.165	0.150	143	132
V.B.	121	121	71	75	90	93	2.57	2.03	104	103	25	20	11	11	2457	3229	900	898	7.41	7.41	50	328	39	42	84	99	2.14	1.96	0.193	0.204	118	100

M.R.A.P. - Mean Right Atrial Pressure; C.P.B.V. - Cardiopulmonary Blood Volume

Values are expressed as the mean ± standard error of the mean, with the standard deviation of the observations in parentheses.

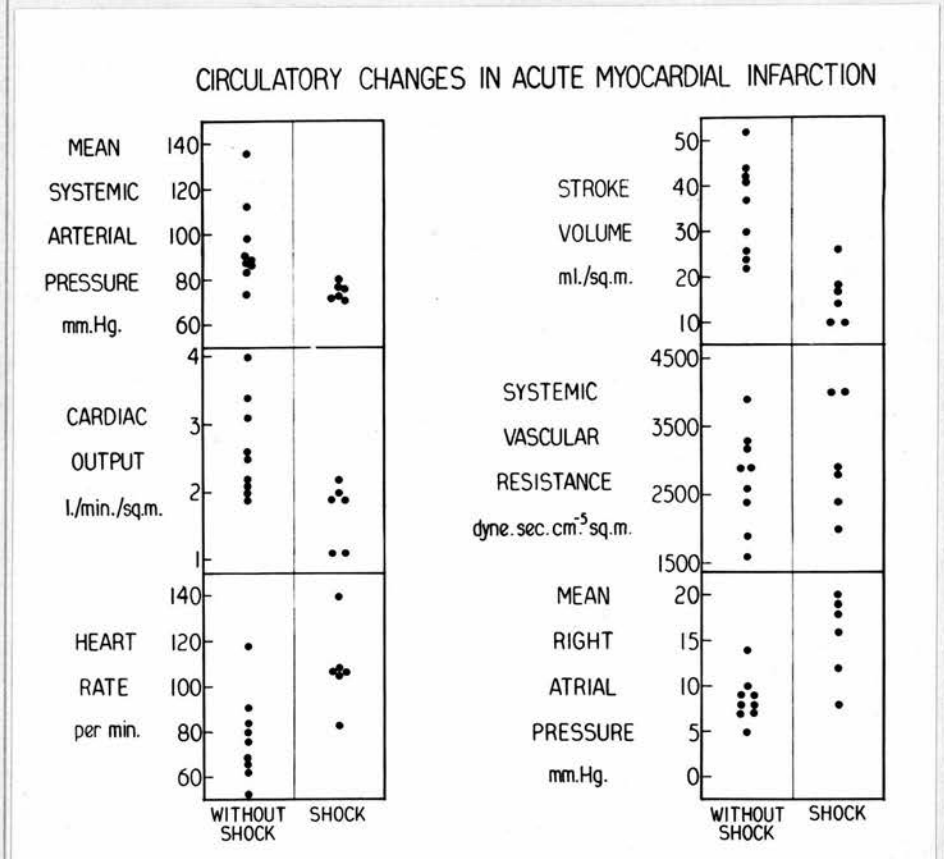


Fig. 14

The circulatory changes breathing room air after acute myocardial infarction with and without shock (Day 1).

greatly reduced in all (mean value 1.67, range 1.08 - 2.16 litres per min. per sq.m.). The calculated values for overall systemic vascular resistance showed an increase in two patients and were within the normal range in the other four patients. All six patients had a very considerable degree of heart failure, as evidenced by the increased right atrial pressure (mean value 16, range 8 - 20 mm.Hg) combined with a raised value for the cardiopulmonary blood volume (mean value 1,104, range 845 - 1,309 ml. per sq.m.). The mean transit time was likewise consistently prolonged (mean value 41.7, range 31.6 - 59.2 seconds). The main circulatory changes are illustrated in fig. 14 in which they are contrasted with the findings in acute myocardial infarction without shock.

Arterial blood gas tension and metabolic changes breathing room air As shown in both the individual tables in the appendix and in the summary table 3 together with figure 15, the most striking and consistent findings in the presence of shock were

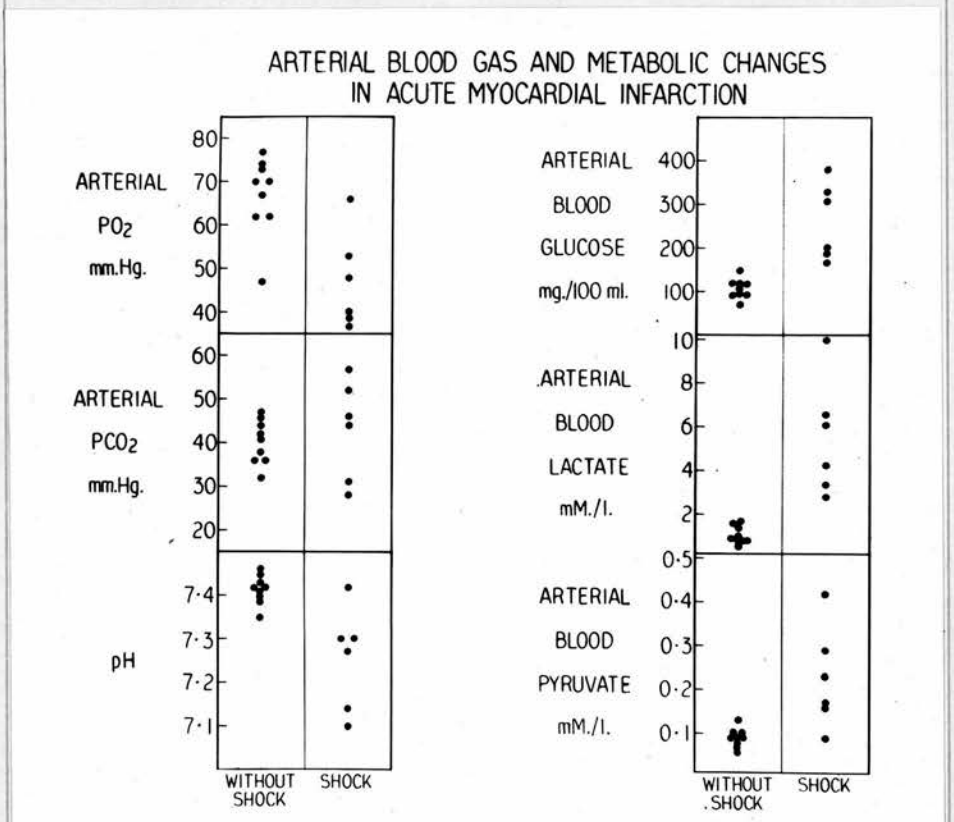


Fig. 15

The arterial blood gas tension and some metabolic changes after acute myocardial infarction with and without shock (Day 1).

severely reduced arterial blood oxygen tensions (mean value 47, range 37 - 66 mm.Hg) in the presence of a considerable metabolic acidosis and lactic acidaemia. The figures for the percentage arterial oxygen saturations, derived from the Dill-dissociation curves (Dittmer and Grebe, 1958), show arterial oxygen unsaturation in all six cases. The arterial carbon dioxide tensions were variable, being low in two cases, normal in two, and slightly raised in two. These changes were accompanied by moderate hyperglycaemia. The serum electrolytes showed no significant abnormality in the sodium and chloride. The serum potassium was elevated in one patient (W.M.) in whom it was 5.7 m.eq./l. The serum phosphate was elevated in most patients (mean value 2.57, range 1.88 - 3.78 m.eq./l.).

ACUTE MYOCARDIAL INFARCTION WITHOUT SHOCK (9 cases)

Circulatory changes breathing room air The mean systemic arterial pressure was below the expected normal range in six of the nine patients, whereas the

cardiac output was within the normal range in six patients. In the other three patients the cardiac output and stroke volume were significantly reduced. The systemic vascular resistance was raised in three of the nine patients, and either reduced or within normal range in the remainder. The right atrial pressure was increased in all cases (mean value 9, range 5 - 14 mm.Hg), and the values for cardiopulmonary blood volume could be regarded as being at the upper limits of normal (mean value 782, range 506 - 1,094 ml. per sq.m.). The mean transit time was only slightly prolonged (mean value 18.7, range 11.8 - 30.5 seconds). The main circulatory changes are illustrated in figure 14 in which they are contrasted with the findings in cardiogenic shock.

Arterial blood gas tension and metabolic changes breathing room air As shown in both the individual tables in the appendix and in the summary table 3 together with figure 15, the arterial blood oxygen tension was moderately reduced in all nine patients, (mean value 67, range 47 - 77 mm.Hg). The

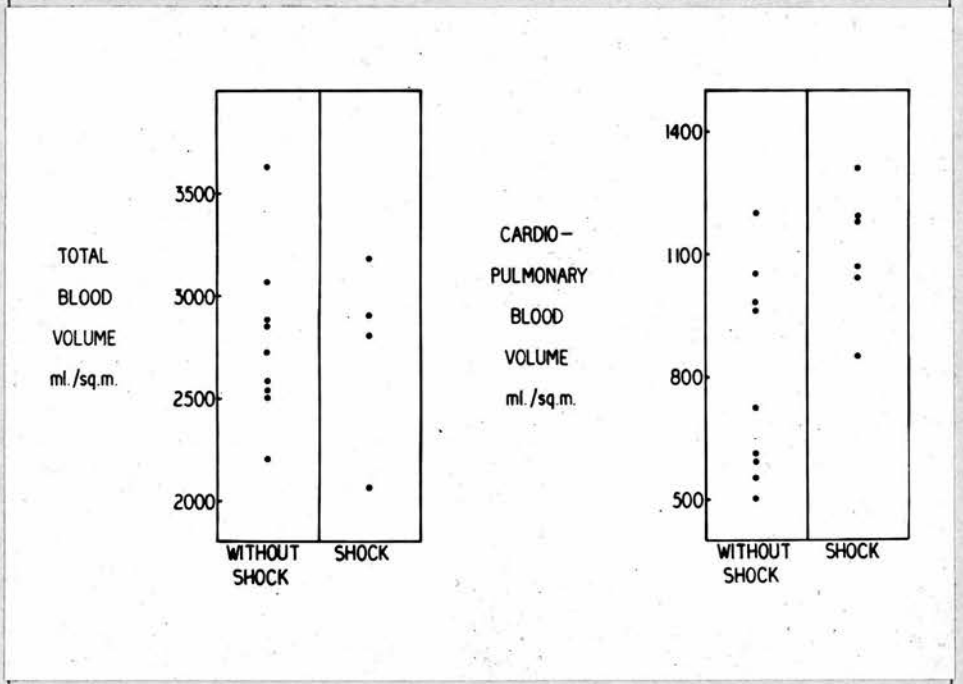


Fig. 16

The changes in total blood volume and cardio-pulmonary blood volume in acute myocardial infarction, with and without shock (Day 1).

measurements of pH, carbon dioxide tension, arterial blood lactate, pyruvate, glucose, sodium, potassium, chloride and phosphate showed no significant deviation from normal.

MEASUREMENT OF TOTAL CIRCULATING BLOOD VOLUME

The individual values for the total circulating blood volume in the acute stage of both groups of patients are reported in table 5 and illustrated in Fig. 16. There is no consistent change or significant reduction in these values in either the shocked or the non-shocked patients.

MEASUREMENT OF LEFT VENTRICULAR PERFORMANCE

The results of the determination of some aspects of left ventricular performance are shown in table 4. These parameters were measured in three shocked patients (A.F., A.C. and M.R.) and in seven of the nine cases of uncomplicated myocardial infarction. Table 4 also illustrates the effects of oxygen administration on these changes and will be considered in a later chapter relating to the evaluation of oxygen therapy.

TABLE 4 LEFT VENTRICULAR PERFORMANCE IN ACUTE MYOCARDIAL INFARCTION

Patient	Cardiac Output l./min./sq.m.		Heart Rate per min.		Stroke Volume ml./sq.m.		Right Atrial Pressure mm.Hg		Pressures mm.Hg				Cycle Duration Sec.				Diastolic Minute Duration Sec./min.		M.R.P.R.A. mm.Hg/sec.		Left Ventricular Work				Pressure-Time Index mm.Hg/sec.				Pressure-Time Index mm.Hg/sec.				Mean Ejection Flow Index ml./ sec./sq.m.		Mean Stroke Power Index g.m./sec./ sq.m.	
									M.S.E.P.		M.A.D.P.		SYST.		DIAST.						Minute Kg.m./sq.m.		Stroke g.m./sq.m.		Systolic Minute		Systolic Stroke		Diastolic Minute		Diastolic Stroke					
	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2
CARDIOGENIC SHOCK																																				
A.F.	2.16	1.64	83	85	26	19	19	18	81	103	65	88	0.26	0.36	0.47	0.43	39.0	36.6	540	441	1.821	1.896	21.9	22.3	1336	1879	16.1	22.1	1793	2559	21.6	30.1	100	73	84	86
A.C.	1.97	1.87	140	133	14	14	20	19	80	84	73	77	0.12	0.12	0.31	0.31	43.4	42.8	472	476	1.608	1.653	11.5	12.0	1008	1063	7.2	7.7	2286	2484	16.4	18.0	117	117	96	100
M.R.	1.85	1.59	105	103	18	15	12	13	90	84	73	71	0.24	0.25	0.34	0.34	35.7	35.0	625	485	1.962	1.535	18.7	14.9	1964	1833	18.7	17.8	2174	2029	20.7	19.7	75	60	78	60
WITHOUT SHOCK																																				
M.L.	2.53	2.50	62	61	41	41	5	6	116	111	81	78	0.31	0.30	0.72	0.73	44.6	44.5	1006	916	3.819	3.570	61.6	58.5	2133	1922	34.4	31.5	3391	3209	54.7	52.6	132	137	199	195
A.S.	2.20	2.17	52	58	42	37	8	9	119	125	90	89	0.40	0.39	0.71	0.73	36.9	42.3	1484	1371	3.321	3.423	63.9	59.0	2309	2622	44.4	45.2	2657	3387	51.1	58.4	105	95	160	151
I.M.	3.10	2.75	84	81	37	34	7	7	160	167	117	124	0.31	0.32	0.40	0.41	33.6	33.2	1180	1078	6.450	5.984	76.8	73.9	3982	4147	47.4	51.2	3696	3888	44.0	48.0	119	106	248	231
L.L.	2.07	1.58	68	63	30	25	10	9	99	103	80	84	0.36	0.37	0.67	0.77	45.6	48.5	520	510	2.506	2.020	36.9	32.1	2176	2192	32.0	34.8	3189	3641	46.9	57.8	83	68	103	87
V.H.	2.61	2.28	118	112	22	20	7	7	129	133	106	109	0.26	0.25	0.26	0.29	30.7	32.5	651	618	4.331	3.907	36.7	34.9	3741	3528	31.7	31.5	3033	3315	25.7	29.6	85	80	141	140
J.M.	4.04	3.62	91	89	44	41	9	9	102	109	80	86	0.28	0.27	0.41	0.41	37.3	36.5	954	953	5.110	4.923	56.2	55.3	2366	2403	26.0	27.0	2648	2812	29.1	31.6	157	152	201	205
G.D.	3.42	3.08	68	64	52	48	9	8	112	120	79	83	0.34	0.33	0.57	0.62	37.6	39.7	705	756	4.791	4.691	72.6	73.3	2310	2368	35.0	37.0	2633	2976	39.9	46.5	153	145	214	222

M.S.E.P. - Mean Systolic Ejection Pressure: M.A.D.P. - Mean Aortic Diastolic Pressure: M.R.P.R.A. - Maximum Rate of Pressure Rise in Aorta.

The cases of cardiogenic shock show a severe impairment of mean stroke power index, (average value 86, range 78 - 96 g.m./sec./sq.m.). The maximum rate of pressure rise in the aorta (M.R.P.R.A.) is markedly reduced (average value 546, range 472 - 625 mm.Hg/sec.). The systolic and diastolic pressure time indices both per minute and per stroke are all greatly reduced and the duration of both systole and diastole is shortened. The work done by the left ventricle both per stroke and per minute is also severely reduced, (average value per minute 1.797, range 1.608 - 1.962 kg.m./sq.m.) and average value per stroke 17.4, range 11.5 21.9 g.m./sq.m.). These estimates show a wide range of values in uncomplicated acute myocardial infarction but in general indicate a much less severe impairment of left ventricular function.

DISCUSSION

Although previous workers have found a great variation in the circulatory state following acute myocardial infarction, there does appear to be general

agreement that the cardiac output and stroke volume tend to be reduced after the acute episode and that the extent of this reduction can be reasonably well correlated with the patient's clinical status; the most severe reduction in cardiac output being found in cases exhibiting the clinical features of cardiogenic shock as shown in table 1. Some of the fallacies inherent in the techniques employed during these previous studies have already been critically discussed and may well be considered to be responsible for some of the variation in the reported results. Furthermore the cardiac output determinations in these studies were based on either one, or at the most two, isolated estimations. The more detailed and serial measurements made in the present study have not only allowed a more critical analysis of the circulatory state but have also correlated these changes with respiratory and metabolic measurements. Although the cardiac output was found to be severely reduced in the presence of cardiogenic shock, equally low values were found in some cases of myocardial infarction without shock. In

contrast there was little significant overlap in the values for stroke volume (as illustrated in fig. 14) and it seems that the cardiac output has been maintained, at least in part, in some of the shocked cases by an increase in heart rate. This severe reduction of the stroke volume in the absence of significant hypovolaemia and in the presence of an increased cardiopulmonary blood volume suggests a serious impairment of left ventricular function. Myocardial infarction in man predominantly affects the left ventricle, and although the left atrial pressure was not measured, it is not unlikely that it was as much increased as the pressure observed in the right atrium. The demonstration of an increased left atrial pressure after occlusion of the left main artery in dogs supports this assumption (Case et al., 1954, Matthes, 1962); likewise the left atrial pressure was found to be elevated after coronary artery embolisation in dogs (Guzman et al. 1962a). The measurements of left ventricular performance in the present study were based on this assumption. It was considered likely

that any error introduced in the calculation would be small and that it would apply equally to the shocked and non-shocked patients. Therefore a comparison of results each based on this assumption would appear to be valid and meaningful. These measurements confirm the original suggestion that cardiogenic shock is associated with a severe degree of impairment of myocardial contractility, as evidenced by the marked reduction in the mean stroke power index and the maximum rate of pressure rise in the aorta (M.R.P.R.A.). There is also a severe reduction in the degree of left ventricular work and in both systolic and diastolic pressure time indices. These results, therefore, demonstrate clear evidence of failure of the left ventricle as a pressure pulse generator in cardiogenic shock. Similar findings and impairment of the left ventricle as a pump were found by Rushmer et al. (1963) in an elegant study of the effects of acute coronary arterial occlusion in the intact unanaesthetised dog. It should be noted that the measurements of left ventricular performance were

carried out in the three shocked cases who were found to have the highest values for cardiac output. Unfortunately this detailed information, for a variety of technical reasons, is not available in the three remaining shocked patients. As already suggested the former three patients werecapable of maintaining a reasonable degree of forward flow by virtue of tachycardia. This feature was again borne out in the analysis of the left ventricular performance when the mean ejection flow index was found to be much less severely impaired than the mean stroke power index. Although this reflex tachycardia may increase the forward flow, it does so, at the expense of a reduction in the systolic and diastolic pressure time indices as shown in table 4. The demonstrable reduction in the diastolic pressure time index is a serious complication and must, of necessity, further impair the coronary arterial blood supply. It is well known that the coronary blood supply depends on the aortic diastolic filling pressure, the duration of diastole and the coronary vascular resistance and is not in fact a

function of the cardiac output or stroke volume (Gorlin, 1959). We have no measurement of the coronary vascular resistance in these patients and the diastolic pressure time index, being the product of the aortic diastolic pressure and the duration of diastole, may be regarded as the critical measurable determinant of coronary blood flow. The increase in forward blood flow due to the development of tachycardia is therefore produced at the expense of the coronary arterial blood supply.

Although the primary factor in cardiogenic shock is therefore impairment of the heart as a pump, the systemic vascular resistance remains unchanged or only moderately elevated. The total unreliability of clinical skin vasoconstriction as an estimate of overall systemic vascular resistance is demonstrated in figures 10 and 24. During the presence of severe clinical cardiogenic shock, the compensatory increase in systemic vascular resistance was by no means maximal as is demonstrated by the ability of the patient to increase this further from approximately

4,000 to 6,000 dyne.sec.cm^{-5}.sq.m.) during the act of vomiting. The absence of a reflex increase of the systemic vascular resistance of sufficient magnitude to compensate for the severe reduction in cardiac output and to maintain the blood pressure indicates a grave disturbance of the circulatory homeostatic mechanisms. In striking contrast, patients with acute left ventricular failure, from a variety of causes, have cardiac outputs of the same order and yet are able to increase the systemic vascular resistance to maintain a relatively normal blood pressure.

These findings are in agreement with those of Agress (1958) who, when reviewing the circulatory data available at that time, suggested that the defect in compensation was a failure of the vascular resistance to rise in the face of a falling cardiac output rather than actual vasodilatation. He postulated that this lack of homeostatic response might be mediated through an inhibitory reflex arising in the injured myocardium and claimed that this could be overcome

by blocking the afferent cardiac sympathetic fibres. Although such a reflex may well exist, it also seems not unlikely that the co-existing arterial hypoxaemia and metabolic acidosis may be equally important factors in the impairment of this fundamental circulatory reflex.

The demonstration of an elevated central venous pressure in these shocked patients is in agreement with the previously reported data and deserves further consideration. The combination of this central venous pressure elevation, the not infrequent radiological (and indeed often pathological) demonstration of pulmonary congestion and oedema and the reported normal or somewhat elevated values for the cardiopulmonary blood volume in this and other studies all support the contention that the venous return is more than adequate. It is somewhat difficult to adequately explain why only one of the six shocked patients was noted clinically to have an elevated jugular venous pressure (see table 2). It is perhaps relevant to note that this was found to be subsequently elevated in those patients recovering from cardiogenic

shock. These features raise the possibility that there is active venoconstriction in shock which, on occasion, may prevent the clinician from observing the soft undulant venous pulsations in the neck. Garai and Shirley Smith (1958) likewise found the appraisal of the cervical veins to be difficult in cardiogenic shock.

One of the most remarkable observations in the resent study was the severe degree of arterial hypoxaemia in the shocked group of patients. In five out of six instances the arterial blood oxygen tensions were of the order found in moderately severe respiratory failure. The adverse effects of this severe arterial hypoxaemia in these patients must be greatly aggravated by the considerable underperfusion of many parts of the body. Approximate calculations of the mixed venous blood oxygen tension show that it must have varied between 30 and 12 mm.Hg (see appendix) and there were, no doubt, far lower tissue and venous oxygen tensions in the zones where underperfusion was greatest. The effect on the coronary vascular bed is worthy of special consideration. The supply of

oxygen to the myocardium is curtailed not only by a direct reduction in the coronary blood flow as already discussed but also by arterial hypoxaemia of the blood actually reaching the coronary vessels. A consideration of the possible causes of this arterial hypoxaemia will be undertaken in the next chapter when evaluating the place of oxygen therapy in management.

The changes in myocardial metabolism consequent upon reduced coronary arterial blood supply were investigated in haemorrhagic shock in dogs by Edwards, Siegel and Bing (1954). Although the coronary blood flow was diminished in these experiments, the oxygen content of the arterial blood was normal. These workers demonstrated a failure of the coronary oxygen extraction to increase and myocardial oxygen usage declined. Myocardial pyruvate extraction declined and frequently a negative pyruvate coronary arterio-venous difference occurred. Despite high arterial blood levels of glucose and lactate, the extraction of these substances was not significantly increased and in fact a negative coronary arterio-venous

difference for glucose was occasionally observed. These essential changes in myocardial metabolism, which were presumably the result of myocardial anoxia, persisted even after transfusion to a normal blood volume. These authors suggested that myocardial ischaemia, resulting from a diminished coronary blood flow might bring about specific chemical or metabolic changes in the heart muscle itself. They, likewise, suggested that the demonstrable increase in pyruvate excretion in the coronary sinus blood might well indicate a destruction of the co-carboxylase enzyme system. This suggestion was supported by the work of Michal et al. in 1959 when they reported that myocardial oxygen lack leads to a rapid dephosphorylation of the high energy phosphate compounds and to the subsequent formation of inorganic phosphorus. These workers also showed that in the heart, deprived of its coronary blood supply for various periods of time the concentration of adenosine triphosphate (A.T.P.) rapidly declines. It would appear possible that at least part of the decline in the ability of the heart to use oxygen is related to the destruction of co-enzymes

and other compounds which require A.T.P. for resynthesis. In 1961 Guyton and Crowell reported the results of a rather ingenious series of experiments in haemorrhagic shock in dogs in which they were able to assess the degree of developing oxygen debt. These workers found that the accumulation of an oxygen debt of the order of 150 cc./kg. was uniformly fatal. The development of such an oxygen debt would obviously be accelerated in areas of more severely reduced blood supply such as the coronary circulation and the authors therefore suggested that the development of such a myocardial oxygen debt may account for the so-called irreversible phase of the shock syndrome. These authors speculated that the period of oxygen deficit might be responsible for myocardial cell damage or loss of some essential metabolic substrate that make it impossible for the tissue to utilise nutrients even after an adequate supply is re-instituted.

Although the preceding discussion of myocardial metabolism relates to animal experimentation, it seems likely that somewhat similar changes may well occur in man as a result of a decrease in coronary blood flow.

The development of a metabolic acidosis and lactic acidaemia as a consequence of inadequate blood flow in extracorporeal cardiopulmonary bypass is well-established (De Wall et al., 1956; Mackenzie et al., 1963). Therefore, althogh the demonstration of similar metabolic changes in the low flow state of cardiogenic shock may not be altogether surprising, they have not previously been documented in detail. The present findings in cardiogenic shock of a metabolic acidosis, lactic acidaemia, hyperglycaemia and elevated levels of inorganic phosphate are similar to those reported in animal shock experiments by McShan et al. in 1945. These workers produced shock in rats using the rotating drum method of Noble and Collip and drew attention to the progressive shift towards anaerobic metabolism in shock. Root et al. (1947) reported similar findings in both haemorrhagic and traumatic shock in dogs. In his Harvey lecture in 1943 Richards had already reported similar findings in four cases of human traumatic shock. The increase in serum inorganic phosphate levels was considered to be due to a steady progressive depletion of high energy

phosphate compounds; the progressive breakdown and ineffective resynthesis of adenosine triphosphate. Thrower et al. (1961) have shown in animal studies that metabolic acidosis, in itself, causes a direct depression of myocardial contractility and a diminished pressor response to both adrenaline and noradrenaline. Both these effects were reversed by correction of the acidosis by either intravenous sodium bicarbonate or the organic buffer THAM (2 - amino 2 - hydroxymethyl 1.3 - propanediol). There is therefore the development of a vicious cycle of events. The basic circulatory disturbance is a severe reduction in cardiac output and forward blood flow resulting in tissue hypoxia and a consequential metabolic acidosis which will in turn further impair the myocardial contractility. The presence of significant arterial hypoxaemia will further aggravate the progressive shift towards anaerobic metabolism. These events may well have their most serious regional effects on the coronary circulation.

The mobilisation of hepatic glycogen by adrenaline is generally regarded as being chiefly

responsible for the hyperglycaemia of haemorrhagic shock (Levenson et al. 1961). During animal studies in haemorrhagic shock, Manger et al. (1962) found that the blood sugar levels paralleled the increase in the plasma concentration of adrenaline. The factors responsible for the hyperglycaemia of cardiogenic shock are presumably similar, and the high blood sugar level may be regarded as being indicative of a raised level of circulating adrenaline. Although pulse wave analysis (table 4) suggests increased sympatho-adrenal activity, it is difficult to adequately separate the possible effects of catecholamines on the pulse wave contour from the effects of tachycardia per se. Adrenaline or increased sympathetic activity would be expected to shorten not only the duration of systole but also increase the M.R.P.R.A. However in the present context of cardiogenic shock the later measurement is already severely reduced by the primary failure of the pump mechanism and therefore cannot be regarded as a reliable index of the degree of sympatho-adrenal stimulation. Although a slight increase in plasma-

catecholamine concentration has been noted in myocardial infarction (Gazes et al. 1959), and a larger increase has been noted in haemorrhagic, anaphylactoid, and endotoxin shock, (Manger et al. 1957, Hökfelt et al. 1962), the actual levels do not appear to have been measured in cardiogenic shock.

The circulatory changes after acute myocardial infarction without associated shock are less marked, and in general they show an impairment of cardiac output and stroke volume associated with an increase in the systemic vascular resistance, although this rise is not sufficient to prevent some systemic arterial hypotension. Malmcrona and Varnauskas (1964) have recently drawn attention to the influence of body temperature on the regulation of the peripheral resistance after acute myocardial infarction. Two cases of myocardial infarction without shock (J.M. and G.D.) in the present study had raised body temperatures, and the measured circulatory changes agreed with those reported by these workers: both of these patients were hypotensive but were well orientated

with warm extremities and peri pheral pulses of good volume. In both cases, the cardiac output and stroke volume were well within the normal range, although the systemic vascular resistance was reduced, indicating vasodilatation and resulting in some degree of systemic arterial hypotension. The increased level of right atrial pressure in patients without co-existent shock has also been observed by Lee (1957) who considered this to be the most consistent haemodynamic finding in his patients. The results presented in the present study are in agreement with this view. Although the changes in cardiac output and systemic vascular resistance are highly variable, there is a consistent elevation in the central venous pressure. The measurements of left ventricular function in these patients show variable results but there is, in general some reduction in myocardial contractility and the degree of left ventricular work.

The respiratory and metabolic studies have revealed only one abnormality. Although the acid-base equilibrium is within the normal range in these patients

there is a mild reduction in the arterial blood oxygen tension levels.

Although the coronary blood flow is probably somewhat reduced in most patients as a result of some reduction in the aortic diastolic pressure, the maintenance of reasonably normal diastolic pressure time indices and only mild arterial hypoxaemia ensures a much more adequate nutritional and oxygen supply to the myocardium than is possible in cardiogenic shock.

Chapter II

An evaluation of oxygen therapy

Results

Statistical analysis, where relevant, are based on orthodox methods (Fisher 1945). Description of the significance of the changes following the administration of oxygen are based on the method of comparison of difference between the means of small samples. In the acute study of these patients the statistical significance given relates to the differences between the averages of the values of the control, air-

breathing period and those of the final 15 minutes of the period of high oxygen administration.

Detailed evaluation of oxygen therapy in this chapter is confined to a consideration of the "high" (approximately 100%) oxygen levels. Although some patients were also administered oxygen at a much lower inspired concentration their numbers are too small for detailed analysis. In addition this lower level of inspired oxygen was usually only given for 20 minutes and in retrospect, it must be questioned if true circulatory stability has been achieved. These results therefore are given in the individual tables when applicable in the appendix for their completion but have not been subjected to further detailed analysis. The full detailed individual results in all patients will be found in the appendix.

I. ACUTE STAGE (DAY 1) STUDIES

Table 3 summarises the circulatory, respiratory and metabolic changes that followed the administration of oxygen in high concentration in the acute stage. The average of the control values, breathing room air have

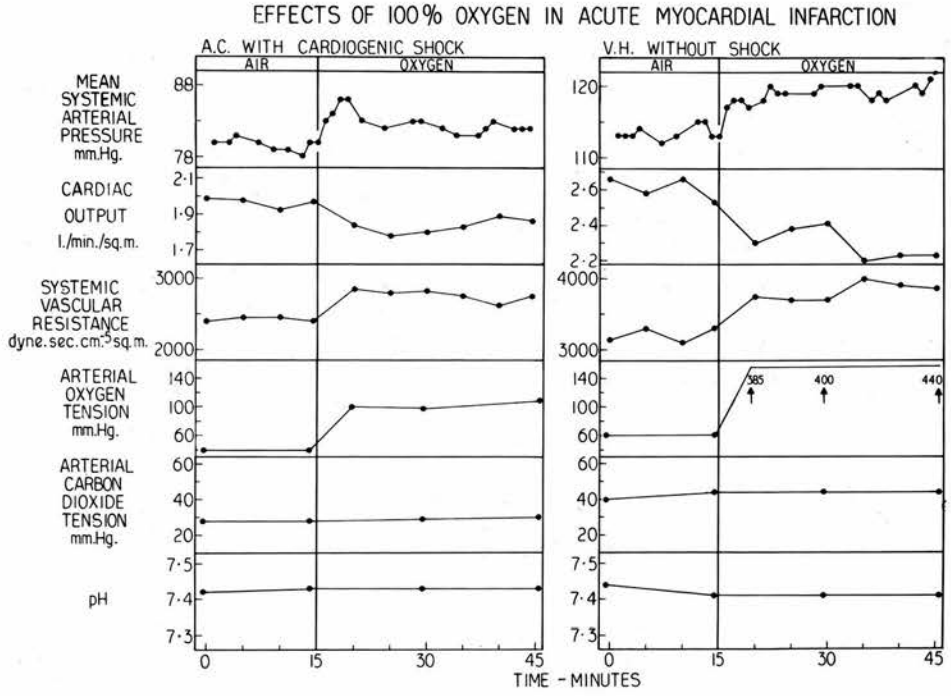


Fig. 17

The detailed investigation and response to 100% oxygen therapy in two typical cases of acute myocardial infarction, A.C. with shock and V.H. without shock.

been compared with the average of the values recorded during the final 15 minutes of oxygen therapy. The changes in left ventricular performance following oxygen administration in some of these patients is also shown in table 4. The circulatory, respiratory and metabolic effects of oxygen administration during this acute stage are also illustrated in figures 17 to 21. Fig. 17 illustrates the investigative details and fairly typical response in two patients.

A. CARDIOGENIC SHOCK

Circulatory Changes The response to breathing approximately 100% oxygen was studied in five out of the six shocked patients (Patient W.M. progressively deteriorated and died before the place of oxygen therapy could be evaluated). In one patient (A.S. aet. 74 years) oxygen breathing resulted in a prompt increase in systemic arterial pressure of 29 mm.Hg owing predominantly to an increase of about 50% in the cardiac output, as illustrated in figs 18 and 24. In the other four patients the response to oxygen was less striking. The heart rate showed no significant change, and the cardiac output

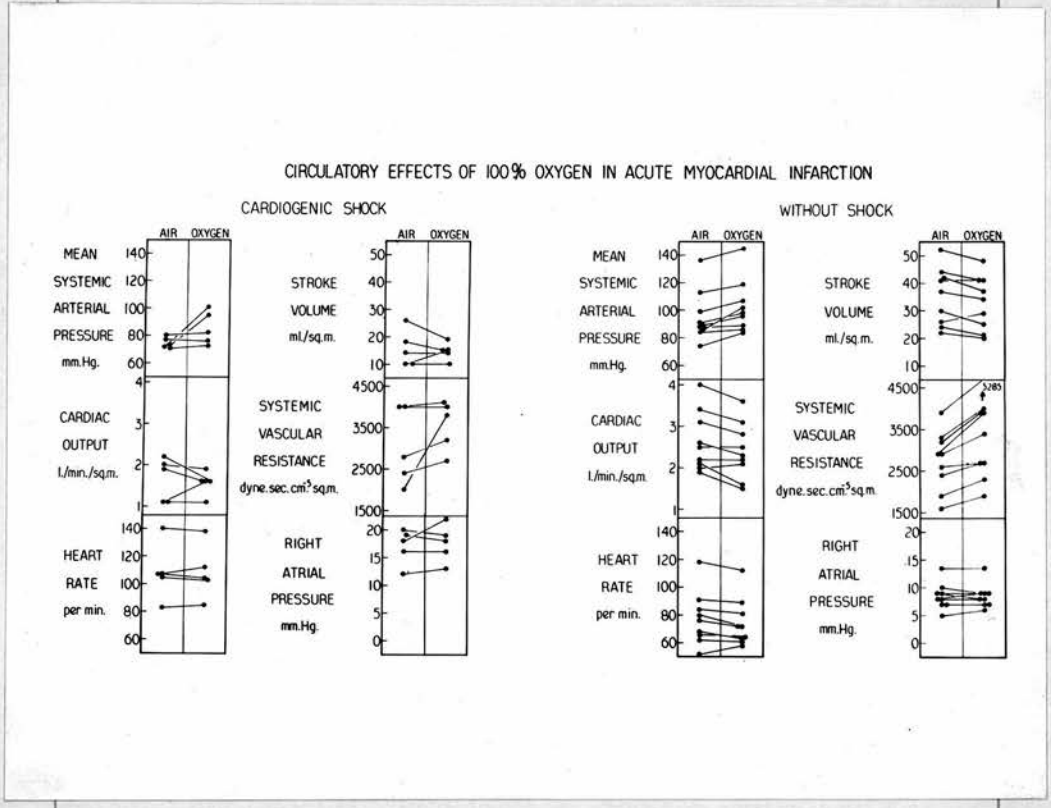


Fig. 18

The circulatory changes while breathing room air and the response to treatment with 100% oxygen in patients after acute myocardial infarction (Day 1) with and without shock.

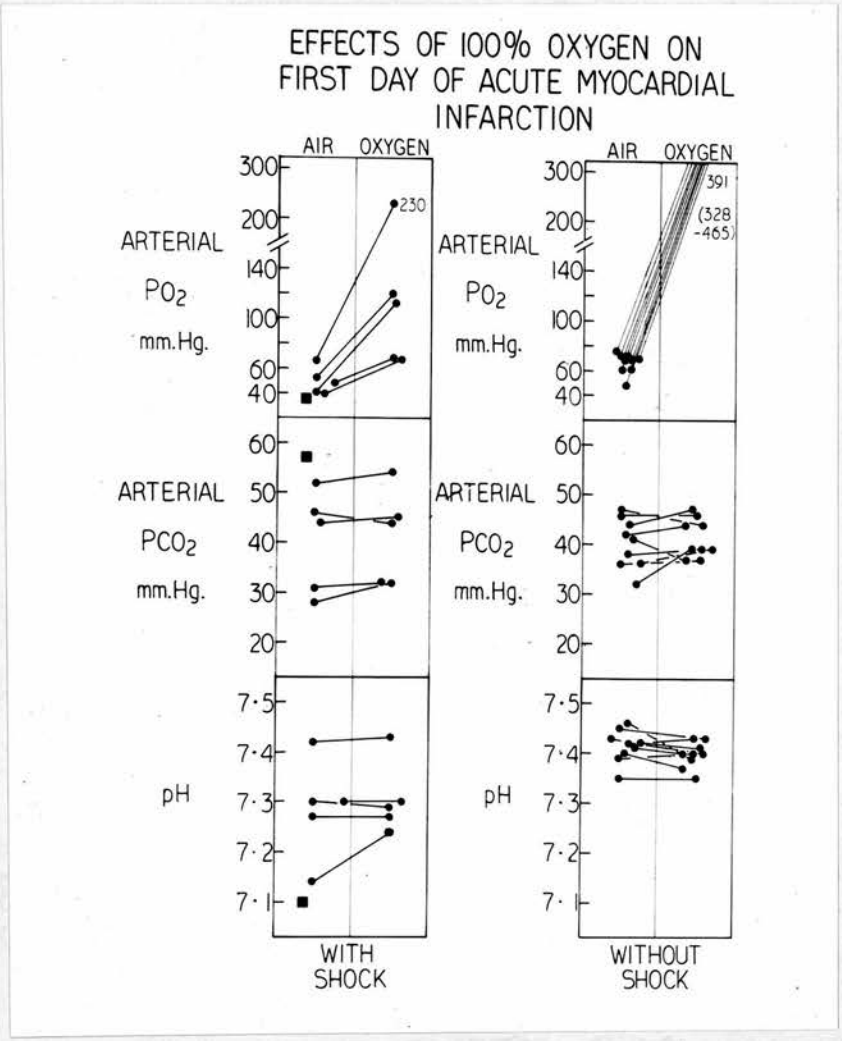


Fig. 19

The effects of breathing 100% oxygen on the arterial blood gas tensions during the 1st day after acute myocardial infarction with and without shock.

■ No figures available during oxygen treatment.

remained either unchanged or was slightly decreased. All four patients showed a small but consistent increase in systemic vascular resistance resulting in slight increase of the systemic arterial pressure in three instances. The right atrial pressure and cardiopulmonary blood volume remained unchanged after oxygen administration. The mean transit time was slightly reduced from an average value of 42.4 to 40.5 seconds (range 33.3 - 50.9).

Arterial blood gas tension and metabolic changes

The response to breathing high oxygen levels was studied in five of the six patients, and the striking finding was that, despite this high concentration of inspired oxygen, the changes produced in the arterial blood oxygen tension levels were surprisingly small, as shown in fig. 19. The actual change in arterial blood oxygen tension level in these five cases was from a mean value of 49 mm.Hg (range 39 - 66) to 119 mm.Hg (range 67 - 230). These changes

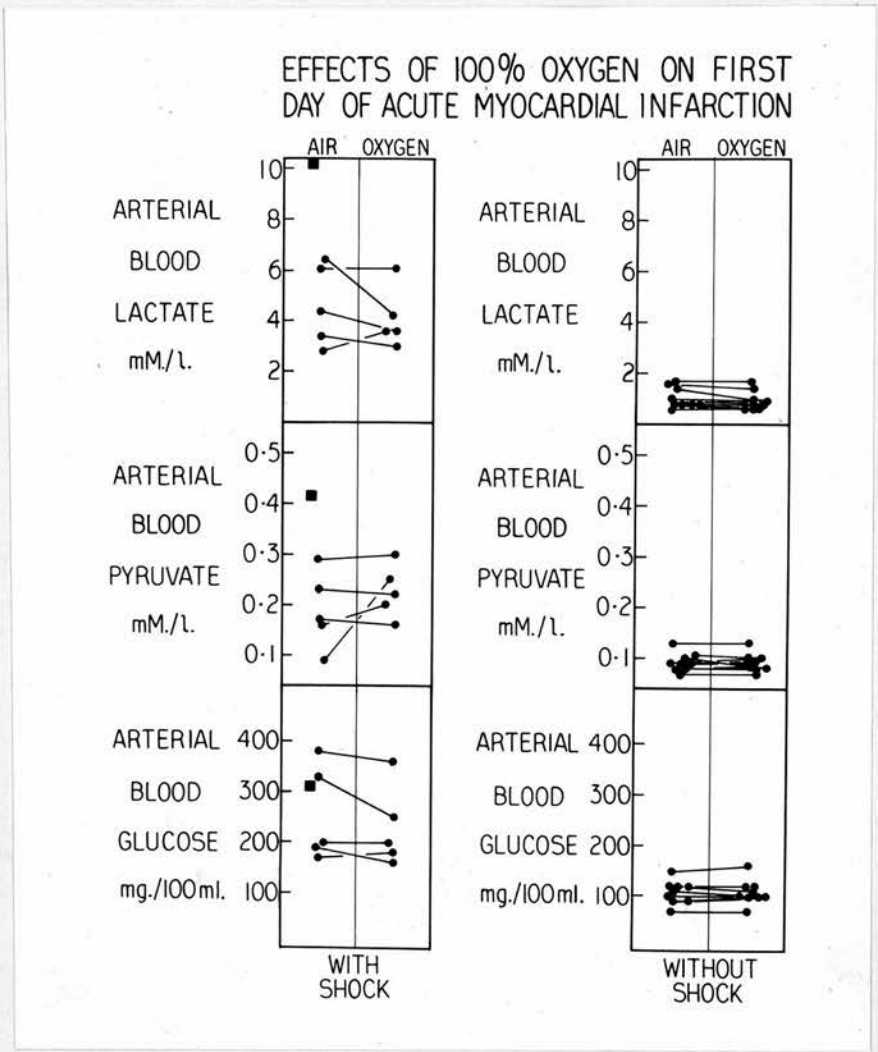


Fig. 20

The effects of breathing 100% oxygen on some metabolic measurements after acute myocardial infarction (Day 1) with and without shock.

■ No figures available during oxygen treatment.

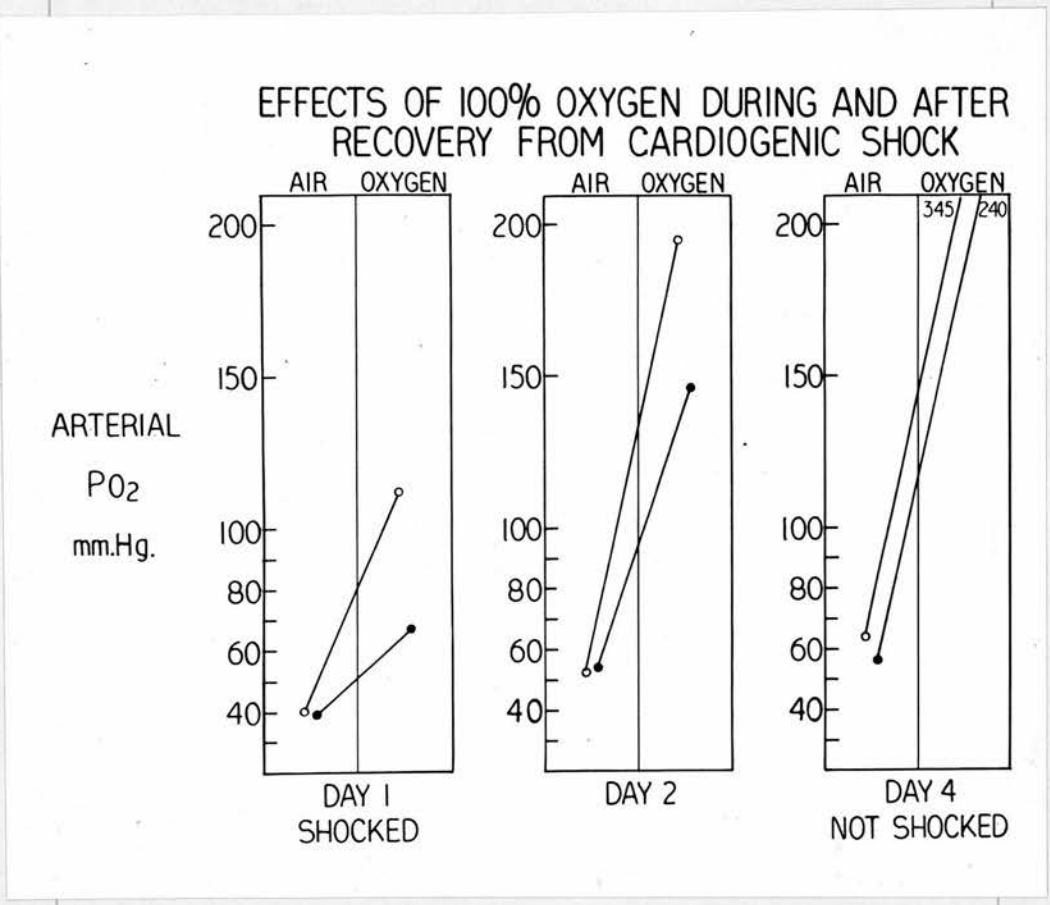


Fig. 21

The effects on the arterial blood oxygen tension of breathing 100% oxygen on two patients during cardiogenic shock and on subsequent days, during and after recovery from shock. (Patients A.S. and A.C.)

are in sharp contrast to the high values achieved after breathing oxygen in cases of acute myocardial infarction without shock (mean 391, range 328 - 465 mm.Hg). There was no significant alteration in the arterial blood glucose, lactate, pyruvate or other electrolyte concentrations when breathing oxygen as shown in fig. 20. Follow-up studies were carried out in two of these five patients, and the results of oxygen administration on subsequent days are illustrated in fig. 21. This shows a progressive return to a relatively normal increase in arterial blood oxygen tension when oxygen is administered after recovery from the state of shock.

B. ACUTE MYOCARDIAL INFARCTION WITHOUT SHOCK

Circulatory Changes The greatest changes observed during oxygen administration were in the heart rate, cardiac output, and systemic vascular resistance. The heart rate was decreased in eight of the nine patients; the

heart rate increased in case AS because ventricular extrasystoles developed when breathing oxygen. The cardiac output was reduced in six of the nine patients, and relatively unchanged in the other three. This significant reduction in cardiac output ($p < 0.01$) was due to the development of a relative bradycardia, the stroke volume showing no consistent or important change. The systemic vascular resistance was increased in all patients ($p < 0.01$), resulting in a small but significant increase in mean systemic arterial pressure ($p < 0.001$). The right atrial pressure and cardiopulmonary blood volume were uninfluenced by oxygen administration. The mean transit time was increased from a mean value of 18.7 to 20.4 seconds (range 13.3 - 36.2 seconds).

Arterial blood gas tension and metabolic changes

The response to oxygen breathing was identical in all nine patients. The arterial blood oxygen

tension levels increased from a mean value of 67 (range 47 - 77 mm.Hg) to a mean value of 391 mm.Hg (range 328 - 465 mm.Hg). This response, in terms of increase in arterial blood oxygen tension may be regarded as normal and it contrasts strikingly with the small degree of change found during cardiogenic shock.

C. ACUTE MYOCARDIAL INFARCTION WITH LEFT VENTRICULAR FAILURE BUT WITHOUT SHOCK

Two patients (I.S. and V.B.) with acute left ventricular failure following acute myocardial infarction but without signs of shock are included in this series for comparative purposes. The relevant abbreviated clinical details are given in table 2 and the average circulatory, respiratory and metabolic changes during room air breathing and following subsequent oxygen administration are shown in table 3. It is not the intention to discuss left ventricular failure in detail and these two patients have been included in the present series for illustrative and comparative purposes only. A summary of the

relevant findings in both patients are given in the appropriate tables as already mentioned but no further detailed circulatory, respiratory or metabolic data are provided in the appendix. The circulatory effects of oxygen administration are identical with those found in the uncomplicated group of patients. The major point of interest is to be found in the arterial blood oxygen tension values. Both patients were found to have low values when breathing room air. The response to "high" oxygen breathing in terms of an increase in arterial oxygen tension levels in both patients was similar to that found in the uncomplicated group of patients with acute myocardial infarction but without shock; the arterial oxygen tension rose to an average value of 350 mm.Hg. This again is in striking contrast to the relatively small increase produced in the presence of cardiogenic shock.

D. LEFT VENTRICULAR PERFORMANCE

The response to "high" oxygen administration in terms of left ventricular performance is shown in table 4 when the findings are again compared with

control observations carried out whilst breathing room air. The available data allowed this comparison to be made in three of the shocked patients and in seven of the non-shocked cases. The changes resulting from such oxygen therapy are minimal. In the presence of cardiogenic shock there is no significant change in the work performed by the left ventricle and likewise no significant change in the mean stroke power or ejection flow indices and no consistent change in the M.R.P.R.A. The diastolic pressure time index is slightly increased both per stroke and per minute in two of the three shocked patients.

The changes resulting in cases of acute myocardial infarction without shock are also small. There is no significant or consistent change in the mean stroke power, or the ejection flow indices nor in M.R.P.R.A. The left ventricular work both per stroke and per minute tended to be reduced but the changes were small. It is however, probably more important to note that the work of the left ventricle was never

increased. Although the systolic pressure time index tended to rise the increase noted both per stroke and per minute in the diastolic pressure time index was not only more striking and more consistent but at least from the point of view of the coronary arterial blood supply, probably more important.

II. FOLLOW-UP STUDIES

The detailed results of the effects of oxygen therapy during the follow-up studies are given individually in the appendix. A typical example of the effects of such treatment has already been shown in fig. 12. A summary of all the results acquired during the follow-up studies are illustrated in figures 22 and 23. Fig. 22 shows the circulatory response to high oxygen administration and fig. 23 shows the response to the removal of such oxygen therapy and a return to air breathing. These figures show that the circulatory changes are similar to those found in the acute stage, i.e. oxygen produced a reduction in heart rate and cardiac output with a slight increase in systemic vascular resistance and systemic arterial pressure.

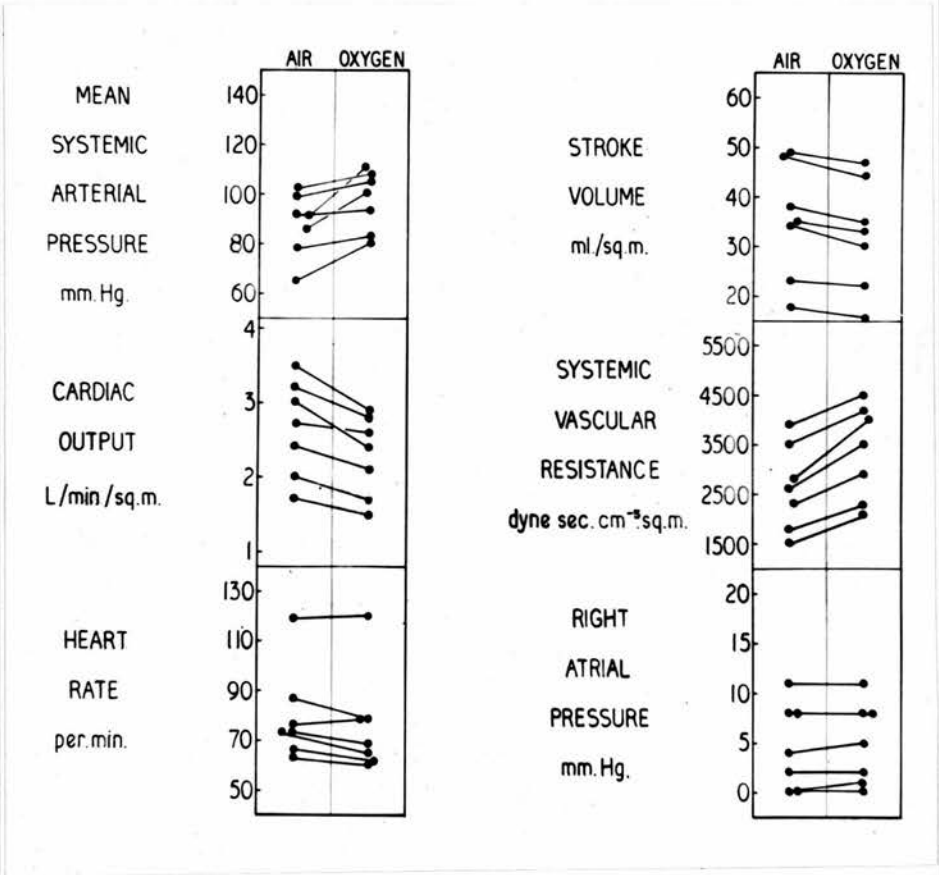


Fig. 22

Follow-up Studies: The circulatory effects whilst breathing room air and the response to the administration of 100% oxygen at various stages of recovery from acute myocardial infarction.

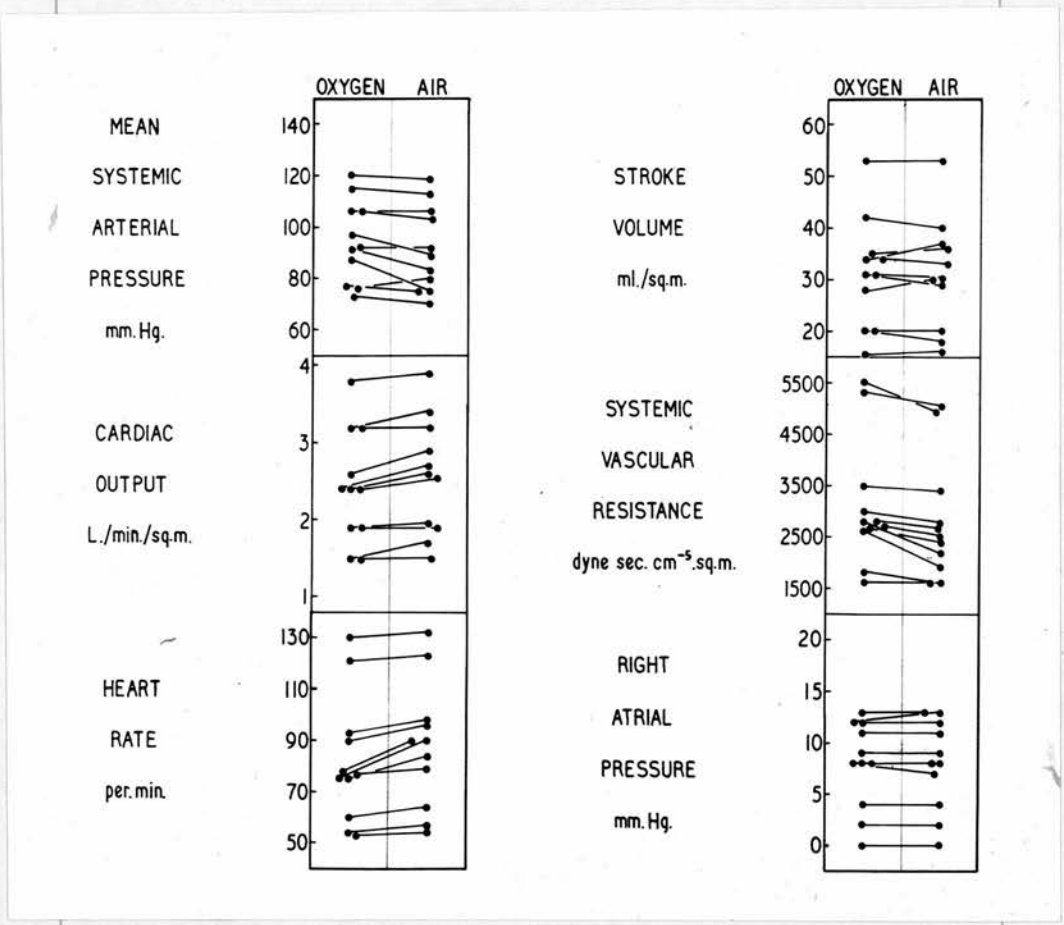


Fig. 23

Follow-up Studies: The circulatory effects whilst breathing 100% oxygen and the response of these changes to breathing room air at various stages of recovery from acute myocardial infarction.

Discussion

As already mentioned, the basis of rational oxygen therapy must surely depend on a knowledge of the underlying circulatory and arterial blood gas tension changes and their response to oxygen administration. One of the most striking findings in the present study was the severe degree of arterial hypoxaemia in the shocked group of patients. Equally important was the observation that the administration of oxygen in high concentration failed to cause the marked increase in arterial blood oxygen tension which is observed in normal subjects, in patients with myocardial infarction uncomplicated by shock and also in the majority of patients with respiratory failure caused by primary lung disease. The data available allows only a partial analysis of the possible underlying aetiological factors in this arterial hypoxaemia. The arterial blood carbon dioxide tension levels indicate that it was not due to an overall reduction of alveolar ventilation. It is helpful to consider first the situation when these shocked patients were breathing

high oxygen. It can be reasonably assumed that high levels of alveolar oxygen were achieved after 30 minutes even in alveoli with very low ventilation-perfusion ratios. Similarly, one can assume that there was no appreciable final oxygen tension gradient between alveolus and the end pulmonary capillary blood. The end pulmonary capillary blood oxygen content can therefore be calculated with reasonable accuracy as the respiratory quotient is not critical in the alveolar air equation at this high level. This especially may be held to apply in the present situation, in view of the relatively normal arterial blood carbon dioxide tensions. If a standard rate of oxygen uptake is assumed, then the mixed venous blood oxygen content can be determined by the Fick principle using the measured cardiac output. This knowledge of the oxygen content of the arterial blood, the mixed venous blood and the end pulmonary capillary blood allows the calculation of the amount of the continuous venous admixture (shunt) under these hyperoxic conditions. The details of the methods used in these calculations will be found in the appendix. The

calculated shunt was of the order of 39 - 10% of the cardiac output (mean 22%). Despite the assumptions necessary to these calculations there can be little doubt that about a quarter of the right heart output was passing through pulmonary vessels inaccessible to gaseous exchange. The disappearance of this remarkable shunting effect in 48 hours, as evidenced by the return to a normal response to breathing high oxygen concentrations in the two cases recovering from shock (Fig. 21) indicates a highly reversible abnormality. The sudden appearance and disappearance of new anastomotic blood channels short circuiting the alveoli appears most improbable. A more likely explanation would be the occurrence of collapse, blockage or oedema flooding of alveoli in some areas of lung in which there is continued circulation. It is feasible that there could be widespread disturbance of small areas of lung which are not evident clinically. The possibility of widespread absorption-collapse occurring after administration of oxygen and causing shunting is considered unlikely in view of the fact that the arterial blood oxygen tension remained unchanged between the five and 30 minute

sampling after the onset of oxygen therapy.

The demonstration of this remarkable shunting effect in cardiogenic shock is in striking contrast to the findings in the two patients suffering from acute left ventricular failure and pulmonary oedema following acute myocardial infarction. Although the arterial blood oxygen tension was somewhat depressed in both these patients, the response to high oxygen administration was similar to that found in the non-shocked patients or indeed in normal subjects; the arterial oxygen tension increased to 350 mm.Hg showing that the venous admixture or shunt (perfusion inaccessible to pulmonary gas exchange) was not greatly raised (5 and 8%). This suggests that the abnormality causing this shunt is not solely related to the raised pressures behind the left heart and the resultant lung changes but to some other or additional phenomenon.

Although it appears likely that there is in fact considerable further venous admixture when breathing room air due to under-ventilation of perfused alveoli, it has been assumed in further calculation that the degree

of shunt is identical in both situations, i.e. breathing room air and high oxygen concentrations. This assumption allows the calculation of the alveolar-arterial oxygen tension gradient in these patients whilst breathing room air. These calculations are again illustrated in the appendix. In this way it can be shown that, even when allowance is made for the large shunt demonstrated in the hyperoxic studies there is a very large component of the alveolar-arterial oxygen tension gradient still unexplained (16 - 65 mm.Hg). This further gradient could be due to underventilated but perfused alveoli or to the impairment of oxygen transfer or to a combination of these disturbances. The present data does not allow of a further differentiation.

Freeman and Nunn (1963) showed a great increase of physiological dead space in dogs with experimental haemorrhagic shock. Although this could be partly due to hyperventilation of perfused alveoli, it was probably mainly due to non-perfusion or underperfusion of ventilated alveoli. No measurements of expired air were made in the present studies, and the physiological

dead-space is not known. But if we assume that such a disturbance occurs in cardiogenic shock, then a considerable amount of unperfused lung will be functionless as regards gas transfer. Again if, as appears likely, there is considerable further venous admixture when breathing air owing to underventilation of perfused alveoli, there will be an even larger total fraction of functionless lung and a great reduction of the alveolar-capillary surface and associated pulmonary-capillary blood volume (Roughton and Forster, 1957) where efficient gas transfer can take place. Donald et al. (1952) showed a large reduction in the diffusing capacity in severe generalised obstructive respiratory disease when the physiological dead space was of the order of 40 - 60% and the venous admixture (including disturbed V/Q relationships and true shunt) was 20 - 45%.

The persistence of a considerable alveolar-arterial oxygen tension gradient while breathing air in patients recovering from cardiogenic shock, who no longer show relative unresponsiveness to high oxygen levels owing to "pure" shunting effect, suggest that

maldistribution of blood and gas, with perhaps an important secondary effect on gas transfer, continues for some days.

The variability in the circulatory response to oxygen in the presence of cardiogenic shock is not surprising when correlated with the slight changes produced in the arterial blood oxygen tension levels. We are not, in these circumstances, dealing with the circulatory effects of high oxygen but rather with the circulatory effects of a small increase in arterial blood oxygen tension. Although there is a slight increase in systemic arterial pressure and vascular resistance, the changes in heart rate and cardiac output are more variable. In one shocked patient (A.S.) oxygen administration, while increasing the arterial blood oxygen tension from 39 to 67 mm.Hg resulted in an increase of cardiac output of about 50%. The measurements of left ventricular performance (table 4) indicate no significant change in these patients after breathing oxygen and in particular there is no increase in the degree of left ventricular work performed. Indeed in two out of the three shocked cases in which left ventricular performance was studied the

diastolic pressure time indices, both per stroke and per minute, were increased after oxygen therapy, thus suggesting an actual increase in coronary blood flow. These patients are therefore in urgent need of oxygen and this must be given in a very high concentration, because, even then it is only partially effective. Such oxygen administration will not only increase the oxygen tension gradient between the arterial blood and the tissues but will increase the coronary arterial perfusion pressure and blood flow. These beneficial effects will be achieved without an increase in heart work.

The circulatory effects of high oxygen administration in patients with acute myocardial infarction but without associated shock are essentially similar to the results reported in normal man (Daly and Bondurant, 1962, and Eggers et al. 1962). Again these circulatory changes are similar during the acute and follow-up studies. There is a significant increase in systemic arterial pressure and vascular resistance with a small decrease in heart rate resulting in a reduction of cardiac output. The measurements of left ventricular work in the acute stage studies reveal no significant

change following oxygen administration. The diastolic pressure time indices were increased in six of the seven patients in which pulse wave analysis was undertaken. High oxygen administration has already been noted to produce the normal marked increase in arterial blood oxygen tension in these patients during both the acute phase and follow-up studies. There is therefore some apparent marginal benefit to be derived from the routine therapeutic use of oxygen in uncomplicated myocardial infarction; the increased oxygen tension gradient between the arterial blood and the tissues must result in an increased supply of oxygen to the ischaemic heart muscle; and the increased diastolic pressure time indices should also ensure an actual increase in coronary blood flow. These effects will be achieved without an increase in heart work.

Chapter III

The change in the pathophysiological state with time and recovery

RESULTS

The detailed individual results are given in the appendix. The mean values for each period of study in

each patient are given in table 5. The values quoted are the means of the figures recorded during the time of breathing room air and therefore represent a period of 15 minutes during the initial acute stage and a period of 30 minutes during subsequent follow-up studies. The standard error of the mean and the standard deviation of the observations during each period are shown. These results related to time are also represented in figures 24 to 31.

CARDIOGENIC SHOCK

Circulatory Changes Follow-up studies were available in two cases (A.S. and A.C.). Each of these cases were again restudied on day 2 and subsequently on day 4. The patients both remained very ill on day 2 although not fulfilling all the criteria necessary for a diagnosis of shock. On day 4 there was complete clinical recovery from all signs of shock.

Recovery from shock in patient A.S. as illustrated in figure 24 (a, b and c) was associated with an increase in mean systemic arterial pressure, (72 to 91 mm.Hg). This was due predominantly to an increase in cardiac output (1.08 to 1.69 l./min./sq.m.). The

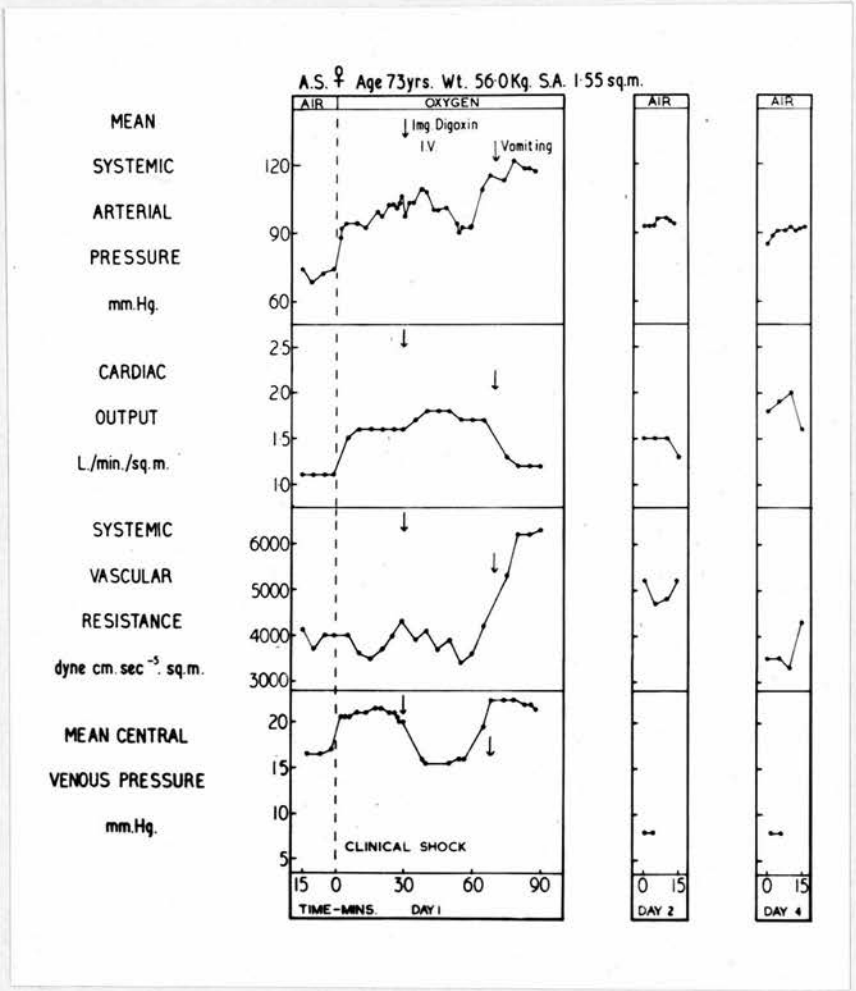


Fig. 24 (a)

The circulatory changes during and after recovery from shock. The patient (A.S.) remained very ill on day 2 but was completely free of all clinical signs of shock on day 4. The circulatory effects of oxygen, intravenous digoxin and also the striking circulatory effects of vomiting on day 1 are shown.

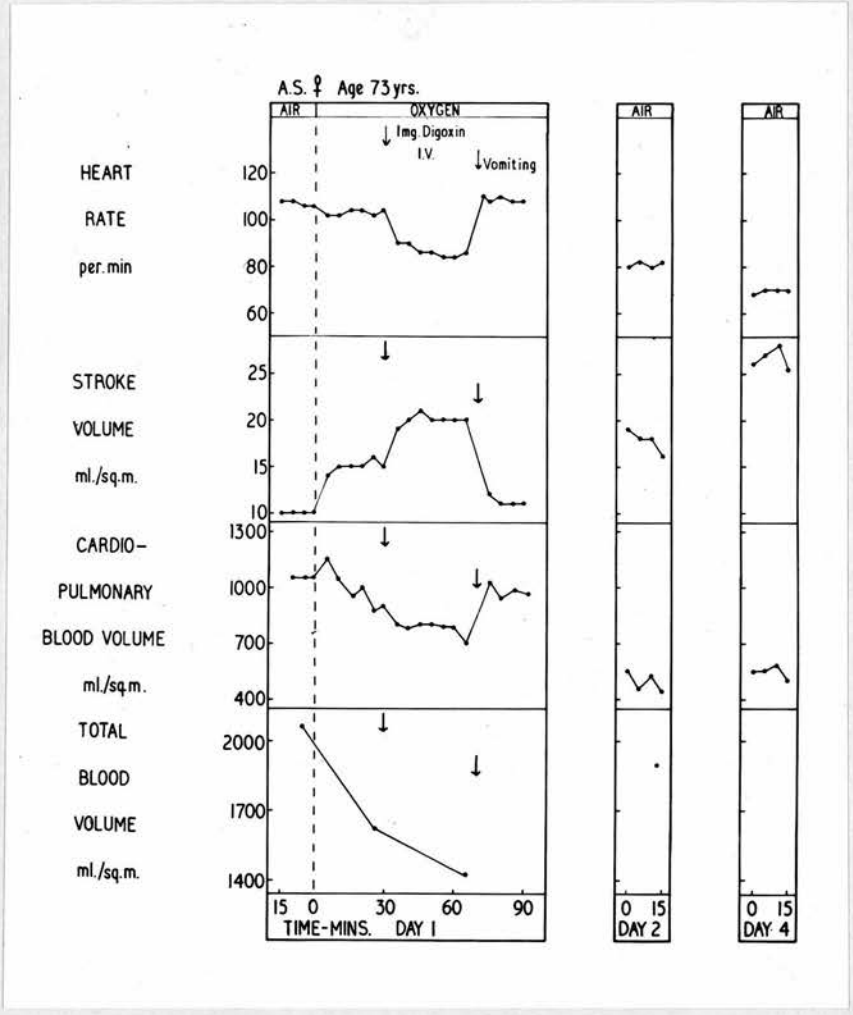


Fig. 24 (b)

Some further circulatory changes in patient A.S. during and after recovery from shock.

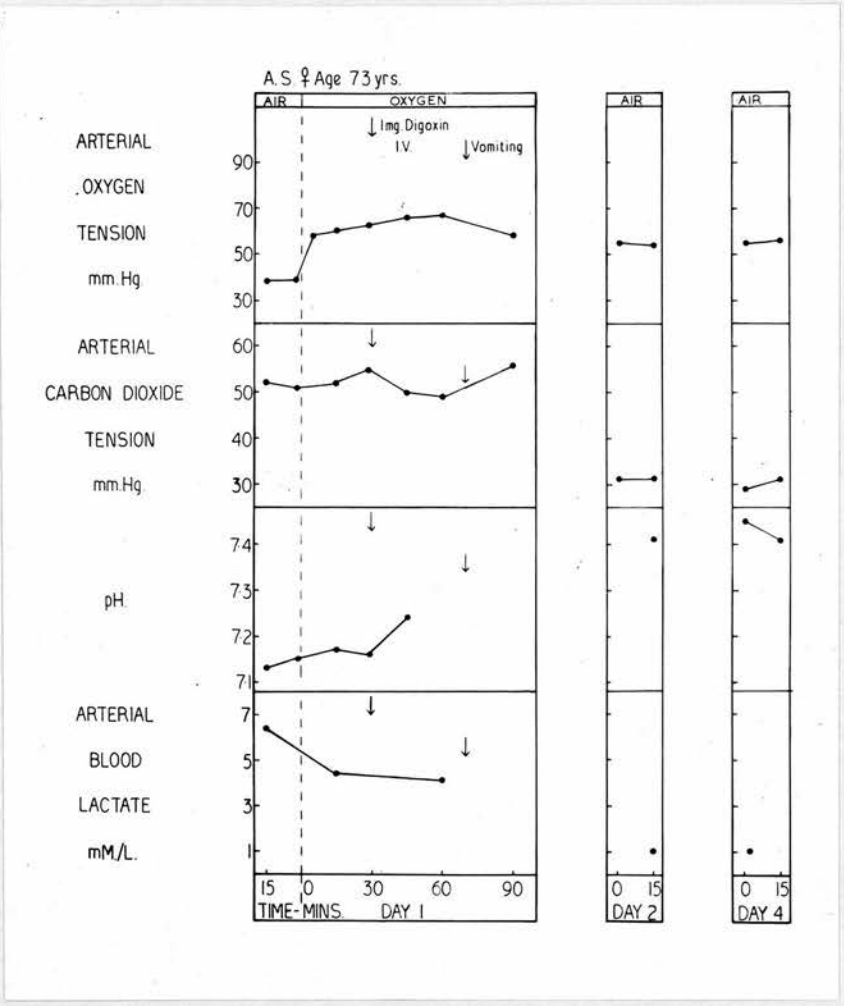


Fig. 24 (c)

The arterial blood gas tension and arterial blood lactate changes during and after recovery from shock in patient A.S.

heart rate decreased from 107 to 73 beats per minute and the stroke volume increased from 10 to 23 ml./sq.m. The systemic vascular resistance increased slightly in day 2, but on day 4 with complete recovery from shock the level was almost identical with the "shock" value (i.e. 3,996 during shock as compared with 3,930 dyne.sec.cm^{-5}.sq.m. after recovery). The mean transit time decreased from 59.2 to 18.1 seconds and the central venous pressure fell from 18 to 8 mm.Hg. The blood volume estimation showed no marked change. The major haemodynamic changes associated with recovery in this patient were therefore an increase in systemic arterial pressure due predominantly to an increase in stroke volume and cardiac output with a reduction in heart rate and central venous pressure with little significant change in overall vascular resistance.

Recovery from shock in patient A.C. as illustrated in fig. 25 (a, b and c) was associated with less dramatic changes and indeed this patient remained very ill although not shocked on day 4. This patient was in fact less well than the previous patient (A.S.) during the final

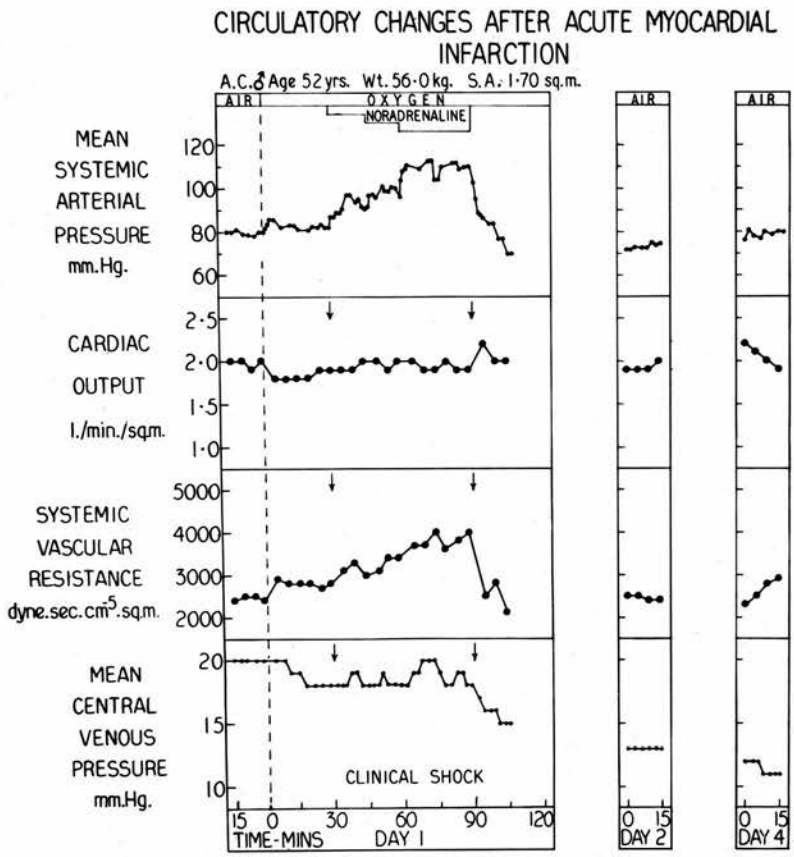


Fig. 25 (a)

The circulatory changes during and after recovery from shock. The patient (A. C.) although remaining very ill on days 2 and 4 did not present the clinical features of shock. The circulatory effects of oxygen and noradrenaline on day 1 are shown.

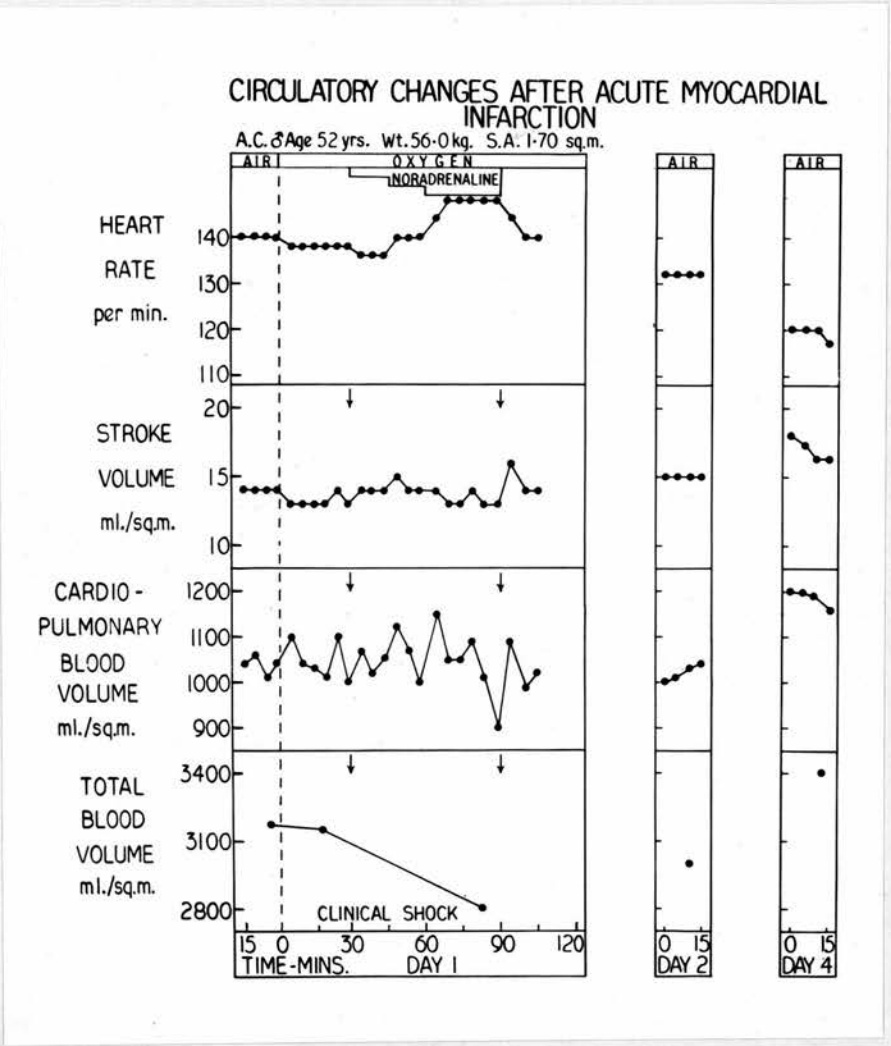


Fig. 25 (b)

Some further circulatory changes in patient A. C. during and after recovery from shock.

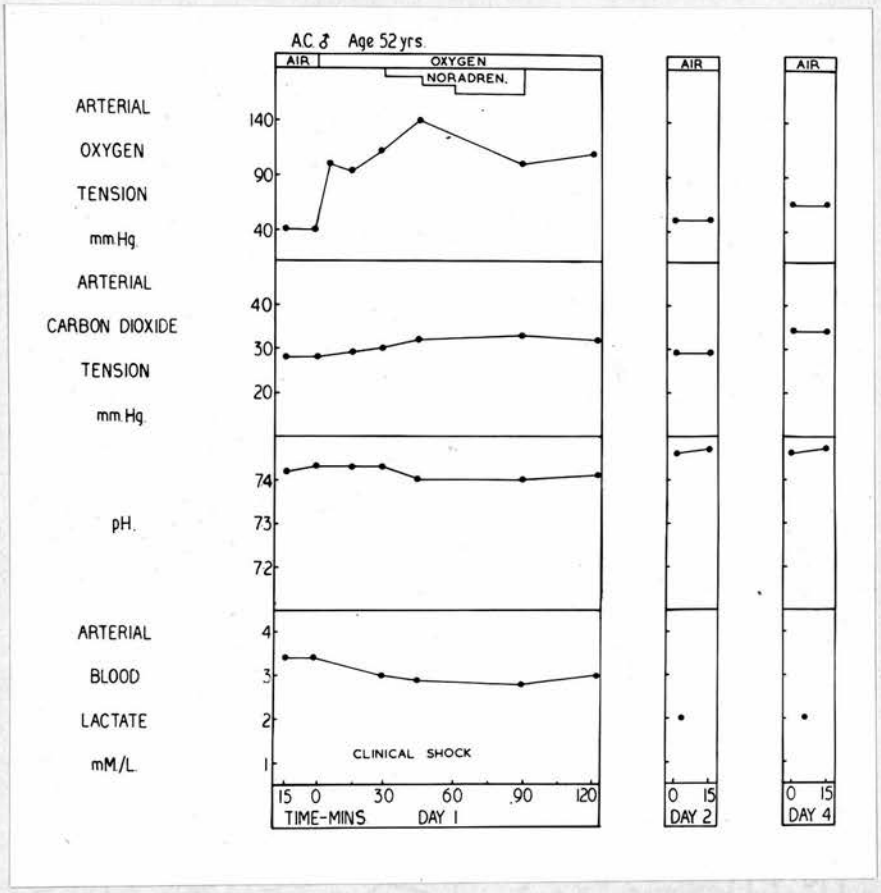


Fig. 25 (c)

The arterial blood gas tension and arterial blood lactate changes during and after recovery from shock in patient A. C.

haemodynamic study. The increase in mean systemic arterial pressure was small (80 to 82 mm.Hg). The cardiac output showed no significant change (1.97 to 2.01 l./min./sq.m.). The heart rate decreased from 140 to 119 beats per minute and the stroke volume increased from 14 to 17 ml./sq.m. The systemic vascular resistance increased slightly (2,434 to 2,823 dyne.sec.cm^{-5}.sq.m.). The mean transit time in fact increased from 31.6 to 36.7 seconds and the central venous pressure fell from 20 to 11 mm.Hg. The blood volume estimations showed no marked changed. The major haemodynamic changes associated with recovery in the patient were therefore a reduction in central venous pressure, a slight drop in heart rate and an increase in stroke volume. The total cardiac output was substantially unchanged and the systemic vascular resistance showed a slight increase.

Serial cardiopulmonary blood volume estimations cannot truly be compared as the actual siting of catheter may well be quite different in two studies.

TABLE 6. MEASUREMENTS OF LEFT VENTRICULAR PERFORMANCE DURING AND AFTER RECOVERY FROM SHOCK

PATIENT	DAY	CLINICAL STATE	CARDIAC OUTPUT l./min./sq.m.	HEART RATE per min.	STROKE VOLUME ml./sq.m.	RIGHT ATRIAL PRESSURE mm.Hg	PRESSURES mm.Hg		CYCLE DURATION sec.		DIASTOLIC DURATION sec./min.	M.R.P.R.A. mm.Hg/sec.	LEFT VENTRICULAR WORK		PRESSURE TIME INDICES				MEAN EJECTION FLOW INDEX ml./sec./sq.m. Index	MEAN STROKE POWER INDEX g.m./sec./sq.m.
							M.S.E.P.	M.A.D.P.	SYST.	DIAST.			Minute Kg.m./sq.m.	Stroke g.m./sq.m.	SYSTOLIC		DIASTOLIC			
															Min.	Stroke	Min.	Stroke		
A.C. (M) 52 years	1	Shock	1.97	140	14	20	80	73	0.12	0.31	43.4	472	1.608	11.5	1008	7.2	2296	16.4	117	96
	2	No shock but very ill	1.94	132	15	13	79	71	0.16	0.30	39.6	486	1.741	13.2	1399	10.6	2297	17.4	94	83
	4	No shock but very ill	2.01	119	17	11	88	79	0.20	0.30	35.7	406	2.105	17.7	1833	15.4	2428	20.4	85	89

Measurements of left ventricular performance in patient A.G. during both the shocked state and after recovery are shown in table 6. Recovery from shock in this patient, was associated with a progressive return towards normal of the systolic pressure time indices with an increase in left ventricular work. There was however a progressive deterioration in myocardial contractility as judged by the reduction in the M.R.P.R.A. and the mean ejection flow index. The capacity to perform work as judged by the mean stroke power index was also further reduced. These changes indicate a progressive deterioration of myocardial function.

Arterial blood gas tension and metabolic changes In each of these patients (A.S. and A.G.) recovery from shock was associated with a reduction of the arterial hypoxaemia and the approximation of the arterial blood oxygen tension levels to a more normal value (as shown in figures 24 and 25). The pH and arterial blood lactate, pyruvate and phosphate levels also returned to normal. In contrast, these patients who died shortly after

investigation and treatment (J.F., M.R. and A.F.) showed a progressive increase in metabolic acidosis and lactic acidaemia or at least no amelioration of the state.

ACUTE MYOCARDIAL INFARCTION WITHOUT SHOCK

Circulatory Changes

Heart rate Recovery was usually associated with a drop in heart rate if tachycardia had initially been present. However the acute attack was associated with a relative bradycardia (less than 70 beats per minute) in four patients and recovery was associated with an increase in rate in three of these cases.

The mean systemic arterial pressure showed no consistent change with recovery as shown in figure 26. In two patients the mean systemic arterial pressure, having been initially low during the acute study (88 and 89 mm.Hg respectively) was even further reduced at follow-up after one month (78 and 65 mm.Hg). It is of some interest to note that this reduction in blood pressure was associated with an increase in cardiac output in one patient (M.L.) and to

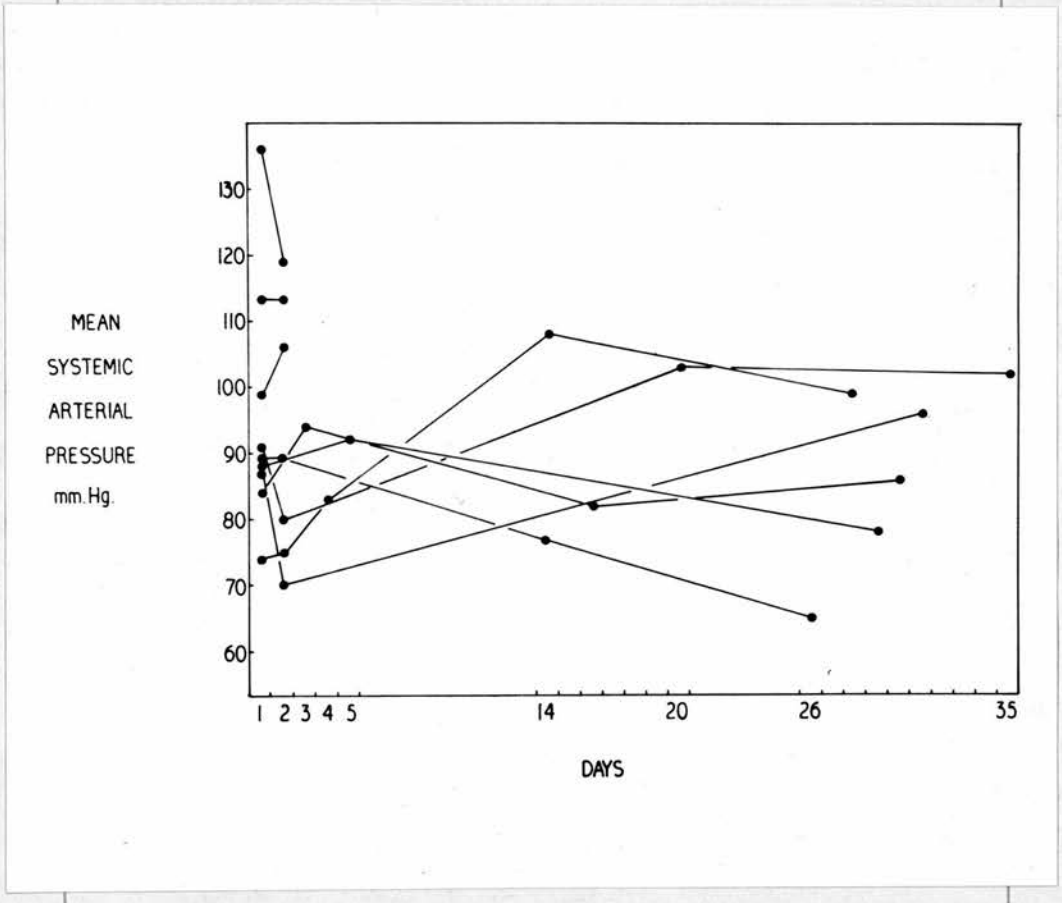


Fig. 26

Acute myocardial infarction without shock - the sequential changes in mean systemic arterial pressure with recovery.

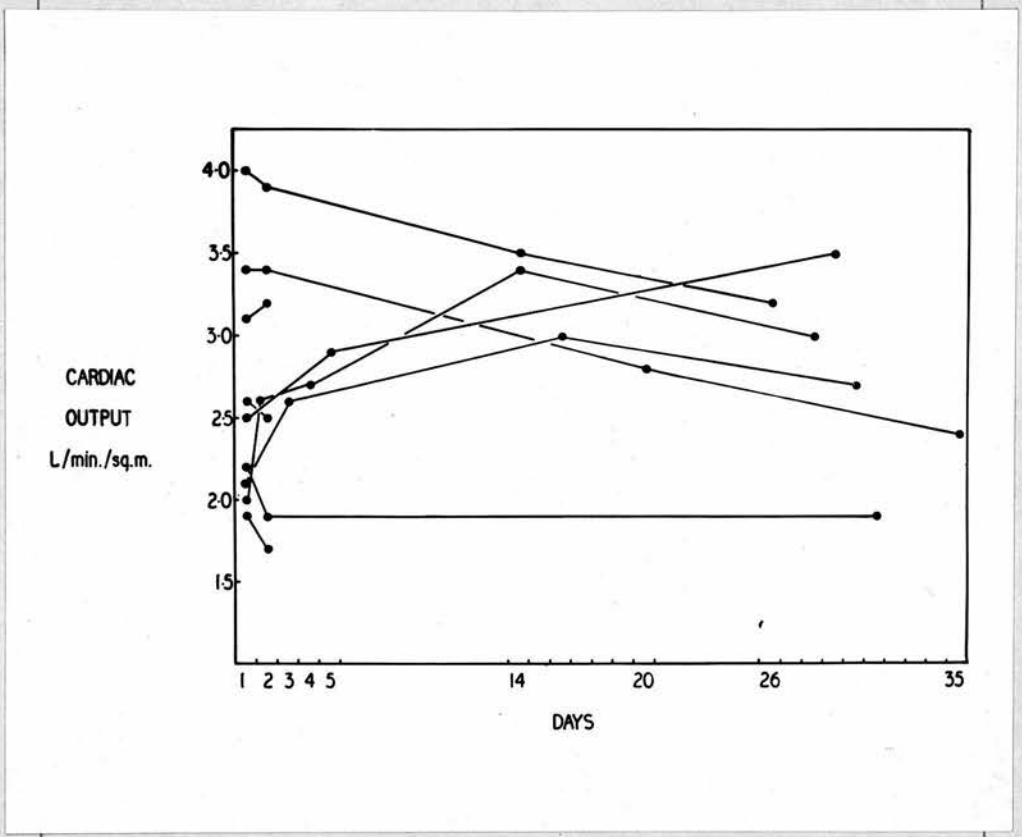


Fig. 27

Acute myocardial infarction without shock -
the sequential changes in cardiac output with recovery.

reduction in the second (J.M.). A significant increase in systemic arterial pressure was noted in three patients during follow-up after one month: these three patients likewise revealed variable changes in cardiac output - falling in two and increasing in one case.

The cardiac output showed variable changes with recovery as shown in fig. 27. The cardiac output was initially low in four of the patients restudied after one month and recovery was found to be associated with an increase in output in three of the four patients. The fourth patient showed a slight reduction (2.20 falling to 1.91 l./min./sq.m.). In a further two patients, the cardiac output had been found to be well within the normal range during the acute study (4.04 and 3.42 l./min./sq.m.). Both of these patients exhibited systemic arterial hypotension at this time and clinically were noted to be pyrexial with a warm periphery and full bounding good volume pulses. Recovery

after one month in each case was associated with a fall in cardiac output. In one patient this reduction in output was accompanied by a reduction in arterial pressure but in the second patient there was an increase in arterial pressure. The stroke volume showed a progressive increase towards normal in all those patients in whom it was initially reduced (as is well shown in fig. 28) and a variable change in the remaining cases. It is noteworthy that the only patient who subsequently died in this uncomplicated group of patients had the lowest value for stroke volume (22 ml./sq.m.). The value is comparable with that found in the presence of cardiogenic shock.

The systemic vascular resistance changes with recovery are highly variable as shown in fig. 29. The persistence of significant systemic arterial hypotension following recovery from acute myocardial infarction was on each of three occasions associated with a cardiac output

with the normal range but with a reduction in systemic vascular resistance.

The elevated central venous pressure fell on recovery in all patients except one. This exceptional case (A.S.) was associated with a persistent impairment in cardiac output after one month (2.20 during acute stage and 1.91 l./min./sq.m. after one month). This reduction in cardiac output was associated with an elevated systemic vascular resistance resulting in only a mild degree of systemic arterial hypertension (96 mm.Hg).

The mean transit time (M.T.T.) decreased with increasing recovery with one exception. This exceptional case was again that of A.S. in whom the M.T.T. increased in association with a reduction in cardiac output.

Arterial blood gas tension and metabolic changes with time With one exception, there was a progressive increase in the arterial blood oxygen tension towards normal values during recovery from myocardial infarction. The individual estimations relevant to

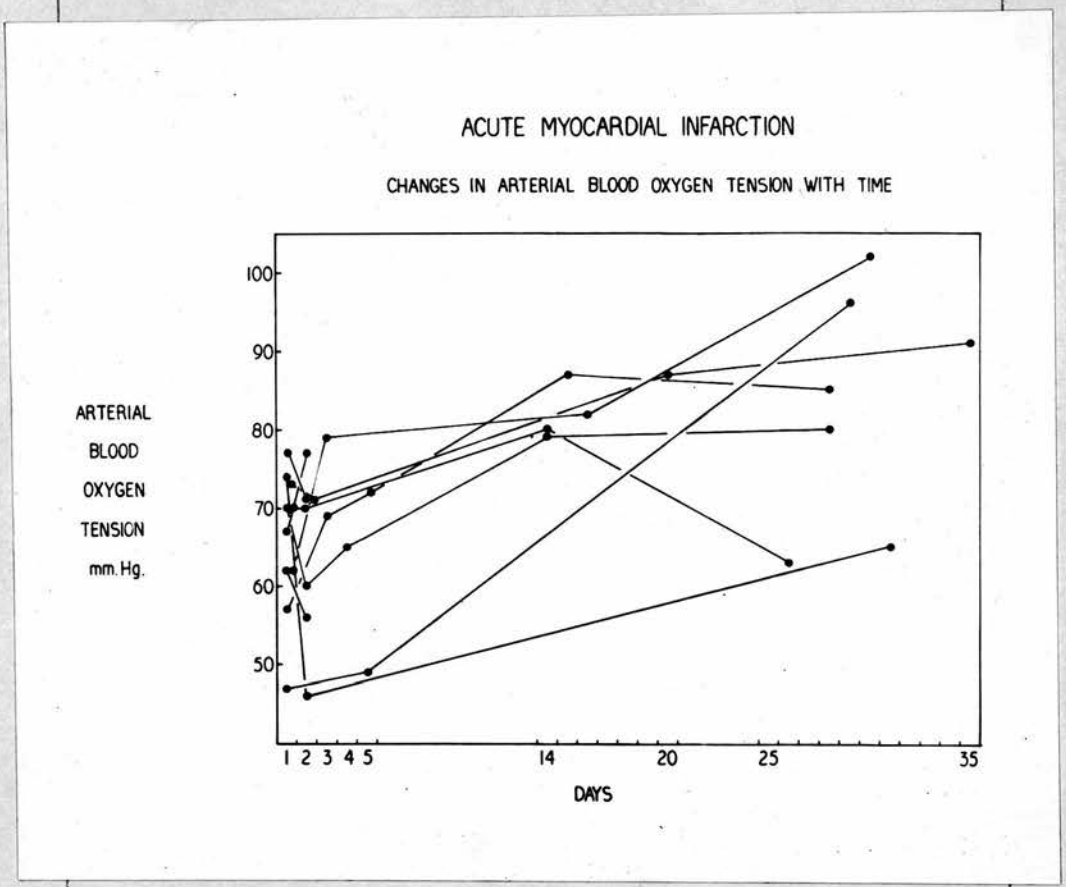


Fig. 30

Acute myocardial infarction without shock - the sequential changes in arterial blood oxygen tension levels with recovery.

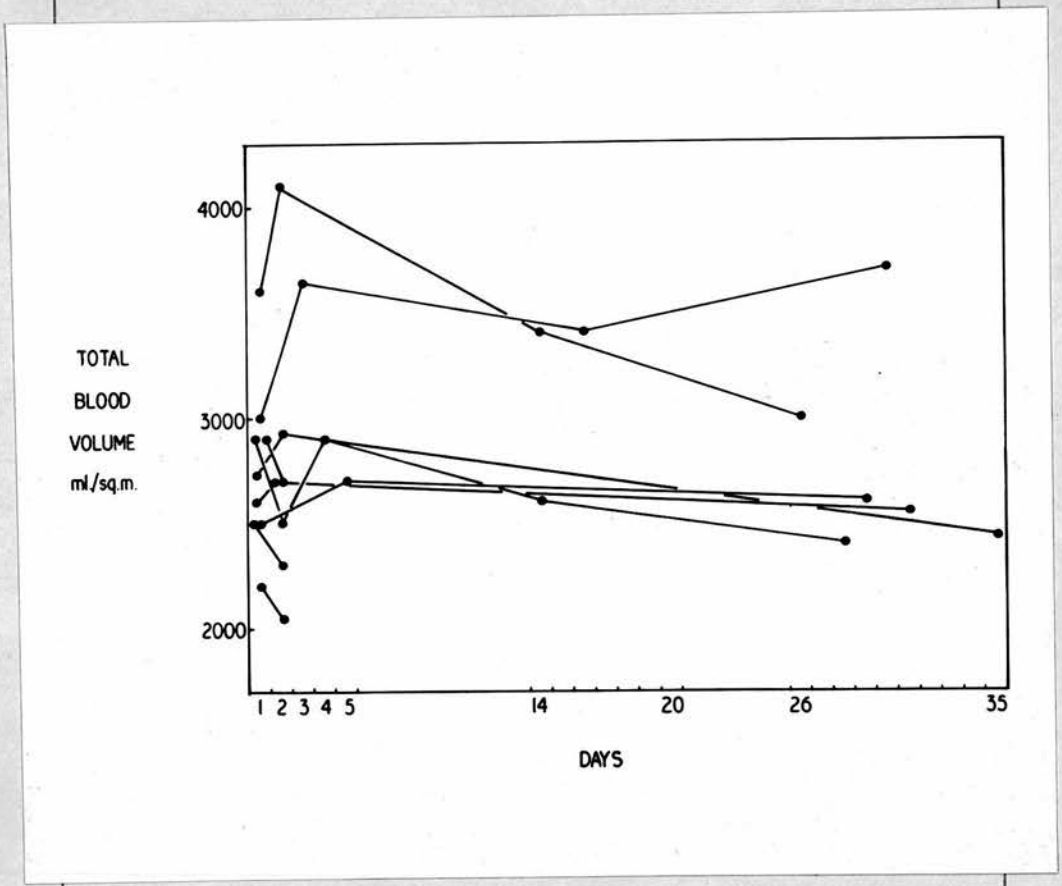


Fig. 31

Acute myocardial infarction without shock - the sequential changes in total circulating blood volume with recovery.

each patient are shown in the appendix and are illustrated diagrammatically in fig. 30. Patient J.M. represented the sole exception in which the arterial blood oxygen tension fell from 70 during the acute stage to 63 mm.Hg after one month. There was no apparent reason, either technical or clinical, to be found for this individual variation.

Total circulating blood volume changes with time show no consistent or significant change as shown in fig. 31.

DISCUSSION

When discussing the underlying pathophysiology of cardiogenic shock, it was suggested that the results indicated not only a severe degree of impairment of left ventricular function but also inadequate compensatory homeostasis. The results reported in the two cases who were restudied after recovery from shock lend further support to this contention. The most consistent change in the circulatory state following recovery from shock was a reduction in the heart rate and central venous pressure with an increase in stroke volume. The systemic vascular resistance showed no significant

change in one patient and a very slight elevation with recovery in the second. Further evidence incriminating inadequate peripheral compensation is afforded by the measurements of left ventricular performance in one patient (A.C.) during and after recovery from shock. These measurements indicate progressive deterioration rather than improvement in myocardial performance with recovery from clinical shock, and would suggest that some additional peripheral factor also contributed to the production of the shocked state. Fries et al. (1952) reported measurements of the circulatory state both before and during shock in one patient and noted not only a drop in cardiac output but also a reduction in systemic vascular resistance with the development of shock. Smith et al. (1954) likewise measured the circulatory state during and after recovery from shock in one patient and reported findings similar to those of the present study. There is therefore some convincing evidence to incriminate the peripheral circulation to some extent in the pathogenesis of cardiogenic shock,

although the primary defect must remain an acute and severe reduction of stroke volume and forward blood flow.

The disappearance of the remarkable arterio-venous shunting of blood in the lungs with recovery from shock has already been discussed. The arterial hypoxaemia, metabolic acidosis and lactic acidaemia have all been shown to gradually decline in severity with progressive recovery. In contrast to these findings on recovery the steady progression of the state of shock has been shown to be associated with a progressive increase in the severity of the metabolic acidosis and the lactic acidaemia or at least no amelioration in these changes prior to death. These findings are in agreement with the opinion recently expressed by Broder et al. (1964) that the excess lactate level (Huckabee, 1958) can be regarded as the most sensitive measure available for the assessment of the degree of oxygen debt, which can likewise be regarded as the fundamental defect that characterises shock, regardless of cause. Indeed the degree of lactic acidaemia can probably rightly be regarded as the most sensitive index available to assess

the severity and degree of circulatory failure and for the physician, it could well serve as the best objective guide to treatment and prognosis.

The most consistent change in the circulatory state during progressive recovery from acute myocardial infarction without associated shock is to be found in the central venous pressure and stroke volume. The acute elevation and progressive return towards normal of the central venous pressure was likewise reported by Lee (1957). Recovery was associated with a progressive return towards normal of the stroke volume in all cases in which it was initially reduced. Similar recovery stroke volume observations were noted by Lee (1957), Broch et al. (1959), and Murphy et al. (1962).

It is obvious that the circulatory measurements of most value from the prognostic point of view are indeed the central venous pressure and the stroke volume. The highest values for the central venous pressure and the lowest values for stroke volume are to be found in the most severely ill or shocked patients. It is of some interest to note that the only patient who subsequently died in the uncomplicated group of cases had the lowest

value for stroke volume recorded in this group. This value was 22 ml./sq.m. which is comparable with some cases of cardiogenic shock.

The systemic arterial pressure and the systemic vascular resistance showed variable changes with recovery. The circulatory status of three patients who exhibited persistent arterial hypotension at the time of final assessment (one month after the onset of illness) deserves further consideration. All three patients were found to have cardiac outputs within the normal range and to have an associated reduction in systemic vascular resistance. The defect in these patients was therefore of inadequate homeostasis in the presence of a normal cardiac output.

The most likely cause of the mild arterial hypoxaemia found in cases of acute uncomplicated myocardial infarction would appear to be associated pulmonary congestion. The progressive reduction in the degree of arterial hypoxaemia and the return of the arterial oxygen tension levels to within the normal

range with increasing recovery could well be explained on the progressive improvement in myocardial function and therefore a progressive reduction in the degree of pulmonary congestion.

Chapter IV

Therapeutic Considerations

The findings reported in the preceding chapters of this section form a rational basis for further therapeutic considerations. The demonstration of both severe arterial hypoxia and a striking metabolic acidosis in patients with cardiogenic shock is of considerable potential therapeutic importance. The combination of the correction of metabolic acidosis and the administration of 100% oxygen in experimentally induced haemorrhagic shock in dogs resulted in a significantly increased survival rate (Manger et al. 1962). These workers postulated that, as a result of this combined procedure, the circulating catecholamines exerted a greater activity and the oxidative metabolism was enhanced. They showed further that neither the correction of acidosis nor the

administration of 100% oxygen alone improved the survival rate. If the acidosis and the arterial hypoxia in cardiogenic shock in man are responsible for diminished sensitivity of both the heart and the peripheral circulation to sympathetic outflow and increased levels of circulating catecholamines the adequate correction of both factors might be expected to result in some improvement in the very high mortality figures. Correction of the acidosis will require careful titration of the required amount of buffering solution against serial acid base determinations in these patients. The value of similar continuous monitoring in the control of treatment in diabetic ketosis and renal and respiratory failure is now well established, and it should receive more consideration in the resuscitation and treatment of circulatory shock. Adequate correction of the arterial hypoxaemia is an even more difficult problem which urgently requires more investigation. If the cause of the relative unresponsiveness to high oxygen levels could be determined and remedied, this would not only relieve tissue hypoxaemia but also

greatly improve or avoid the considerable metabolic acidosis. Those with the appropriate facilities may resort to treatment by hyperbaric oxygen but this has many potential risks as well as advantages, and at present it is available only to a very small number of patients. Cameron (1965) has published a preliminary report of the results obtained during a controlled clinical trial designed to assess the value of hyperbaric oxygen (two atmospheres absolute) in the treatment of acute myocardial infarction. Under the conditions of this trial, hyperbaric oxygen therapy had no appreciable beneficial effect on the early mortality of acute infarction and in particular no effect on the mortality rate in cases exhibiting the features of cardiogenic shock. However, Cameron admitted that the B.L.B. mask used for continuous oxygen administration was inefficient and the degree of oxygenation achieved could be improved by a more efficient face mask. While the more efficient administration of oxygen at two atmospheres absolute may prove effective in reducing the mortality rate as

suggested by this author, it may well be that a combined "therapeutic attack" on the hypoxaemia and the coincidental metabolic acidosis will even further improve the mortality figures of cardiogenic shock.

The circulatory results indicate the existence of heart failure and a very severe degree of impairment of left ventricular function in cardiogenic shock. It is therefore logical to assess more critically the place of digitalis as a therapeutic measure. Likewise the demonstration of an inadequate compensatory increase in systemic vascular resistance in the face of a reduced cardiac output and stroke volume demands a more critical assessment of vasopressor therapy.

The results of the investigation designed to assess the value of both intravenous digoxin and noradrenaline infusion therapy are reported and discussed in the following two sections.

Summary and Conclusions

The circulatory, arterial blood gas tension and metabolic changes following acute myocardial infarction have been studied serially in patients with and without

cardiogenic shock. The effects of oxygen administration on these changes has been investigated. Follow-up studies have been undertaken following recovery from shock and at various stages of convalescence in most patients.

Cardiogenic shock has been shown to be associated with a severe impairment of left ventricular function with a reduced cardiac output and markedly reduced stroke volume, an elevated central venous pressure and an inadequate compensatory increase in systemic vascular resistance. These circulatory changes were accompanied by a very considerable degree of arterial blood hypoxaemia, as well as a metabolic acidosis, lactic acidaemia and hyperglycaemia.

In uncomplicated acute myocardial infarction the circulatory changes were found to be highly variable. The cardiac output and stroke volume varied from normal to very low values. The systemic vascular resistance varied between high and low values, resulting in the maintenance of the blood pressure at moderate to normal levels. Uncomplicated acute myocardial

infarction was accompanied by only a mild degree of arterial blood hypoxaemia and a complete lack of metabolic disturbance.

The patients without shock showed a normal rise in arterial blood oxygen tension when breathing oxygen. In contrast, those with shock showed a relatively small increase of arterial blood oxygen tension following oxygen therapy. This impaired response has been shown to be due to the shunting of about 25% of the cardiac output through vessels inaccessible to pulmonary gas exchange. These patients are therefore in urgent need of oxygen and this must be given in as high a concentration as possible.

The circulatory effects of oxygen therapy in patients with uncomplicated myocardial infarction are similar to those found in normal subjects - that is, a fall in heart rate and cardiac output with a slight increase in systemic vascular resistance and arterial blood pressure. It is possible that the poor and variable response of arterial blood oxygenation in cases of cardiogenic shock accounts for the less marked and equally variable circulatory response to such therapy.

Recovery from cardiogenic shock was found to be associated with a reduction in tachycardia and central venous pressure with an increase in blood pressure, stroke volume and cardiac output and only small variable changes in systemic vascular resistance. The arterial hypoxaemia, metabolic acidosis and lactic acidaemia progressively declined with recovery.

Progressive recovery from uncomplicated acute myocardial infarction was associated with a reduction in central venous pressure and an increase in stroke volume. There was a progressive increase in the arterial blood oxygen tension levels towards normal with increasing recovery.

The pathophysiological and therapeutic implications of these findings are discussed.

SECTION III

Evaluation of digoxin therapy

INTRODUCTION

When Herrick published his classical article on myocardial infarction in 1912, he recommended the use of digitalis. Levine and Brown (1929) considered that while digitalis may be useful in the treatment of manifest congestive heart failure, it was best avoided after myocardial infarction "as it is more likely to do harm than good". Fishberg et al. (1934) considered digitalis to be contra-indicated and emphasised the following theoretical dangers: 1. increased irritability of the heart muscles, predisposing to ventricular tachycardia or fibrillation, 2. increased force of systolic contraction predisposing to rupture of the heart, 3. similarly increased liability to embolisation, 4. the production of coronary arterial vasoconstriction. Gilbert and Fenn (1932) produced the first evidence to suggest that cardiac glycosides caused coronary arterial vasoconstriction and more recently Gracey et al. (1963)

have shown a similar effect. Both these studies were however carried out on healthy mongrel anaesthetised, open-chested dogs and it is doubtful if a similar action can necessarily be held to apply in the diseased coronary vessels of the human patient. Gorlin (1959) has suggested that the coronary vascular resistance is in fact fixed in such patients. Travell et al. (1938) showed that the tolerance of the experimentally infarcted heart of the cat to digitalis was decreased and consequently there was an increased susceptibility to ventricular tachycardia and fibrillation. Goodman and Gilman (1941) stated that both myocardial infarction and digitalis increase the likelihood of ventricular irritability and arrhythmia and that their effects may be additive in the same patient. In 1951 Askey and Neurath gave digitalis to 50% of 84 patients with acute myocardial infarction and atrial fibrillation. They failed to show an increased incidence of arrhythmia or sudden death in the digitalis treated group although there was a higher incidence of systemic embolisation. Wood (1956) expressed the opinion that the danger of digitalis glycosides in the treatment of acute myocardial infarction, should not be

overemphasised and they must not be withheld when the need for them arises. This opinion is not however universally accepted and there still remain many disciples of the view expressed by Conner who stated in 1938 that "among clinicians, the opinion is almost always, in fact almost universally, held that digitalis is dangerous".

The value of cardiac glycosides in the treatment of cardiogenic shock is much debated. Goodman and Gilman (1941) strongly oppose the use of these drugs "Digitalis is contraindicated, during the first few days following acute coronary thrombosis. The clinical picture is usually one of shock rather than congestive cardiac failure, and digitalis, by further decreasing cardiac output, may make the patient worse". More recently, Friedberg (1961) considered digitalis to be of little therapeutic value unless there was also associated and manifest congestive cardiac failure. Master et al. (1962) expressed an even stronger opinion and suggested that in the absence of heart failure, digitalis may be actually harmful in shock and should be

avoided. Stead and Ebert (1942) reported an increase in blood pressure resulting from the use of ouabain in six cases of cardiogenic shock. Fink et al. (1953) described the use of Lanatoside C in ten patients with varying degrees of shock. The blood pressure rose in all cases despite a variable effect on the venous pressure. Gorlin and Robin (1955) likewise reported a beneficial effect of digitalis compounds in four cases of cardiogenic shock. Three of these patients had signs of pulmonary oedema as well as shock and one had "pure" cardiogenic shock without manifest pulmonary oedema. Three of these four patients ultimately survived. Gilchrist (1952 and 1960) has long advocated the value of intravenous digoxin in cardiogenic shock and reports an elevation in blood pressure and survival resulting from such therapy. The true place of digitalis compounds in the treatment of cardiogenic shock therefore remains to be defined.

Although there have been isolated clinical reports and also measurements of the arterial and venous pressures, there has been, as yet, no definitive

circulatory evaluation of digitalis compounds in either acute myocardial infarction or cardiogenic shock. This section deals with such an evaluation.

RESULTS

Intravenous digoxin was given and the response monitored for the following 60 minutes in six patients without associated shock and in four patients with cardiogenic shock. The detailed individual circulatory, respiratory and metabolic measurements are given in the appendix. The circulatory results are also illustrated in diagrammatic form. Figures 32 to 37 show the resultant circulatory effects in six non shocked patients and figures 38 to 43 show the changes in the four shocked patients. It is appreciated that any interpretation of results of specific therapy in these patients must be cautious. This must particularly apply to the shocked patients who may frequently vomit during the 60 minute period of evaluation. These patients are far from being in a steady state. The results, therefore, are interpreted as showing trends and have not, for these reasons, been subjected to detailed statistical analysis of

change. It is helpful to consider the uncomplicated cases first.

MYOCARDIAL INFARCTION WITHOUT SHOCK

Systemic arterial pressure As shown in figure 32 the injection of digoxin was followed by an immediate initial increase in mean systemic pressure in all patients. In most cases, this elevation of pressure commenced towards the end of the two minute period taken to perform the injection. This initial peak of pressure was not sustained and, usually lasting from 2 - 5 minutes was followed by a reduction in pressure. However the actual pressure, at this time, remained in excess of the control levels. A subsequent secondary and persistent elevation of blood pressure occurred in four of the six patients. The remaining two patients showed a different response. Patient G.B. showed a progressive reduction in blood pressure to the pre-existing control values. Patient J.M. showed no real change in blood pressure throughout.

Cardiac output An increase in cardiac output was observed in three of the six patients (B.G., G.B., and V.H.) and was questionably elevated in a fourth (patient

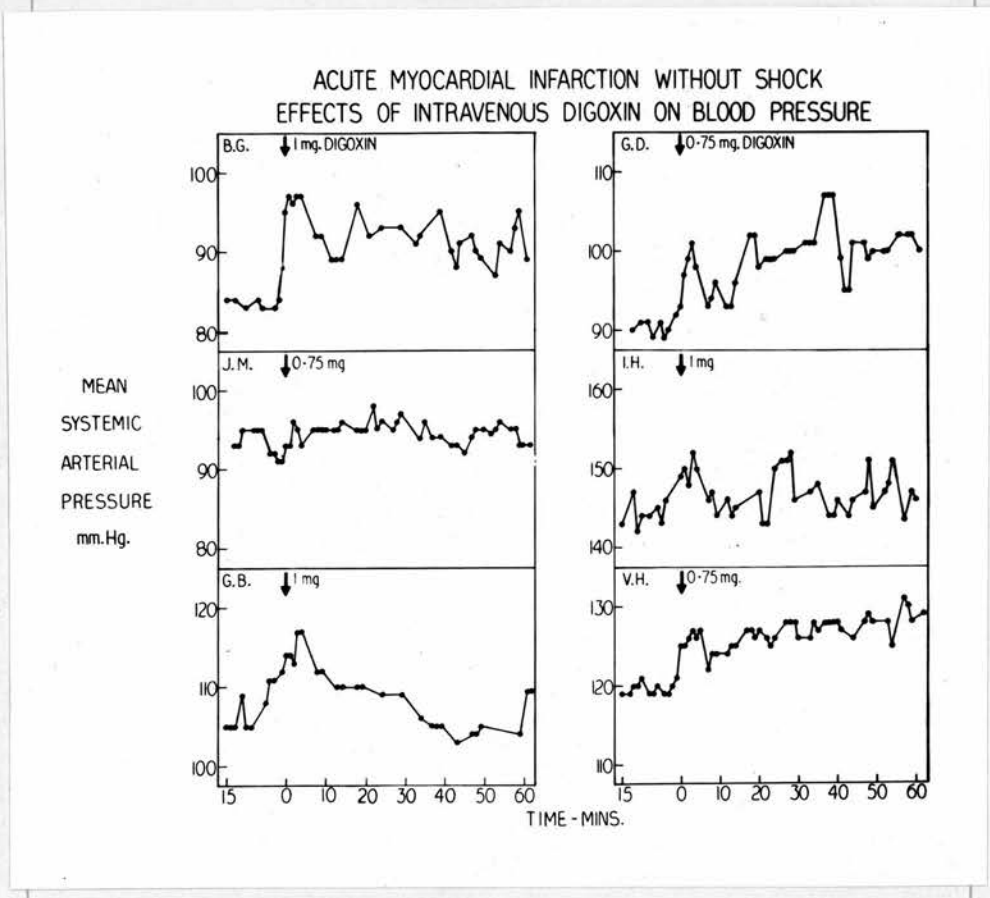

ACUTE MYOCARDIAL INFARCTION WITHOUT SHOCK
EFFECTS OF INTRAVENOUS DIGOXIN ON BLOOD PRESSURE
MEAN SYSTEMIC ARTERIAL PRESSURE mm.Hg.
B.G. ↓1 mg. DIGOXIN
G.D. ↓0·75 mg. DIGOXIN
J.M. ↓0·75 mg
I.H. ↓1 mg
G.B. ↓1 mg
V.H. ↓0·75 mg.
TIME - MINS.

Fig. 32

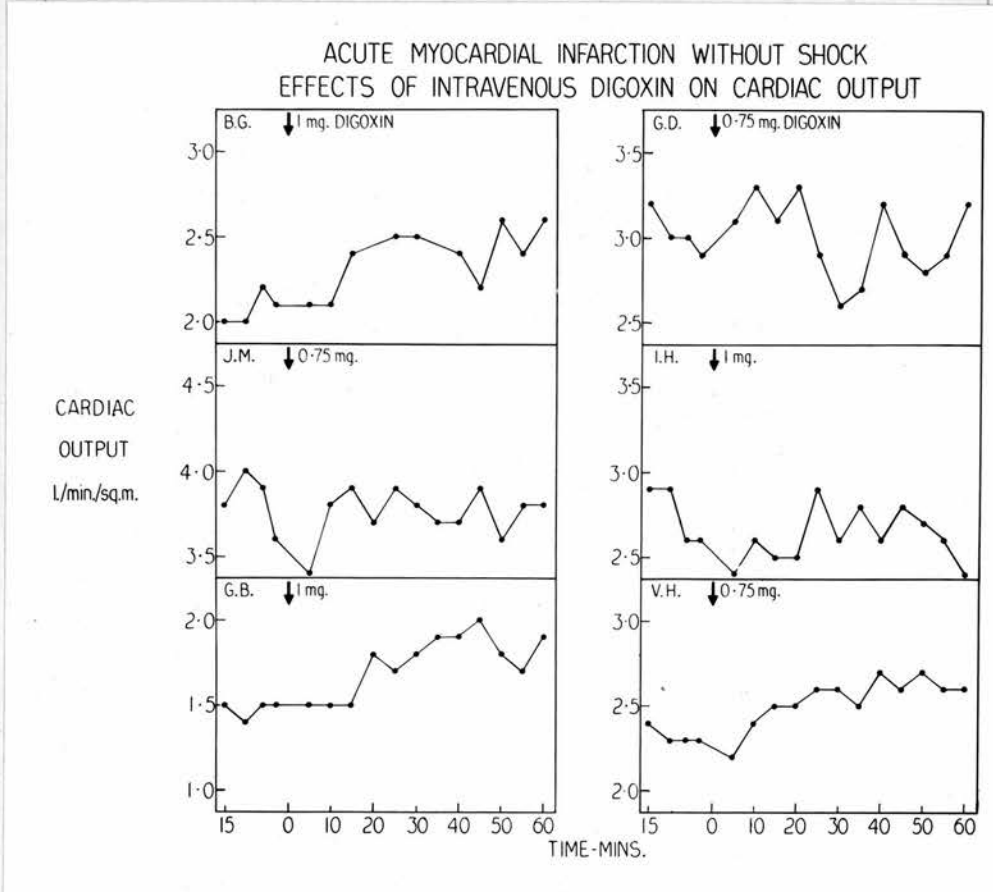

ACUTE MYOCARDIAL INFARCTION WITHOUT SHOCK
EFFECTS OF INTRAVENOUS DIGOXIN ON CARDIAC OUTPUT
CARDIAC OUTPUT l/min./sq.m.
B.G. ↓1 mg. DIGOXIN
G.D. ↓0·75 mg. DIGOXIN
J.M. ↓0·75 mg.
I.H. ↓1 mg.
G.B. ↓1 mg.
V.H. ↓0·75 mg.
TIME-MINS.

Fig. 33

I.H.) as shown in figure 33. The cardiac output in each of these three patients was initially significantly reduced (< 2.5 l./min./sq.m.). In the fourth patient (I.H.) the control values were variable and make final interpretation of change more uncertain. The data in this patient does however suggest an increase in cardiac output from an initial low level (2.5 l./min./sq.m.). The increase in cardiac output in each patient commenced about 15 minutes after digoxin injection and progressively increased thereafter. In the remaining two patients the initial cardiac output estimations were within the normal range of values and no increase was found.

Right atrial pressure and heart rate showed no consistent change as shown in figs. 36 and 37.

The systemic vascular resistance As shown in fig. 34 the S.V.R. usually showed an initial slight increase following injection and thereafter showed variable changes in individual cases. The first estimate of cardiac output, and therefore of systemic vascular resistance was not undertaken until five minutes after injection when the peak elevation of pressure was already subsiding.

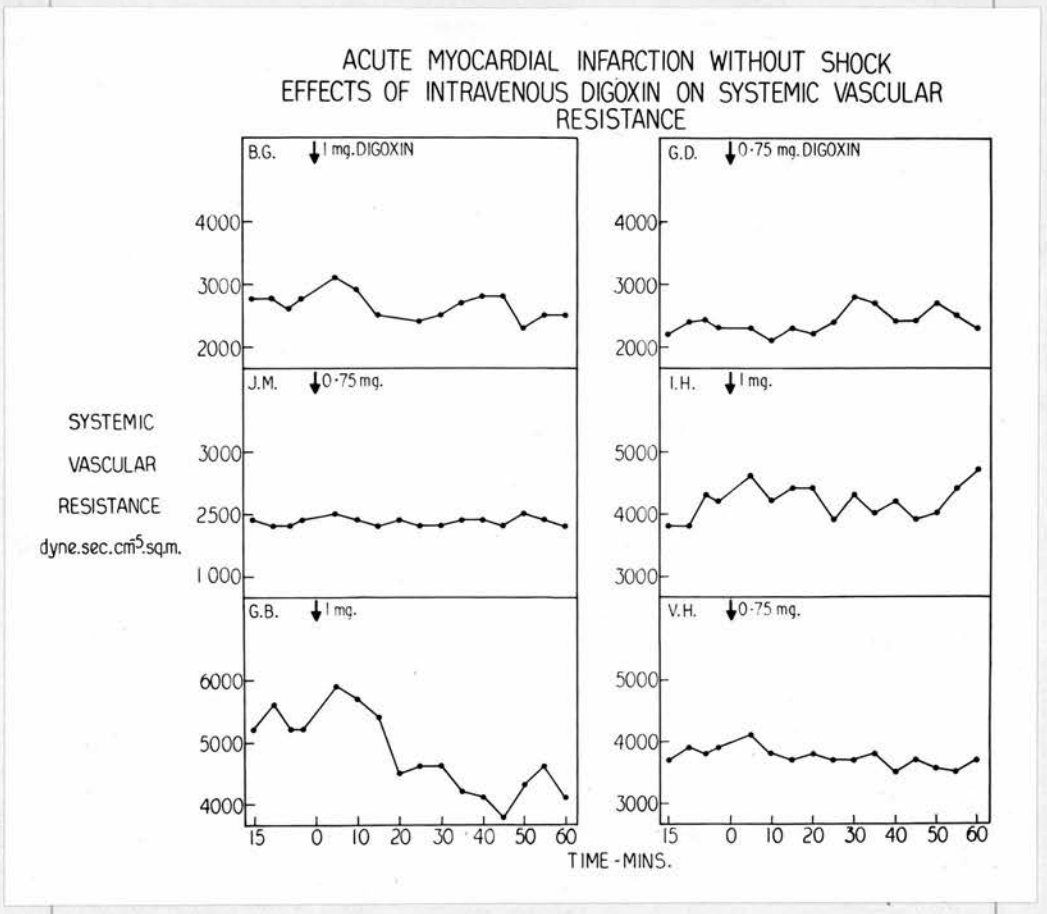

ACUTE MYOCARDIAL INFARCTION WITHOUT SHOCK
EFFECTS OF INTRAVENOUS DIGOXIN ON SYSTEMIC VASCULAR RESISTANCE
B.G. ↓1 mg. DIGOXIN
G.D. ↓0·75 mg. DIGOXIN
J.M. ↓0·75 mg.
I.H. ↓1 mg.
G.B. ↓1 mg.
V.H. ↓0·75 mg.
SYSTEMIC VASCULAR RESISTANCE dyne.sec.cm⁻⁵.sq.m.
TIME - MINS.

Fig. 34

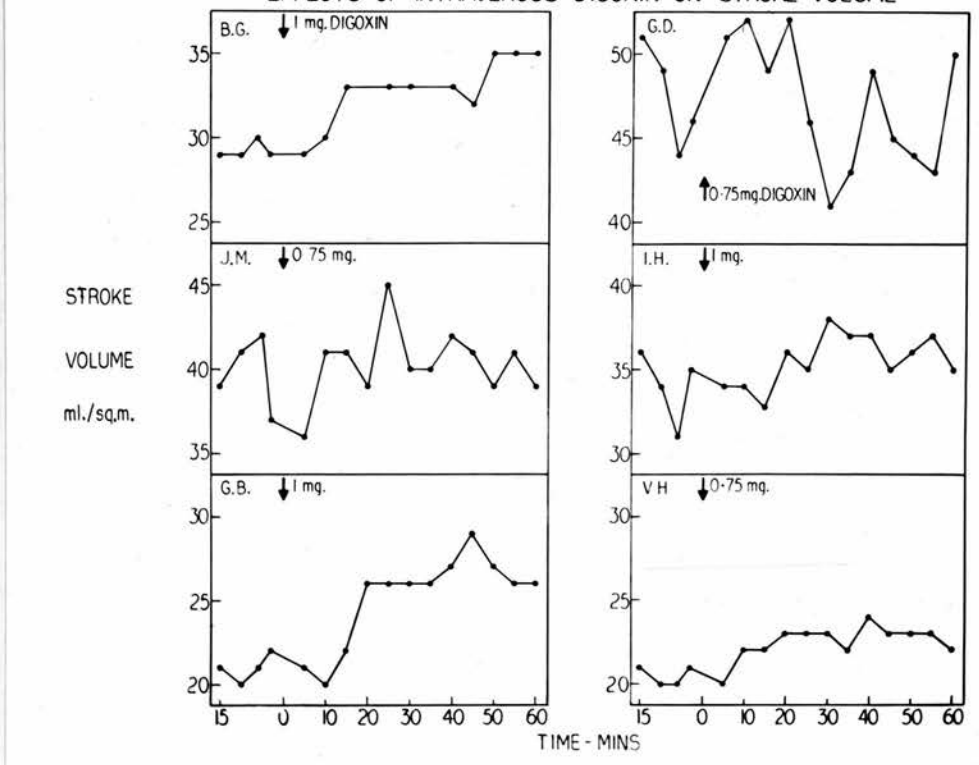

ACUTE MYOCARDIAL INFARCTION WITHOUT SHOCK
EFFECTS OF INTRAVENOUS DIGOXIN ON STROKE VOLUME
B.G. ↓1 mg. DIGOXIN
G.D.
↑0·75mg. DIGOXIN
J.M. ↓0 75 mg.
I.H. ↓1 mg.
G.B. ↓1 mg.
V H ↓0·75 mg.
STROKE VOLUME ml./sq.m.
TIME - MINS

Fig. 35

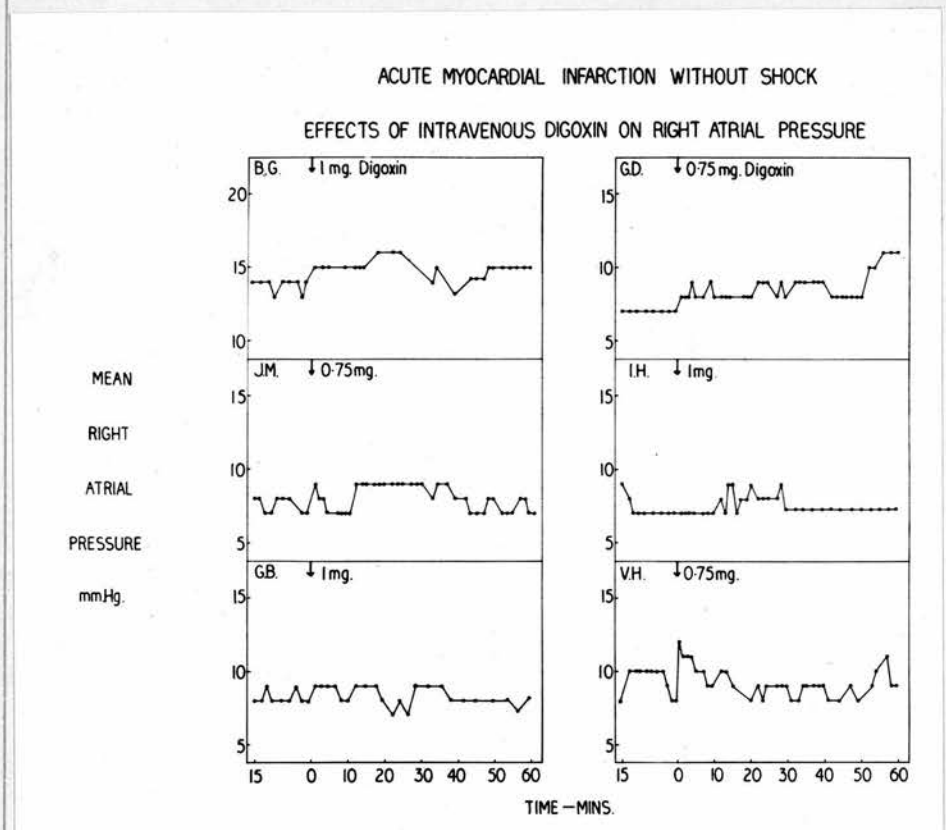

ACUTE MYOCARDIAL INFARCTION WITHOUT SHOCK
EFFECTS OF INTRAVENOUS DIGOXIN ON RIGHT ATRIAL PRESSURE
B.G. ↓1 mg. Digoxin
G.D. ↓0·75 mg. Digoxin
J.M. ↓0·75mg.
I.H. ↓1mg.
G.B. ↓1mg.
V.H. ↓0·75mg.
MEAN RIGHT ATRIAL PRESSURE mm.Hg.
TIME — MINS.

Fig. 36

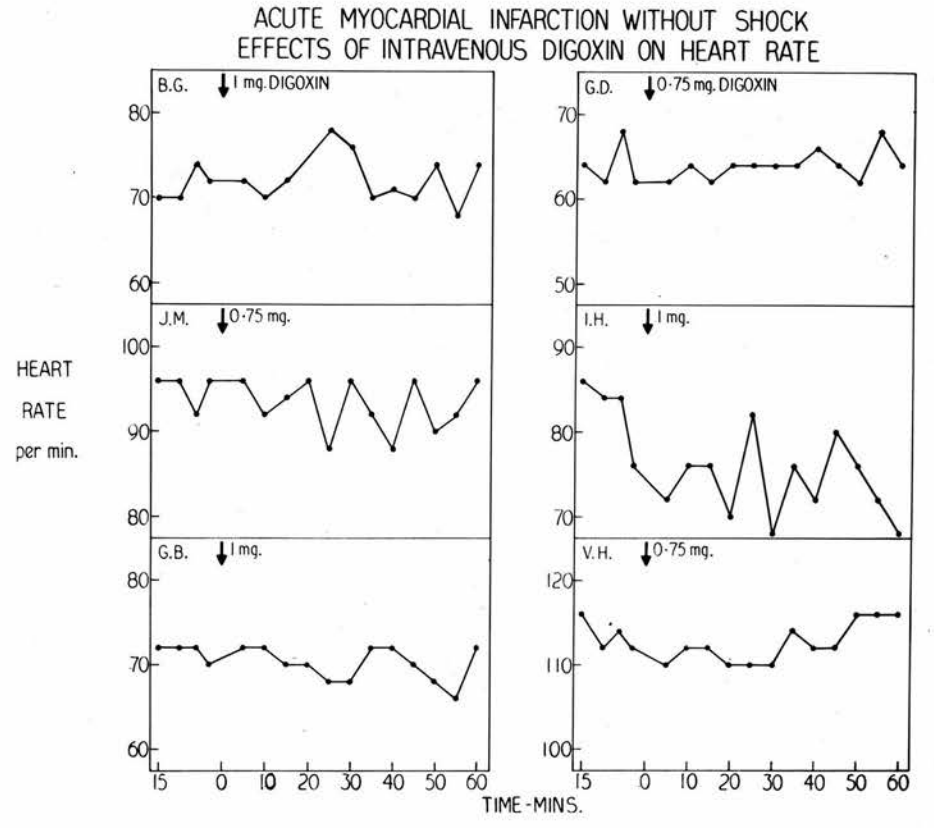

ACUTE MYOCARDIAL INFARCTION WITHOUT SHOCK
EFFECTS OF INTRAVENOUS DIGOXIN ON HEART RATE
B.G. ↓1 mg. DIGOXIN
G.D. ↓0·75 mg. DIGOXIN
J.M. ↓0·75 mg.
I.H. ↓1 mg.
G.B. ↓1 mg.
V.H. ↓0·75 mg.
HEART RATE per min.
TIME - MINS.

Fig. 37

It may well be that a more marked increase would have been demonstrated in the first two or three minutes. The same reasoning may apply to explain the apparent lack of increase in S.V.R. in patient G.D. The three patients who showed a definite increase in cardiac output had an associated reduction in systemic vascular resistance. In the remaining three patients, the S.V.R. remained substantially unchanged in two (J.M. and I.H.) and actually increased in the patient G.D.

The stroke volume As shown in fig. 35 the changes in stroke volume are similar to the cardiac output changes. There was an increase in four of the six patients and this increase commenced about 15 minutes after injection.

Arterial blood gas tension and metabolic measurements No significant change was produced in any of these measurements during the 60 minutes following digoxin injection.

Complications and progress There were no complications such as arrhythmias arising from this digoxin therapy. One patient (V.H.) did however die suddenly on day 4 of her illness. She was the most seriously ill,

yet clinically not shocked patient in the series who was found haemodynamically to have a very low stroke volume. Her sudden death on day 4 might well be rightly attributed to the disease process itself without invoking any incriminating role for the digoxin therapy. This, however, must remain a possible complicating factor. All the remaining patients survived to leave hospital fit and well.

CARDIOGENIC SHOCK

Possibly the most striking and consistent finding in these four shocked patients are the marked haemodynamic changes that occur with vomiting. Three of these four patients vomited during the course of digoxin evaluation. The initial haemodynamic response to vomiting would appear to be a consistent increase in systemic vascular resistance with the development of a tachycardia and a reduction in both stroke volume and cardiac output. The resultant effect on the systemic arterial pressure in these three patients was an increase in two and no significant change in level in the third patient (M.R.). The right atrial pressure was elevated

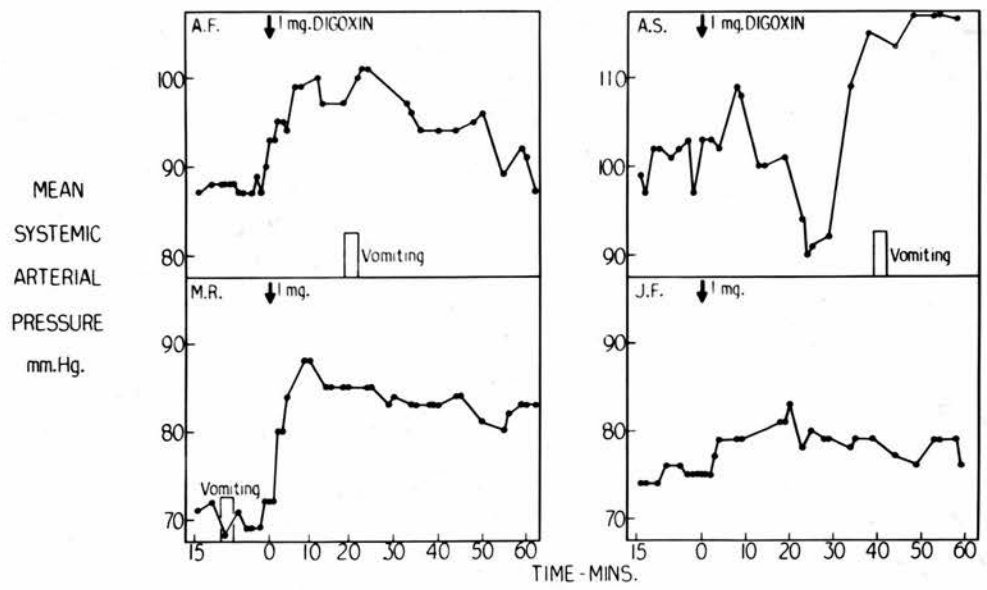

CARDIOGENIC SHOCK
EFFECTS OF INTRAVENOUS DIGOXIN ON BLOOD PRESSURE
MEAN SYSTEMIC ARTERIAL PRESSURE mm.Hg.
A.F.
1 mg. DIGOXIN
Vomiting
A.S.
1 mg. DIGOXIN
Vomiting
M.R.
1 mg.
Vomiting
J.F.
1 mg.
100
90
80
70
110
100
90
80
70
15 0 10 20 30 40 50 60
TIME - MINS.

Fig. 38

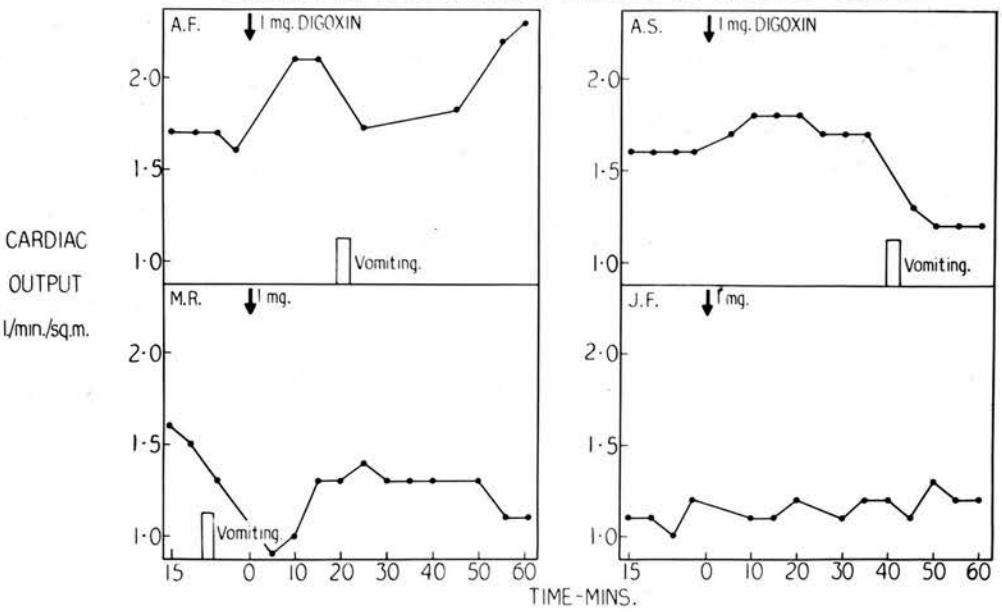

CARDIOGENIC SHOCK
EFFECTS OF INTRAVENOUS DIGOXIN ON CARDIAC OUTPUT
CARDIAC OUTPUT l/min./sq.m.
A.F.
1 mg. DIGOXIN
Vomiting.
A.S.
1 mg. DIGOXIN
Vomiting.
M.R.
1 mg.
Vomiting.
J.F.
1 mg.
2·0
1·5
1·0
15 0 10 20 30 40 50 60
TIME - MINS.

Fig. 39

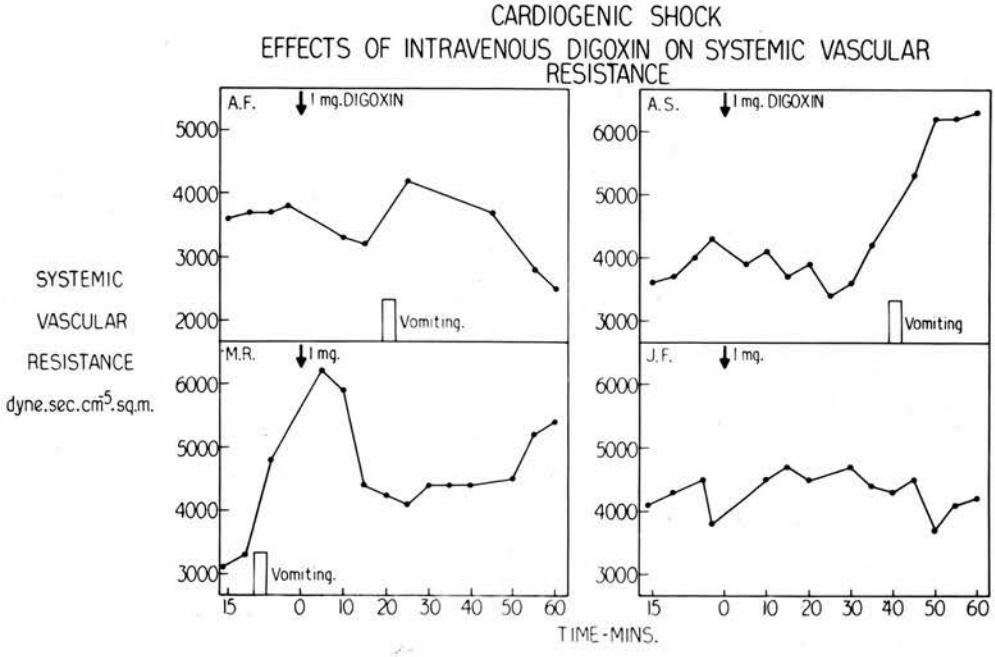

CARDIOGENIC SHOCK
EFFECTS OF INTRAVENOUS DIGOXIN ON SYSTEMIC VASCULAR RESISTANCE
SYSTEMIC VASCULAR RESISTANCE dyne.sec.cm⁻⁵.sq.m.
A.F.
1 mg.DIGOXIN
Vomiting.
A.S.
1 mg. DIGOXIN
Vomiting
M.R.
1 mg.
Vomiting.
J.F.
1 mg.
5000
4000
3000
6000
2000
15
0
10
20
30
40
50
60
TIME - MINS.

Fig. 40

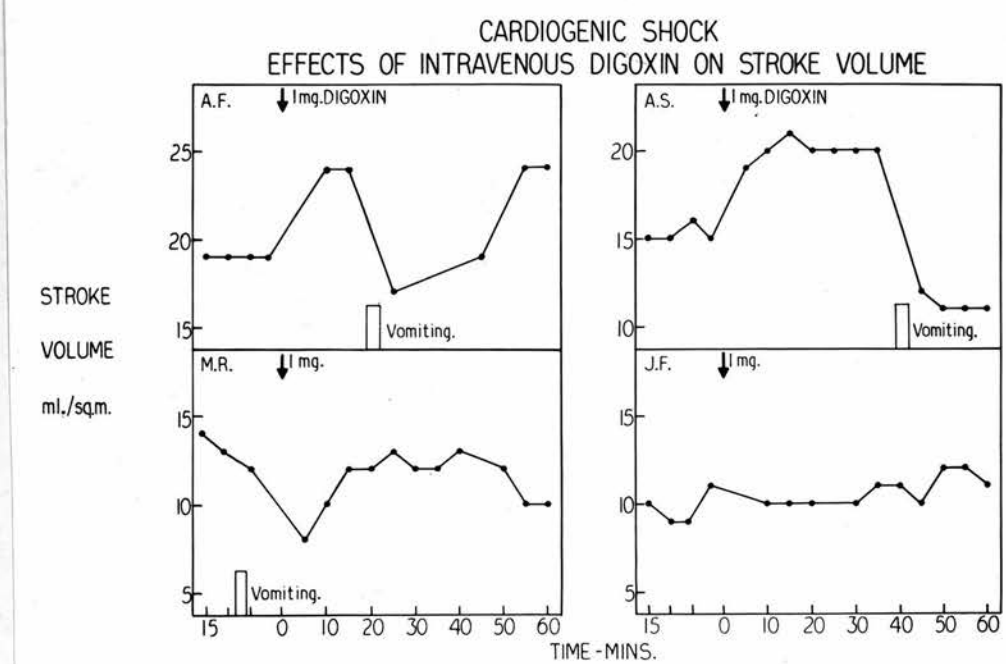

CARDIOGENIC SHOCK
EFFECTS OF INTRAVENOUS DIGOXIN ON STROKE VOLUME
STROKE VOLUME ml./sq.m.
A.F.
1mg.DIGOXIN
Vomiting.
A.S.
1 mg.DIGOXIN
Vomiting.
M.R.
1 mg.
Vomiting.
J.F.
1 mg.
25
20
15
10
5
15
0
10
20
30
40
50
60
TIME - MINS.

Fig. 41

CARDIOGENIC SHOCK

EFFECTS OF INTRAVENOUS DIGOXIN ON RIGHT ATRIAL PRESSURE

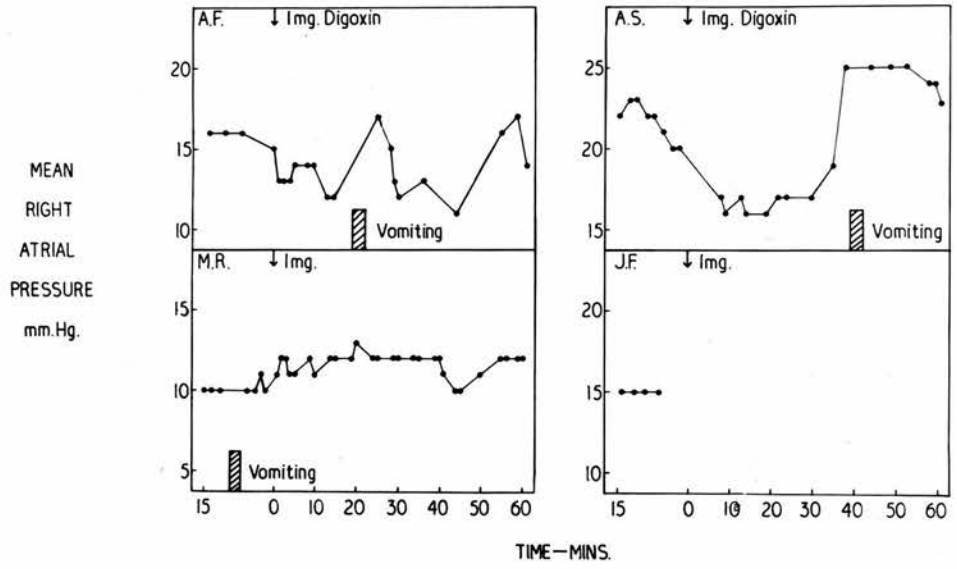


Fig. 42

CARDIOGENIC SHOCK

EFFECTS OF INTRAVENOUS DIGOXIN ON HEART RATE

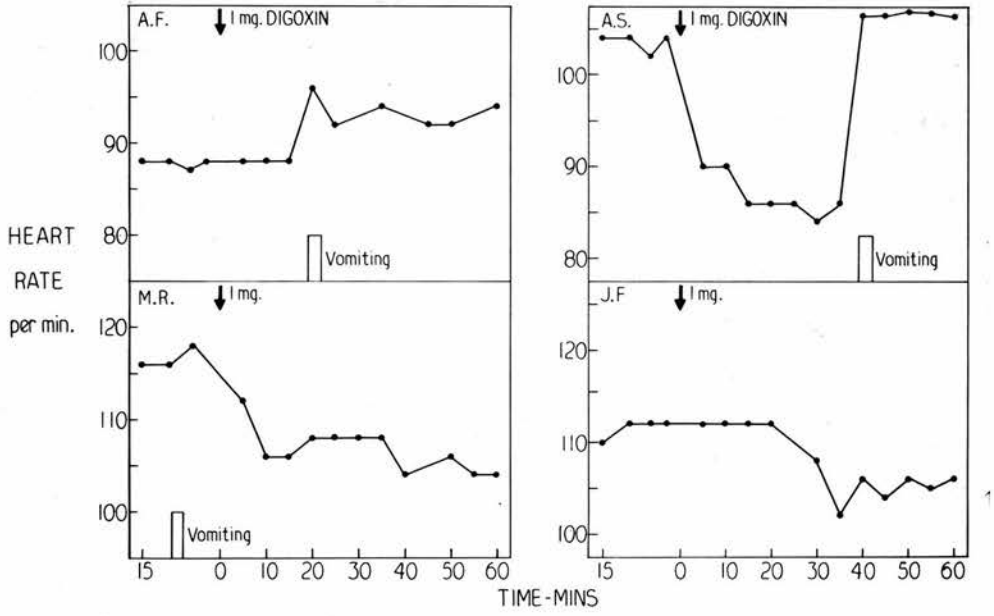


Fig. 43

in two of the patients but showed no significant change in the third (again patient M.R.). The occurrence of these dramatic circulatory effects during the course of digoxin evaluation, must inevitably raise serious doubts as to the value of the measurements. However patient J.F. did not vomit during the time of study. The results in this patient will therefore be considered in more detail and reference made to the remaining cases when vomiting has apparently interfered little with the measurements. Intravenous digoxin (1 mg.) in patient J.F. produced an initial very small increase in blood pressure due to a slight increase in systemic vascular resistance and no significant change in cardiac output or stroke volume. The resultant increase in mean arterial pressure was only of the order of 2 - 3 mm.Hg. For technical reasons the central venous pressure was only recorded at the onset of the study.

The remaining three patients showed a more marked initial elevation in arterial pressure, which was reasonably well sustained in two patients (A.F. and M.R.). In patient A.S. this pressure elevation was followed by a gradual reduction until it was subsequently

further elevated by the act of vomiting.

The cardiac output and stroke volume showed parallel changes. No significant change was observed in patient M.R.(as was similarly noted in patient J.F.). However both the cardiac output and stroke volume did increase to some extent in patient A.S. and A.F. until these measurements were subsequently reduced by vomiting. The two patients who showed no response to digoxin both had initially very low cardiac output values, i.e. less than 1.5 l./min./sq.m.

The heart rate decreased in three of the four patients following digoxin therapy but again the assessment was affected by the tachycardia induced by vomiting in three patients. The right atrial pressure was convincingly reduced in only one patient (A.S.) in whom it was subsequently further elevated by vomiting.

The systemic vascular resistance showed an overall slight reduction in those cases where the cardiac output had increased (A.S. and A.F.) and variable changes in the two remaining patients. These measurements are again much upset by the act of vomiting.

Arterial blood gas tension and metabolic changes No significant change was produced in any of these measurements during the 60 minutes following digoxin injection.

Complications and progress Patient A.S. received no further therapy other than continuous oxygen and maintenance oral digoxin therapy. All signs of clinical shock had disappeared about 12 hours after the start of digoxin therapy. The patient progressively improved as shown in fig. 24 but suddenly died on day 4. Patients M.R., J.F. and A.F. did not show any marked clinical improvement following digoxin therapy; shock progressively increased in all three patients with a fatal outcome but without the production of any cardiac arrhythmia.

DISCUSSION

The effects of digitalis on the heart have recently been excellently reviewed by McMichael (1963). He considered that the myocardium had to be in some sort of hypodynamic state before the positive inotropic action of digitalis improving myocardial contraction could be demonstrated. This view is in accord with that of most workers who consider that digitalis has little effect on

the normal heart (Selzer et al. 1959; Dresdale et al. 1959; Rodman et al. 1961; Weissler et al. 1964 and many others). Although Braunwald (1961) and his co-workers demonstrated by direct measurements on the human heart at the time of cardiopulmonary bypass, that strophanthin increased the contractility of the non-failing left ventricle, they did however agree that the actual cardiac output remained unchanged in the presence of a normal heart. The work of McMichael is in general agreement with the view expressed by Marvin (1926) that non-valvular left ventricular failure is the type of cardiac disability in which the most favourable response to cardiac glycosides would be anticipated. As myocardial infarction in the present study has been shown to be associated with varying degrees of left ventricular failure it is not therefore surprising to find that the circulatory response to intravenous digoxin therapy is also variable.

It is helpful to consider first the circulatory response of the cases without associated shock. An increase in cardiac output was observed in all four patients who had previously been shown to have a reduced level following acute myocardial infarction. In

contrast no change was observed in the two patients who had been previously shown to have cardiac outputs well within the normal range. The clinical condition and picture presented by these two patients is worthy of some further comment. Both of these patients were markedly pyrexial and were noted to have significant systemic arterial hypotension but in the presence of warm hands and with good volume bounding peripheral pulses. The basic haemodynamic status of these patients has already been described. The arterial hypotension has been shown to be due to peripheral vasodilatation as a consequence of the high temperature.

The initial increase in systemic arterial pressure immediately following intravenous digoxin is probably due to arteriolar vasoconstriction. Buchert and Schwab (1952) demonstrated such vasoconstriction with intravenous strophanthin in the isolated perfused hind limb and more recently Ross, Waldhausen and Brannwald (1960) have provided convincing evidence that digitalis produces increased tone in both arteriolar and venular smooth muscle. This initial vasoconstrictive response

is however short-lived and of doubtful therapeutic significance. The secondary increase in blood pressure is due to the increased cardiac output and commences about 15 minutes after injection. These effects in the presence of impaired left ventricular function are presumably due to a direct effect on myocardial contractility as neither the right atrial pressure or the heart rate showed any significant change.

Although there would therefore appear to be little doubt that intravenous digoxin improves myocardial function when the cardiac output has been reduced following acute myocardial infarction, its value in the treatment of cardiogenic shock is less certain. It has already been stated that the interpretation of circulatory changes in response to treatment in such an unsteady state and in the presence of occasional vomiting must indeed be cautious. However, the data acquired does suggest that intravenous digoxin has a less striking beneficial effect on the cardiac output in the presence of cardiogenic shock. A slight increase in both stroke volume and cardiac output was demonstrated in the two patients whose initial control cardiac output levels were

greater than 1.5 l./min./sq.m. This increase was, however, much less than that observed in the non-shocked group. In contrast, the two patients in whom no increase of cardiac output was observed had initial control cardiac output values of considerably less than 1.5 l./min./sq.m. It would appear therefore that the more severe the reduction of cardiac output in the presence of cardiogenic shock, the less likely is digoxin to improve the myocardial function. It may be that in the more severe cases the insult to the myocardium is too great for any specific drug therapy to be of value. It is however interesting to postulate that the highly abnormal metabolic state which has been shown to exist in these patients, may be responsible, in some way for blocking the cardiotonic effect of digoxin. The vasoconstrictive effect of digoxin with a resultant increase in blood pressure can be seen to be unimpaired in these patients and frequently it is sustained, at least during the 60 minute period of drug evaluation which was undertaken. This vasoconstrictive effect may therefore be of more therapeutic value than the cardiac effects in these patients.

The mode of action of digitalis remains uncertain (McMichael, 1963). It is however thought that digitalis may produce its effects on cardiac muscle cells by altering the physico-chemical properties of the contractile protein myosin (Bowen, 1952) to which it is firmly bound (Kako and Bing, 1958). Olson (1959) has shown that the myosin of cardiac muscle is altered in cardiac failure, becoming more viscous. He has also shown that when digitalis becomes bound to this myosin, the viscosity is decreased towards normal. The part played by intracellular electrolytic changes in these reactions is poorly understood. McMichael (1963) considered it possible that the effect of digitalis on the heart may take place by a subtle re-arrangement of intracellula. ions in which calcium may play the most important part. The inter-relationship between the action of digitalis and the trans-membrane potassium gradient is well-known and has been recently well reviewed by Hoffman and Singer (1964). Several studies have demonstrated that metabolic acidosis, experimentally produced by means of mineral acids or ammonium

chloride, is accompanied by a loss of intracellular potassium and a corresponding increase in serum potassium (Tobin, 1958). The demonstrable metabolic acidosis in the shocked patients in the present study might well be expected to upset the "subtle re-arrangement of intracellular ions" upon which the action of digitalis may depend, and may account for the poor response of such patients to this therapy. An increased tolerance of digitalis in the presence of acidosis has been demonstrated in animal studies (Schafer et al. 1960 and Bliss et al. 1963). Both groups of workers suggested that the changes in ion flux (particularly of potassium) induced by the altered pH were probably more important than the actual pH levels themselves.

There is obviously a need for more research into the importance of pH and the associated changes in ionic distribution in relation to the action of digitalis. At the present moment and in our ignorance, it seems reasonable to suppose that marked pH changes, whether acidosis or alkalosis, might affect the action of the cardiac glycosides. The correction or buffering of the

coincidental metabolic acidosis in patients with cardiogenic shock might therefore also be expected to restore at least in part the responsiveness of the myocardium to digitalis compounds.

SUMMARY AND CONCLUSION

The place of intravenous digoxin in the treatment of both cardiogenic shock and acute myocardial infarction without associated shock has been evaluated. In the presence of acute myocardial infarction uncomplicated by shock, intravenous digoxin has been shown to improve a previously impaired cardiac output. In contrast the drug has been shown to have no effect when the cardiac output is already within the normal range.

The value of intravenous digoxin in the treatment of cardiogenic shock remains more uncertain. In two of the four patients digoxin produced no effect on cardiac performance while in the remaining two patients a small increase in both stroke volume and cardiac output was observed. It has been postulated that the coincidental metabolic acidosis may, in some way, block the usual cardiotonic effect of digoxin in the presence of a hypodynamic left ventricle.

SECTION IV

Evaluation of Noradrenaline Therapy

INTRODUCTION

The introduction of L - noradrenaline as a pressor agent in the treatment of hypotension complicating sympathectomy by Goldenberg et al. in 1949 was followed by many clinical reports as to the value of the drug in the treatment of cardiogenic shock. The results of the earlier studies (Hellerstein et al. 1952; Kurland et al. 1952; Smith and Guz 1953; Sampson and Zipser 1954; Miller et al. 1953, and many others) were interpreted as showing a beneficial effect in the shocked state, both in restoring a more normal blood pressure and in reducing the overall mortality. Malach and Rosenberg reviewed the literature, when reporting their own clinical experience in 1960. This review consisted of 13 series and included 200 patients who had received treatment with noradrenaline. Although a significant pressor response was noted in most series, the mortality rate showed a wide variation: ranging from 14

per cent as reported by Gazes et al. (1953) to 100 per cent as reported by Littler and McKendrick (1957) and Malach and Rosenberg (1960). Similar absence of beneficial effect was noted by Gunton et al. (1957) and more recently a report by the Scientific Sub-Committee of the Scottish Society of Physicians (Lancet, 1964) reached similar conclusions.

A critical evaluation of the effects of noradrenaline therapy in cardiogenic shock is therefore difficult in view of the contradictory published information. This difficulty in evaluation is due, at least in part, to a lack of uniformity in defining the state of shock and the inclusion, therefore, in many series of patients often not seriously ill. The inclusion of patients merely exhibiting arterial hypotension but without other clinical signs of shock will result in more favourable mortality statistics in any given series. The observation that hypotension associated with acute myocardial infarction can be easily distinguished from shock and that the prognosis is distinctly different in the two conditions has recently been re-emphasised by Heyer (1961).

The rationale underlying the use of noradrenaline in the initial studies was that the drug produced an increase in blood pressure and that this response was due entirely to peripheral vasoconstriction (Binder et al. 1955). Brigden (1956) in fact advanced the opinion that the value of noradrenaline was enhanced by the complete absence of any central effect on the myocardium. These views were held despite evidence of a positive inotropic effect on isolated mammalian heart muscle (Ahlquist, 1948; Burn and Hutcheon, 1949; and Garb, 1950) and on the heart of the intact dog, (Luduena et al. 1949; and Gazes et al., 1953). In 1953 Baker showed that the drug produced direct stimulation of the isolated perfused foetal heart and in 1960 Goldberg and his colleagues unequivocally demonstrated an increase in myocardial contractility resulting from administration of the drug to human patients. These workers measured this effect by direct application of a Walton-Brodie strain gauge arch to the myocardium in patients undergoing open-heart surgery.

In 1959 Aviado reviewed the accumulated and somewhat conflicting evidence as regards the circulatory

effects of both adrenaline and noradrenaline. Although noradrenaline has a direct stimulating action on the myocardium the end result in normal man appears to be no change or a reduction in cardiac output. The absence of an increase in cardiac output appears to be due to the marked reflex bradycardia induced by the pressor response. Wilber and Brust (1958) showed quite convincingly that the reduction in cardiac output was rate dependent and that when the powerful reflex vagal effect was blocked by either tetraethyl ammonium chloride or atropine, noradrenaline produced an increase in cardiac output.

In clinical practice Littler and McKendrick (1957) have demonstrated that noradrenaline is not devoid of cardiac effect and in fact produces arrhythmias, particularly when given in large doses.

Metaraminol (aramine) is another potent vasopressor agent which is much used in clinical practice. It has the advantage that it can be given by intramuscular injection and appears to have a longer duration of action. The circulatory studies undertaken in both dogs and man

have shown identical changes to those found after noradrenaline. Sarnoff et al. (1954) first demonstrated an increased myocardial contractility in dogs and in 1960 Goldberg and his associates demonstrated similar changes in man. More recently Malmcrona and his colleagues (1964 a and b) have measured the circulatory effects of the drug in both normal man and in patients following acute myocardial infarction. None of the patients in this latter group were shocked. The predominant changes in both groups were those of bradycardia with an increase in stroke volume, blood pressure andperipheral resistance. Sambhi et al. (1964) have recently reported the circulatory effects of metaraminol and noradrenaline in the treatment of 14 patients with shock of varied aetiology. These workers reported an increase in cardiac output when moderate elevations of blood pressure were produced. Further elevation of the blood pressure did not however result in a further increment of cardiac output. These observations on the use of metaraminol are perhaps relevant to the present discussion as Harrison and his colleagues in

1963 suggested, on the basis of animal experimentation, that the major action of the drug probably resulted from the release of noradrenaline and that prolonged administration resulted in a reduction of tissue noradrenaline stores.

Noradrenaline has been found to increase the coronary blood flow in dogs by a local vasodilating effect (Sayen et al. 1960). The relevance of this finding to the human patient shocked following an acute myocardial infarct is however doubtful. Gorlin (1959) has shown that trinitrin administration results in an increase of coronary blood flow in normal man but that no such change occurs after the drug in the presence of angina. The coronary vascular resistance in these patients appears to be fixed. It is therefore unlikely that noradrenaline is capable of producing further significant coronary arterial vasodilatation in the patient who is suffering from cardiogenic shock. The recent work of Yurchak et al. (1964) in fact suggests that noradrenaline does not cause actual coronary arterial vasodilatation even in normal man.

There is therefore still much confusion and debate as to the real value of noradrenaline or indeed any vasopressor therapy in cardiogenic shock. Friedberg (1961) has stated that "the sympathomimetic drugs which appear to be frequently effective in all forms of shock, accomplish their pressor effect by increasing the peripheral vascular resistance. This action corrects a deficient compensatory mechanism but does not significantly improve the severe reduction in cardiac output, which is the fundamental disturbance in shock". Whilst this statement may well be true, there is little or no direct evidence of the circulatory effects of noradrenaline in cases of true cardiogenic shock. Gilbert (1962) reports, that he measured the cardiac output in two cases of cardiogenic shock before and during noradrenaline therapy and found a further reduction in output. He did not however publish any actual measurements. There is therefore a clear need for further information as to the circulatory effects in cardiogenic shock.

Nickerson (1962) is a strong protagonist of the theory that the vasoconstriction which is a cardinal

feature of the classical shock syndrome is itself deleterious and must be relieved rather than accentuated by additional vasopressor therapy. This view is based on the concept that blood flow through certain critical areas, rather than blood pressure, is the main determinant of survival. This author however states that "cardiogenic shock .... involves aetiological factors sufficiently different from those responsible for other types to require that all aspects of its treatment be considered separately". This view is somewhat difficult to reconcile with that of Friedberg (1961) that "the initiating mechanism in shock with myocardial infarction differs from those in other forms of shock, but the subsequent functional disturbances that actually produce the clinical picture of shock are essentially the same in all". Von Euler in his closing remarks to the CIBA Symposium on Shock (1962) expressed the opinion that the use of vasodilator drugs in shock was a significant advance in that the sympathetic overactivity "may be said to act as a kind of internal tourniquet and is therefore, of course, highly undesirable. The effects of Dibenzyline

..... are most revealing in this respect, although we must not forget the use of conventional pressor drugs may be indicated in certain stages". The present state of our knowledge therefore remains highly unsatisfactory and leaves many questions unanswered, e.g. should cardiogenic shock be necessarily an entirely different therapeutic problem or should vasodilator therapy be applied in this circumstance also? There can be no denying that it is an improvement in flow rather than pressure which is primarily important in alleviating the shocked state.

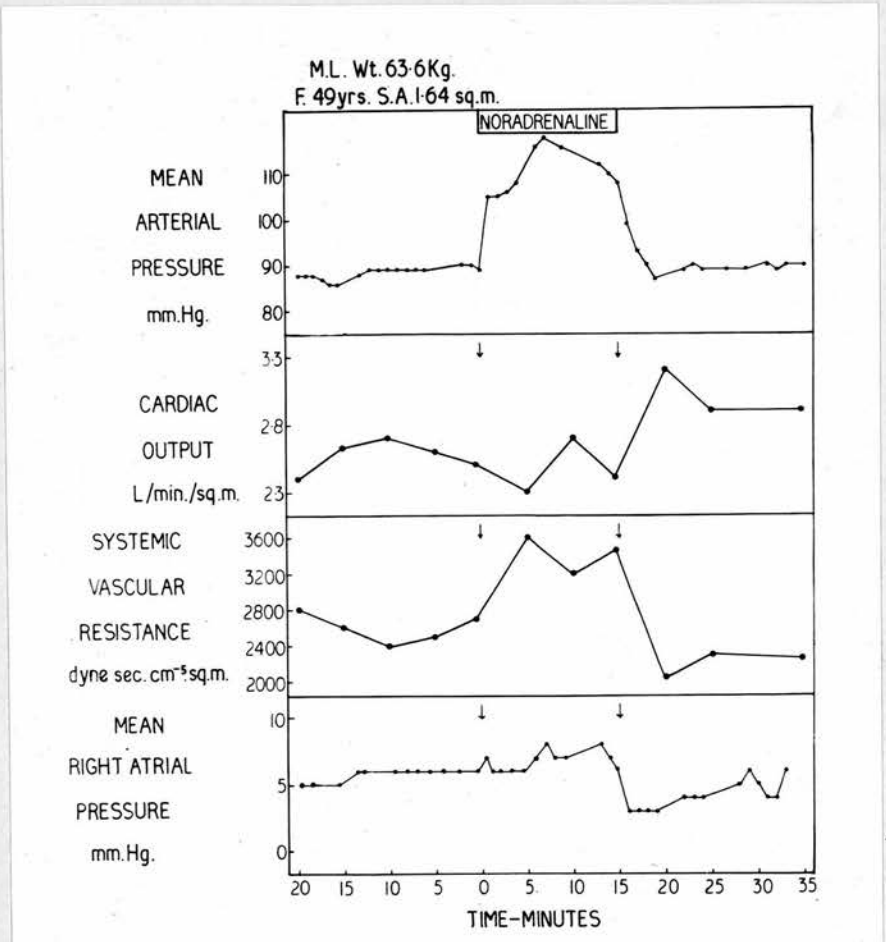
However the present status of vasopressor therapy also leaves many questions unanswered. This section deals with an attempt to start a definitive evaluation of such treatment in both shock and uncomplicated hypotensive states after acute myocardial infarction.

RESULTS AND DISCUSSION

Noradrenaline infusion therapy was given and the response monitored in five patients. In one of the hypotensive but not shocked patients (A.S.) the response of the cardiac output could not be measured due to a

technical fault. However the detailed circulatory response was measured in the remaining four patients. Two of these patients (M.R. and L.L.) exhibited systemic arterial hypotension but no other features of shock. The remaining two patients exhibited the clinical features of severe cardiogenic shock. The individual results in each patient are tabulated in the appendix and are expressed in diagrammatic form in figs. 44 to 47. As the material in this section is somewhat limited it is convenient to present the relevant details and discuss each case individually.

Patient M.L., female, aged 49 years had had an acute myocardial infarction complicated by systemic arterial hypotension but without other clinical features of shock. Noradrenaline infusion therapy in a dose of 16 μg./min. (Fig. 44) produced an increased blood pressure due to an increase in systemic vascular resistance with no convincing change in cardiac output. Bradycardia was produced with an associated increase in stroke volume allowing the maintenance of forward blood flow. There was also an increase in both the mean right atrial



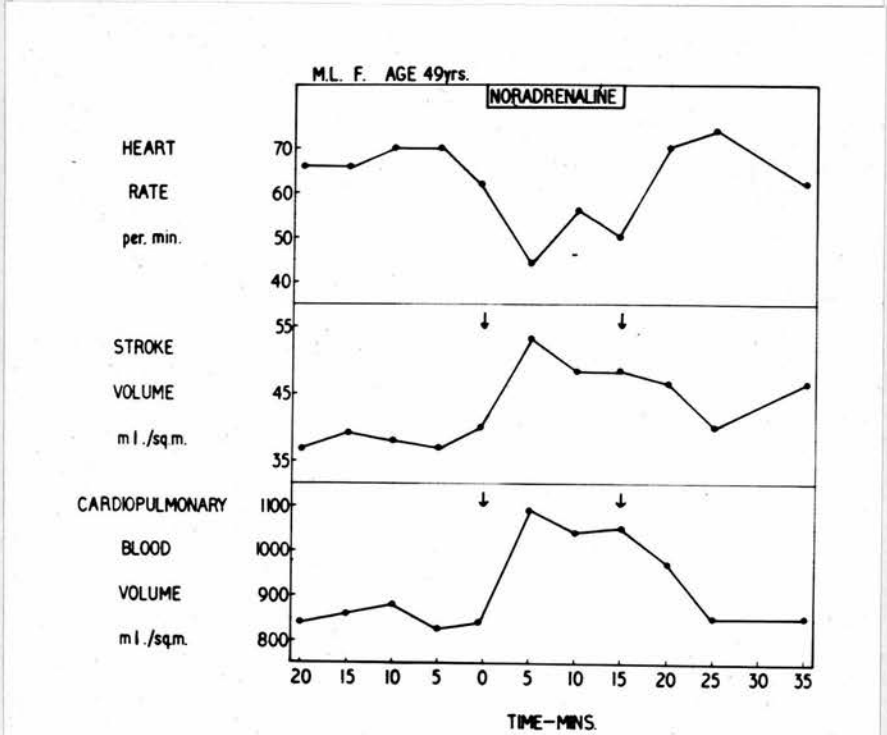


Fig. 44

The circulatory effects of noradrenaline (8μg./min.) in hypotensive but not shocked patient.

pressure and the cardiopulmonary blood volume. The cessation of the infusion can be seen to be associated with a reduction in the systemic vascular resistance but the blood pressure was maintained by an increase in cardiac output due largely to an increase in stroke volume.

This response is similar to that reported in normal man (Aviado, 1959). The major effect of the drug is to produce an increase in peripheral resistance with the development of a reflex bradycardia. These changes will obscure any direct effect on myocardial contractility. A direct venoconstrictor effect of noradrenaline on "post-arteriolar vessels" accompanied by an increased venous return has been demonstrated in dogs (Rashkind et al. 1953) and the drug has been reported to cause a shift of blood from the periphery to the heart and lungs both in animals (Shadle et al. 1955) and in man (Fritts et al. 1960). While the increased right atrial pressure in the present case might be regarded as being indicative of increased venous tone and venous return to the heart, it is just as likely to be a reflection of an increased right ventricular end diastolic

pressure. The available data does not allow of a further differentiation on these points.

Patient M.R., female, aged 68 years, had had an acute myocardial infarction and was in a state of severe cardiogenic shock. The changes produced by noradrenaline infusion in a dose of 16 µg./min. in this shocked patient showed some essential differences to those recorded in the previously described non-shocked patient. The results are illustrated in fig. 45. The systemic arterial pressure was increased again due to an increase in systemic vascular resistance. Although the estimations of cardiac output show some variation, there is obviously no increase and indeed possibly a slight reduction in values. The essential difference between this patient and the previously described non-shocked patient is to be found in the response of the heart rate: instead of a reflex bradycardia, there was actually an increase in heart rate and consequently no change or possible slight reduction in stroke volume. Again, although the right atrial pressure rises there is in this case no associated increase in cardiopulmonary blood volume.

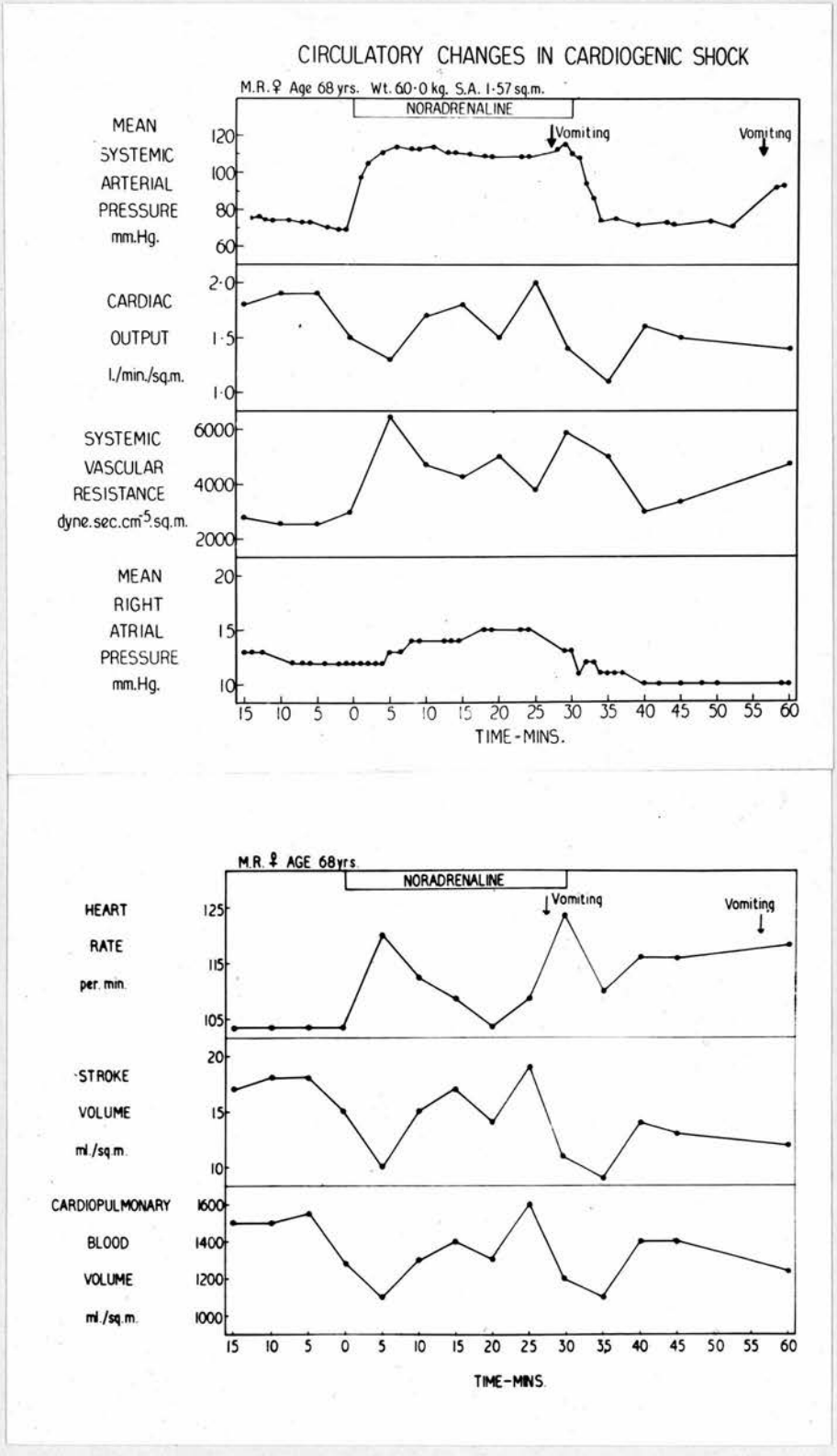
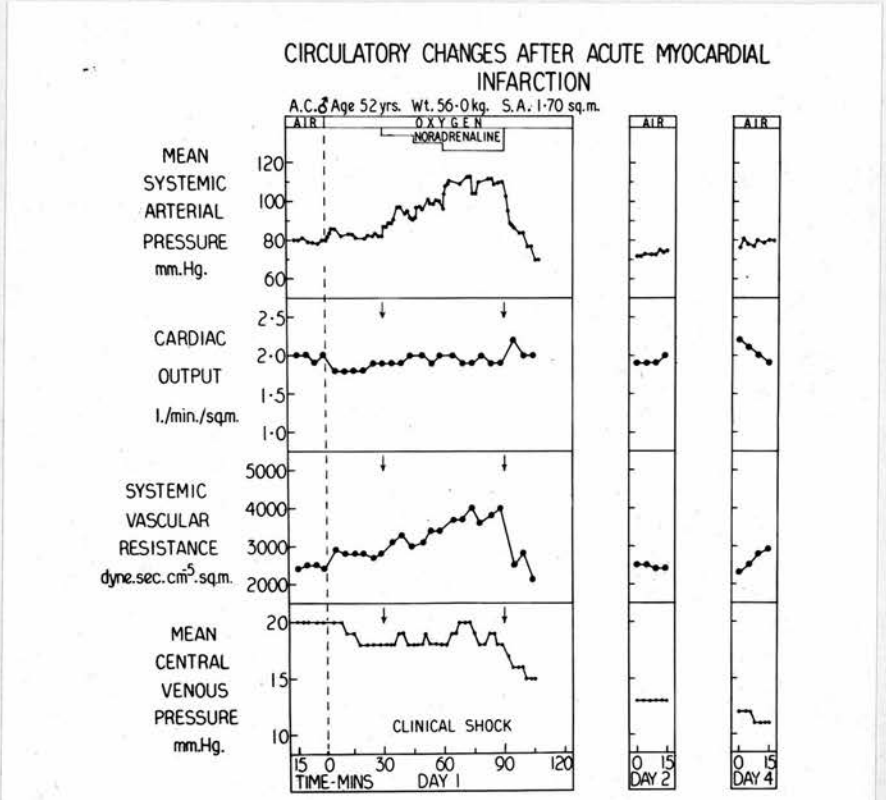


Fig. 45

The circulatory effects of noradrenaline (16 μg./min.) in patient M.R. with cardiogenic shock.

These findings would suggest that the increase in blood pressure has been achieved at the expense of a significant increase in cardiac work. Malmcrona et al. (1964b) when studying the circulatory effects of metaraminol in non-shocked patients considered that although the increase in aortic blood pressure may improve the coronary blood flow and myocardial oxygen supply "the decrease in heart rate may however be more important because it decreases the need for oxygen". Berglund et al. (1958) and Sarnoff et al. (1958) have shown that myocardial oxygen consumption at any given work load increases with increasing heart rate. Noradrenaline, therefore, in this shocked patient increased the work of the heart and the oxygen demands of the myocardium at a time when the heart was probably already accumulating an oxygen debt (see page 113). These features will be discussed further in conjunction with a discussion on the following case.

Patient A. C., male, aged 52 years, had had an acute myocardial infarction and was in a state of severe cardiogenic shock. Noradrenaline infusion therapy was given in three increasing levels - 8 μg./min. for 15



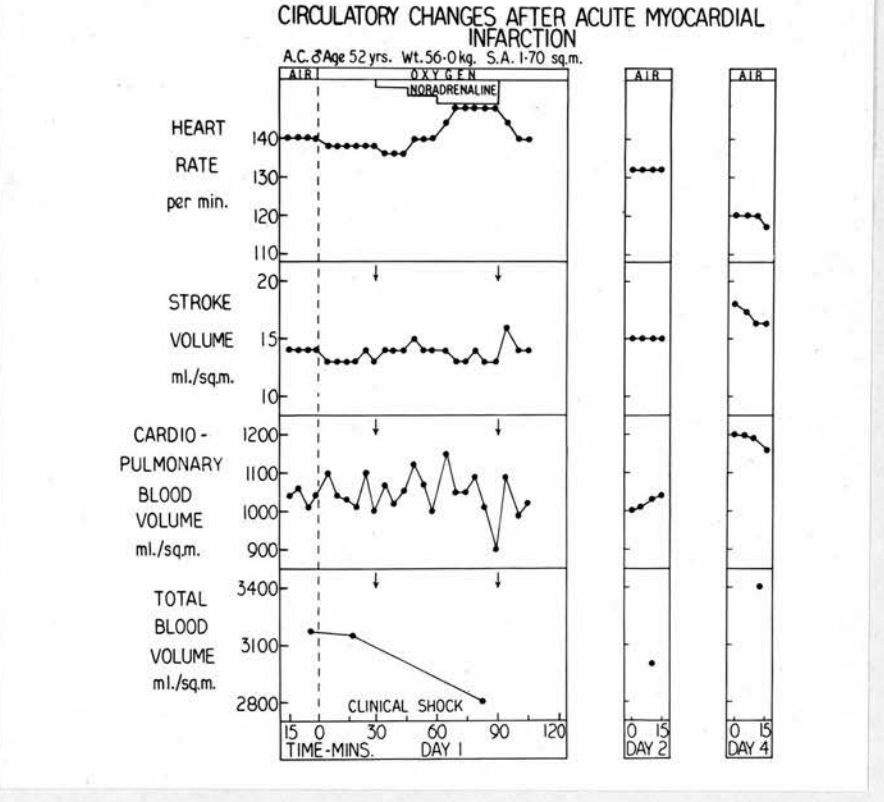


Fig. 46
(Fig. 25 a and b)

The circulatory effects of noradrenaline 8, 16 and 32 μg./min. in patient A.C. with cardiogenic shock.

minutes, 16 μg./min. for the following 15 minutes and finally 32 μg./min. for 30 minutes. The results are illustrated in fig. 46. The systemic arterial pressure showed progressive increases with increasing concentration. This increase was due to a progressive increase in systemic vascular resistance. The cardiac output remained unchanged at all levels of therapy. There was no significant change in stroke volume or cardiopulmonary blood volume. Although the heart rate fell from 138 to 136 during the first infusion period (8μg./min.) an increasing tachycardia developed with increasing concentration: 140/min. during the second period and 148/min. during the infusion of 32 μg./min. The right atrial pressure showed a doubtful degree of elevation during the infusion. Some aspects of left ventricular performance have been calculated at the three levels of concentration in this patient and are reported in table 7. There is a progressive reduction in both the mean ejection flow index and maximum rate of pressure rise in the aorta (M.R.P.R.A.) indicating a deterioration of myocardial contractility. The work of the left ventricle

TABLE 7. CARDIOGENIC SHOCK - LEFT VENTRICULAR PERFORMANCE DURING NORADRENALINE INFUSION
A.C., (M), Age : 52 years

	CARDIAC OUTPUT l./min./sq.m.	HEART RATE per min.	STROKE VOLUME ml./sq.m.	RIGHT ATRIAL PRESSURE mm.Hg	PRESSURE mm.Hg		CYCLE DURATION sec.		DIASTOLIC DURATION sec./min.	M.R.P.R.A. mm.Hg/sec.	LEFT VENTRICULAR WORK		PRESSURE-TIME INDICES				MEAN EJECTION FLOW INDEX ml./sec./sq.m. Index	MEAN STROKE POWER INDEX g.m./sec./sq.m.
					M.S.B.P.	M.A.D.P.	SYST.	DIAST.			Minute Kg.m./sq.m.	Stroke g.m./sq.m.	SYSTOLIC		DIASTOLIC			
													Min.	Stroke	Min..	Stroke		
Control Period	1.87	138	14	19	84	77	0.12	0.31	42.8	476	1.653	12.0	1063	7.7	2484	18.0	117	100
Noradrenaline I 8 µg./min.	1.92	136	14	18	98	89	0.16	0.28	38.1	424	2.039	15.4	1741	12.8	2706	19.9	85	96
Noradrenaline II 16 µg./min.	1.97	140	14	18	104	92	0.17	0.26	36.4	430	2.304	16.5	2044	14.6	2688	19.2	92	97
Noradrenaline III 32 µg./min.	1.95	148	13	19	116	104	0.17	0.23	34.1	461	2.572	17.4	2442	16.5	2901	19.6	76	102
Recovery Period																		
Noradrenaline stopped	2.00	140	14	15	82	73	0.15	0.28	38.2	317	1.822	13.0	1414	10.1	2268	16.2	93	87

is progressively increased but its capacity to perform this work as evidenced by the small changes in mean stroke power index, has not been increased. There is a marked and progressive increase to be noted in the systolic pressure time index but a much less marked increase in the diastolic pressure time index. In fact the tachycardia can be seen to occur at the expense of the duration of diastole which is progressively reduced.

The pressor response of noradrenaline in this shocked patient has therefore been shown to be dependent on its peripheral vasoconstrictive effects. No increase, in fact a deterioration of myocardial performance, has been observed and the available evidence suggests the work of the heart is increased disproportionally to any resultant increase in coronary blood flow.

The findings are therefore substantially the same as those already reported and discussed in the preceding shocked patient.

There is experimental evidence to support the contention that myocardial performance will be enhanced by the correction of any associated arterial hypotension.

Corday et al. (1949) showed that, in dogs there was a loss of contractility and ballooning of the myocardium in the area of myocardial infarction in the presence of hypotension. The restoration of a satisfactory blood pressure in these animals by blood transfusion lead to a loss of the systolic ballooning and an increase in cardiac output. However in the two patients under discussion the increase in blood pressure has been associated with a deterioration rather than an improvement of myocardial function. There is evidence to suggest that the infusion has increased the oxygen demands of the myocardium. The correlation between an increase in heart rate and an increased myocardial oxygen consumption has already been discussed. Sarnoff et al. (1958) consider the major haemodynamic determinant of myocardial oxygen consumption to be the systolic pressure (or tension) time index. This was found to progressively increase during noradrenaline therapy and can thus be regarded as further evidence suggesting greatly increased myocardial oxygen demands. These demands occur at a time when the heart is probably already accumulating an oxygen debt (see page113) and there is the added embarrassment

of both arterial hypoxaemia and associated lactic acidaemia. As shown in fig. 25(c) the noradrenaline therapy had no effect on these latter measurements during the time of study.

There is therefore much evidence to suggest that at least in these two shocked patients, a satisfactory elevation of the blood pressure was achieved by peripheral mechanisms at the expense of the heart and long continued use of the drug would be expected to further decrease myocardial function. The possible importance of catecholamines in cardiovascular pathology has recently been reviewed by Raab (1960) when he stressed that the increase in myocardial oxygen consumption consequent upon either adrenaline or noradrenaline was "wasteful" in that only a fraction of the oxidative energy was transferred into mechanical energy. There is now general agreement that myocardial oxygen extraction remains remarkably constant over a wide variety of conditions and that increased oxygen requirements are met almost entirely by an increase in coronary blood flow (Goodale and Hackel 1953; Messer and Neil 1962). Case et al. (1955) confirmed these

observations in the normal dog but noted that when coronary arterial stenosis was included in the experimental protocol any increased myocardial oxygen consumption was accomplished by an increase in oxygen extraction rather than increased coronary blood flow. Gorlin et al. (1959) were likewise unable to demonstrate an increase in coronary blood flow following nitroglycerine therapy in patients with angina. Raab et al. (1962) have reported the changes in the surface electrocardiogram in vagotomised cats following catecholamine or sympathetic stimulation with and without coronary arterial constriction. On the basis of these experiments they considered that neurogenic or blood-borne catecholamines could cause some regional myocardial hypoxia when the normal compensatory coronary vasodilatation was impaired. Yurchak et al. (1964) have recently suggested that, even in normal man, the increased myocardial oxygen requirements resulting from a noradrenaline infusion are partly met by an increased oxygen extraction which implies an inadequate compensatory increase in coronary blood flow. It seems unlikely that the coronary vascular tree of a patient

in cardiogenic shock is capable of significant active vasodilatation. It therefore seems reasonable to suggest that at least in some cases, noradrenaline therapy will depress myocardial function and intensify the accumulation of an oxygen debt which may lead to the development or progression of "irreversibility" (see page 113). Szakacs and Cannon (1958) have reported the production of a "noradrenaline myocarditis" in man after prolonged infusion of the drug. These authors also found similar lesions in some patients with phaechromocytomata and reported the production of similar myocardial lesions in dogs after prolonged infusions of noradrenaline in amounts comparable to therapeutic doses. Szakacs and Mehlman (1960) have also reported the production of similar myocardial lesions in the dog and noted that in all animals in whom the myocardial lesions developed, tachycardia or arrhythmias were regularly present. Maling et al. (1960) have likewise reported noradrenaline induced myocardial lesions in the dog. There is therefore fairly convincing human and animal evidence to suggest that, in certain circumstances, noradrenaline can significantly and

possibly permanently adversely affect the myocardium. Patient L.L., male, aged 64 years, had had an acute myocardial infarction complicated by systemic arterial hypotension but without other clinical features of shock. The results in this patient, both during noradrenaline infusion therapy and during subsequent follow-up studies are shown in figs. 47 (a), (b) and (c). Noradrenaline infusion therapy was given for 30 minutes in a dose of 8 μg./min. and produced an increase in blood pressure which was due initially to an increase in systemic vascular resistance but during the final 15 minutes there was a progressive increase in cardiac output accompanied by a reduction in peripheral resistance. Bradycardia was produced and there was a striking increase in stroke volume. The right atrial pressure increased and there was also an increase in cardiopulmonary blood volume. The cessation of the infusion can be seen to be associated with a reduction in systemic vascular resistance but the cardiac output remains elevated for at least 30 minutes after stopping the drug. There was a reduction of blood pressure on stopping the drug but because of the increased blood flow the actual level remained above that of the

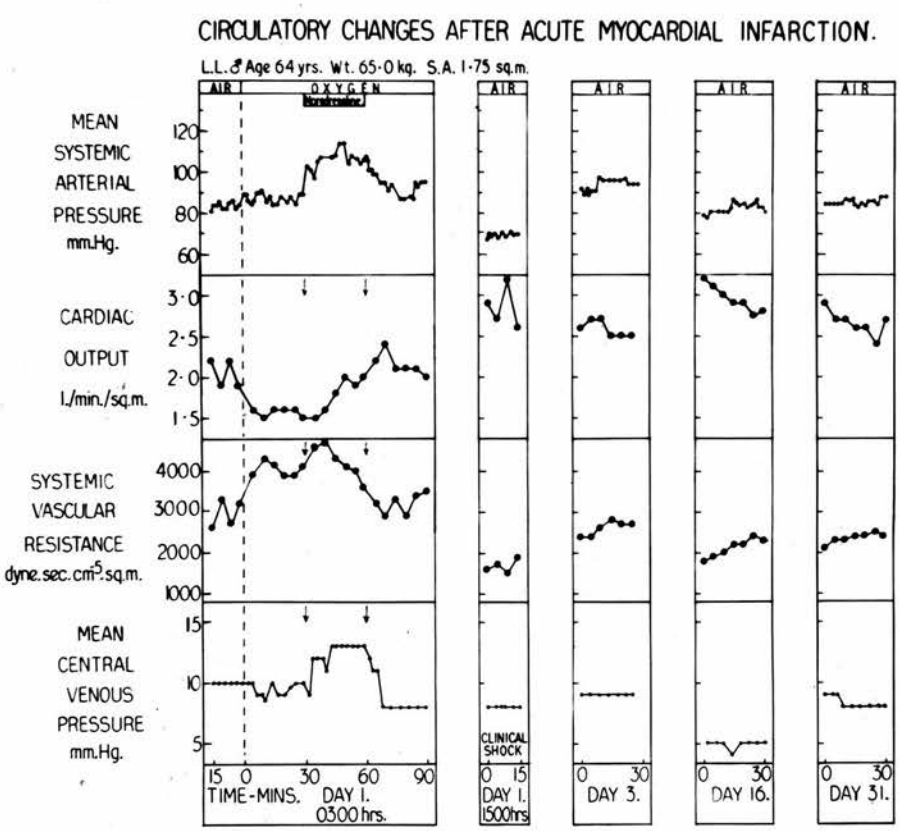


Fig. 47 (a)

The circulatory effects of treatment with oxygen and noradrenaline (8μg./min.) in a hypotensive but not shocked patient (L.L.) after acute myocardial infarction are shown (Day 1, 03.00 hours). Noradrenaline therapy was re-instituted and the circulatory measurements during the state of "peripheral circulatory collapse" probably precipitated by such therapy are shown (Day 1, 15.00 hours). (See text).

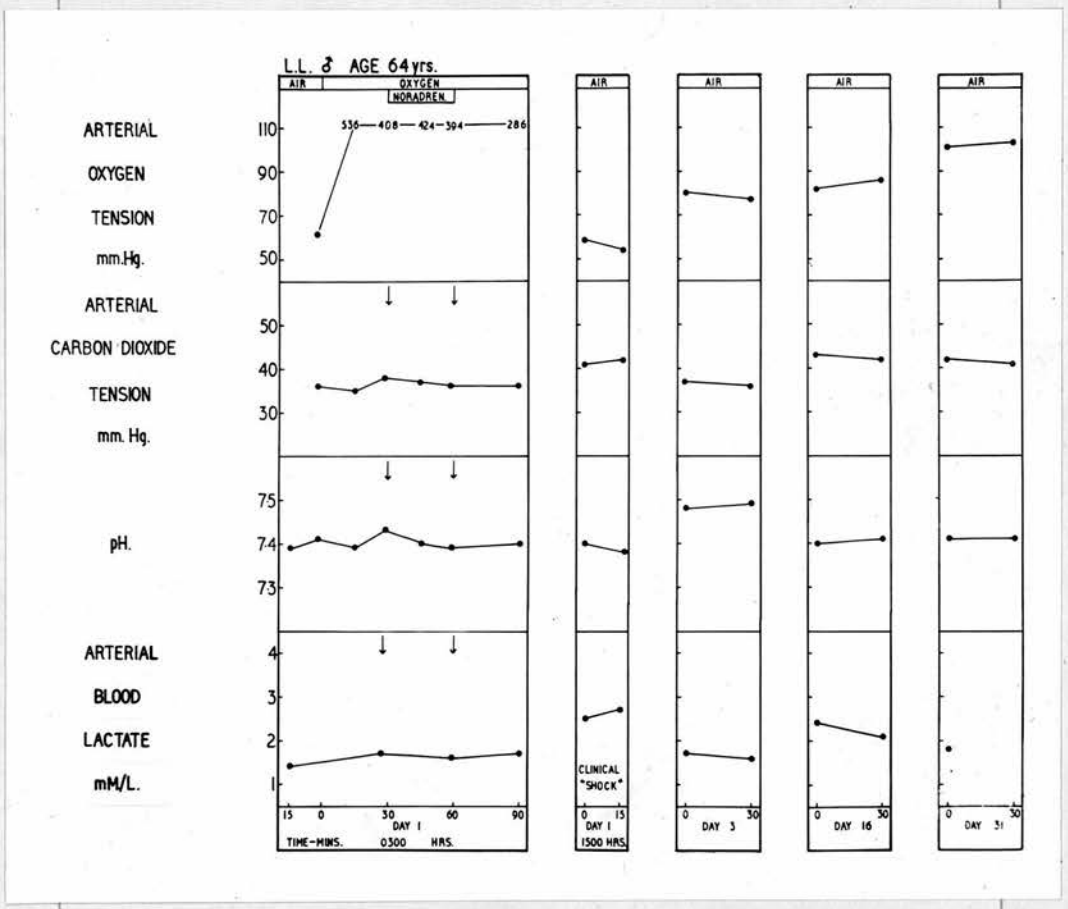


Fig. 47 (c)

Some arterial blood gas tension and metabolic changes in patient L.L.

control period. The circulatory response in this patient bears a close similarity to the first non-shocked patient with the one essential difference that an increase in cardiac output was observed on this occasion. This increase in cardiac output cannot however be upheld as evidence of a positive inotropic effect as the increase in stroke volume and cardiac output may conceivably have been due to an increased venous return.

The further treatment and progress of this patient is of some interest and will be discussed in some detail. Following the completion of the first circulatory evaluation at 0.300 hours, the patient was restarted on noradrenaline, the concentration of which was controlled by auscultatory blood pressure measurements. The dosage of noradrenaline was increased gradually and progressively whilst the blood pressure response became less and the patient's clinical condition deteriorated. Some 12 hours after the completion of the first circulatory study the patient had become completely unresponsive to noradrenaline therapy. The blood pressure was unobtainable. The patient appeared cold, clammy,

sweating with cyanosed extremities yet he retained complete mental clarity. The last mentioned clinical finding seemed out of place with the rest of the clinical picture and by the definition of this series appeared to exclude a diagnosis of "true" cardiogenic shock.

The noradrenaline infusion was stopped and a second investigative study was undertaken in an attempt to establish the underlying circulatory and pathophysiological state. The results of this study are illustrated in figs. 47 (a), (b) and (c) (Day 1, 1500 hours). The circulatory measurements at this time showed an increased, in fact normal cardiac output with associated marked reduction of the systemic vascular resistance. A relative tachycardia had been produced and was in the main responsible for the increase in cardiac output as the stroke volume showed a slight reduction. The central venous pressure had fallen. It is of some interest to note that the mean intravascular systemic arterial pressure was 68 mm.Hg at a time when the blood pressure was unrecordable by clinical auscultation in the arm. Fries et al. (1954) have likewise commented on the fact

that the intravascular measurement of arterial pressure in these shocked patients is often surprisingly high when compared with the sphygmomanometer readings obtained in the arm.

These circulatory findings demonstrate the existence of what might be described as "true peripheral circulatory collapse". It was considered at least likely that the clinical situation had deteriorated because of, rather than in spite of noradrenaline therapy. This pressor amine treatment was therefore discontinued and as the patient appeared to be "in extremis" massive doses of intravenous hydrocortisone were given on an emperical basis. The underlying rationale and value of such treatment may be questioned. A recent report by the Scientific Sub-Committee of the Scottish Society of Physicians (Lancet 1964) has shown no statistical benefit to be derived from the use of hydrocortisone in cardiogenic shock. The patient under consideration, however, either because of or in spite of such therapy, steadily and progressively improved and was discharged home from hospital free of any cardiac disability some five weeks later. This clinical improvement can be seen to have

been associated with a gradual reduction in tachycardia and an increase in both stroke volume and systemic vascular resistance (see fig. 47).

There are various points of interest arising out of this case which merit further consideration. As already discussed, the patient's retention of complete mental clarity raised doubts on clinical grounds as to whether this could be classified as "true cardiogenic shock". The acceptance of such a classification would imply a prolonged deficiency of blood flow and would be associated with a high mortality rate. The results of the circulatory and metabolic study are most revealing in this respect. The normal cardiac output allowed an adequate perfusion of the tissues (including presumably the brain, thereby explaining the mental clarity) and there was therefore little significant metabolic acidosis or accumulation of lactic acid as shown in fig. 47 (c). There was however some arterial hypoxaemia but this responded to 100% oxygen therapy in a satisfactory manner (the arterial oxygen tension increased from 57 to 304 mm.Hg). These findings contrast sharply with those of the low flow state and associated metabolic consequences as described in

cases of "true cardiogenic shock". It is not surprising to find that the prognosis is excellent in this condition with a normal cardiac output and this again contrasts sharply with the previously described shocked cases.

There would appear therefore to be ample justification for considering this patient separately from the group of cases exhibiting all the clinical features of cardiogenic shock. Although there is no direct evidence it would also appear to be a reasonable assumption that over-zealous noradrenaline therapy was responsible for the production of "peripheral circulatory failure". Burn and Rand (1959) have shown that during a noradrenaline infusion the blood vessels become increasingly insensitive to its pressor action. This lowered sensitivity appears to be due to the vessels taking up the drug and holding it in some kind of store from which it is slowly discharged. This slow discharge leaves few receptors free on which noradrenaline, present in the blood stream, can act. The progression of this stage to complete insensitivity of the blood vessels could explain the present case of "peripheral circulatory collapse" and

may well also explain many cases of apparent decreasing sensitivity to infused noradrenaline. The co-existence of a significant metabolic acidosis to explain decreasing sensitivity to noradrenaline as suggested by Matthes (1962) was clearly not responsible in the present case. Although Miller and Kaplan (1961 and 1963) formed the opinion that patients with hypotension following acute myocardial infarction should be treated with vasopressor drugs to prevent the onset of shock Heyer, (1961) considered such treatment to be unnecessary. Heyer further pointed out that these patients usually had a good prognosis without specific therapy. The evidence of the present case suggests that over-zealous noradrenaline therapy in such patients may in fact be positively harmful. The excellent prognosis in this case, who was hypotensive for a considerable period of time but with an adequate, indeed normal cardiac output demonstrates very adequately the relative importance of blood pressure and blood flow in shock. The essential central and critical factor in shock is the adequacy of blood flow, not pressure. Nickerson (1962) considered that the physicians

pre-occupation with the blood pressure was largely responsible for the popularity of vasopressor therapy. This reliance on the blood pressure is understandable in that it is not only easily measured but also appears to convey an accurate and objective scientific measurement of considerable importance. In fact, the auscultatory measurement of blood pressure is often quite unreliable in the presence of shock. While there can be no denying the value of a blood pressure measurement there would appear to be a tendency amongst clinicians to forget the physiological fact that blood pressure is the resultant of the cardiac output and the peripheral resistance. The maintenance or improvement in blood pressure cannot be regarded as synonymous with similar changes in blood flow. In the absence of direct blood flow measurements the direct monitoring of changes in the urinary output, or changes in the degree of metabolic acidosis or lactic acidaemia are probably more reliable long term indices than the measurement of blood pressure in the assessment of the value of treatment and the prognosis in shock of any cause.

SUMMARY AND CONCLUSIONS

An attempt has been made to evaluate the place of noradrenaline infusion therapy in cardiogenic shock.

The circulatory effects in the hypotensive but otherwise non-shocked patient have been shown to be similar to those found in normal man, i.e. the predominant observed effect is an increase in systemic vascular resistance producing an increase in blood pressure with a resultant reflex bradycardia and increase in stroke volume. The circulatory effects observed in the two patients with cardiogenic shock have shown not only predominantly a peripheral effect with an increase in systemic vascular resistance but have also shown the development of a tachycardia and a progressive deterioration of myocardial performance. Although noradrenaline may well have a place in the treatment of some patients, the evidence presented suggests that, in certain circumstances the excessive increase in myocardial oxygen demands resulting from such therapy may lead to progressive myocardial deterioration.

The production of a state of "peripheral circulatory collapse" due to over-zealous noradrenaline therapy in a

hypotensive but non shocked patient has been demonstrated and discussed.

These findings can only be described as a beginning in an attempt to evaluate the place of vasopressor therapy in cardiogenic shock. The measurement of overall systemic vascular resistance leaves completely unanswered the effects of this treatment on the various regional circulations. There is an obvious need to study not only more patients but also to extend the circulatory flow measurements to include the regional territories. There are also many other pressor amines which would deserve more definitive evaluation in a similar manner.

PROSPECTS FOR THE FUTURE

Although these studies may be regarded as having added to our knowledge and understanding of the basic pathophysiology of cardiogenic shock, there are many problems which remain unanswered, both from the aetiological and the therapeutic aspects. At the completion of such a study, the clinical investigator, who has been working along a comparatively small and narrow aspect of a large and complicated problem is reminded of the words used by Richards (1944) to end his Harvey lecture on the circulation in traumatic shock in man "..... the greatest mistake is to suggest, as some have done, that shock is a problem that has been solved". There is indeed much need for further research.

The results of the present study have not only indicated this need but have also suggested clear lines for further research activity. The logical continuation of the present investigation would be to test the validity or otherwise of the various therapeutic postulates, which

have been advanced, e.g. will a "combined therapeutic attack" on the metabolic acidosis and arterial hypoxaemia improve the mortality statistics of cardiogenic shock and will the correction of the acidosis improve the cardiotonic effect of digoxin in these patients?

The abnormalities causing the disturbance of ventilation-perfusion relationships in shock require a more definitive evaluation if a logical approach is to be adopted to the adequate correction of the arterial hypoxaemia. The fact that these patients usually have shallow breathing and are treated lying flat suggests that further investigation of the hypoxaemia should include the effects of both deep breathing and of change in posture. It is tempting to suggest that if the underlying cause was found to be predominantly widespread alveolar collapse, it may well be considered that the best method of ensuring adequate oxygenation would be by means of positive pressure respiration. The respiratory advantages of this technique could, however, at least theoretically, be outweighed by the possible circulatory complications, involving a reduction in

cardiac output. A definitive evaluation of such theoretical considerations could be undertaken in a manner similar to the presently reported study.

This present study has suggested that, at least in some cases, noradrenaline may lead to a deterioration of myocardial function with a progressive increase in the degree of myocardial oxygen debt. An investigation into the value of blocking or at least mitigating the central cardiac effects whilst maintaining the apparent advantages of an increased perfusion pressure may appear to be worthwhile. In a simplified form Ahlquist's (1948) theory of adrenergic cellular receptor mechanisms distinguished between two types of receptor, 1. alpha receptors predominantly associated with peripheral sympathetic excitatory functions, and 2. beta receptors associated with predominantly central sympathetic excitatory functions. In 1958 Powell and Slater first introduced a specific adrenergic B-receptor antagonist. Moran and Perkins (1958) showed that this drug effectively antagonised the changes produced in both myocardial rate and tension by catecholamines. Although

Dornhorst and Robinson (1962) have advised caution in the use of such "beta blocking" drugs in circulatory failure, there may well be a place in the treatment of cardiogenic shock for a combined approach with both noradrenaline and a beta-receptor antagonist. Such a hypothesis could be investigated and evaluated in a similar manner to the present study and would necessitate a careful titration of the required amounts of each drug with a constant monitoring of response. Luria et al. (1964) have recently successfully used such a combination of drug therapy for the treatment of prolonged hypotension on the basis that the latter was due to a peripheral imbalance between alpha and beta receptor mechanisms. Similar mechanisms may be operating in cardiogenic shock and are certainly worthy of more detailed study.

Finally it should of course be stated that the various artificial methods of maintaining the circulation are worthy of further research and investigation. Stuckey et al. (1957) demonstrated in three patients with cardiogenic shock refractory to vasopressor therapy that partial cardiopulmonary bypass may temporarily

maintain the blood pressure. However total cardiopulmonary bypass is not readily applicable clinically. In 1961 Claus et al. introduced a new technique of mechanical circulatory assistance which they termed synchronous arterio-arterial pumping. This involved the rapid aspiration of blood from the lower aorta during systole and its re-injection under pressure during diastole, the action of the pump being synchronised with the R-wave of the electrocardiogram. The purpose of such synchronous arterio-arterial pumping is to reduce the systemic arterial pressure and resistance and thus reduce the work of the left ventricle while at the same time increasing the diastolic blood pressure and improving coronary blood flow.

In the present state of our knowledge a combined therapeutic approach involving synchronised counterpulsation in a high pressure oxygen chamber with efficient administration of oxygen and correction of associated complicating metabolic acidosis may be regarded as the most likely to result in some improvement of the presently reported high mortality statistics.

An evaluation of such an approach by those who have the appropriate facilities would appear to be worthwhile.

Further progress in the technical field of cardiovascular research is also to be anticipated. The development and application of less cumbersome techniques in both patient investigation and analysis of data will greatly facilitate the undertaking of such studies. The advent of indirect, yet precise methods of circulatory measurement allied to automatic and computor methods of data analysis will allow the immediate interpretation of the basic circulatory abnormality. The appropriate specific therapy may then be instituted and the circulatory response evaluated with an ease and rapidity which is at present impossible.

In the future, the intensive care of the patient with acute myocardial infarction may well profitably combine continuous physiological as well as electrocardiographic monitoring systems.