MYOCARDIAL PRESERVATION DURING AORTIC VALVE REPLACEMENT: A PROSPECTIVE RANDOMISED COMPARISON OF TWO DIFFERENT METHODS

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A number of people inspired, guided and helped me to carry out the work on which this thesis is based. The work was carried out between October 1972 and September 1973 in the Department of Surgery, The Medical Centre, The University of Alabama in Birmingham, Alabama, The United States of America. Dr. John W. Kirklin, as Chairman of this Department, has long been known for his essentially practical approach to research in cardiovascular surgery. This approach has led to the publication of the results of many good contributory pieces of work carried out in his departments, first at the Mayo Clinic and then in Birmingham, Alabama, during a career that has spanned the history of open heart surgery. He has nearly always used coronary perfusion to preserve the myocardium during aortic valve surgery, but not without regard, firstly to the reports of the safety of other methods or, secondly, to the hazards and drawbacks of coronary perfusion itself. As a consequence he together with some of the other surgeons in his Department commenced using a method of profound myocardial hypothermia without coronary perfusion on some patients and found that there was no noticeable difference in their mortality and morbidity figures. He therefore posed the question: Was one or other method superior if they were compared using more sensitive indices?

During the carrying out of the work, Dr. Kirklin continued to guide and advise in a way that greatly contributed to the validity of the conclusions finally reached.

The work was carried out on patients under the care of Dr. Kirklin and his three colleagues in the Department. Drs. Robert B. Karp, Nicholas T. Kouchoukos and Albert D. Pacifico were all encouraging and helpful in their suggestions and criticisms of the aims and methods employed in the study and co-operated very generously in allowing their patients to be studied and in carrying out the necessary instrumentation during operation.

Special mention must be made of Dr. Eugene H. Blackstone. He took a very active part in the work. His advice during the formulative period was invaluable, based on a wide experience of experimental method and the technical problems of carrying out a project of this nature. The project generated a large amount of data and Dr. Blackstone was entirely responsible for helping in reducing this data to usable proportions, using his knowledge and experience in computer science. His enthusiasm, interest and knowledge were a source of continuous inspiration.

Dr. Charles R. Roe was approached during the early stages of the project to help with the enzyme and isoenzyme determinations. He readily agreed and from that point on took a very active interest in the

project and provided many ideas as well as a considerable body of information about these determinations and their value in assessing myocardial cell necrosis during cardiac surgery.

The study generated a large body of data which required statical evaluation. Dr. Edwin L. Bradley, PhD, of the Department of Biostatistics, at the School of Medicine and Medical Centre, The University of Alabama in Birmingham, Alabama, undertook to help me with this daunting task and his help proved to be invaluable in answering the many questions put to him in the form of statistical statements and values which allowed us to draw our conclusions, without fear of serious criticism on these grounds.

I received technical help from a group of people, all of whom played an essential part in the study and to whom I am indebted. William G. Tracy, BS, played a large part in the overall project. He helped to provide the haemodynamic monitoring equipment, by modifying a portable multichannel recorder to the needs of the study. He helped with the acquisition of the raw data and he was particularly helpful in ensuring the supply and maintenance of all disposable and re-usable equipment necessary for the day-to-day running of the project.

I also received valuable technical assistance from Mrs. Nona Roberson, Mrs. Myra Barbaree, Mr. Robert Brown and Mr. Dean Pappas. Without the help of these persons the acid-base and metabolic studies would not

have been possible.

One of the largest tasks in the preparation of a thesis is the secretarial help and typing. I am greatly indebted to Mrs. Christine Froomes, of the Hospital for Sick Children, Great Ormond Street in London and Miss Maureen Murray of the Hammersmith Hospital in London for help with this daunting task.

Dr. John W. Kirklin posed a question and I was left the task of working out how this question could best be answered. I spent the first four months of my year in Birmingham Alabama reviewing the literature to bring myself up to date with all work that had been done in this field before. This review led me to believe that no previous prospective and randomised trial of this type had been carried out. The first task, therefore, was to devise a system of prospective randomisation which would leave the study beyond criticism from this point of view. I looked at various methods to do this and finally decided on the method using random digit tables as the one least likely to raise criticisms of selection. The next major problem was to select from a very large number of possible studies and determinations, those which would be in the first place sufficiently sensitive to show up any differences between the two groups of patients studied - if there were any and, secondly to be of sufficient practical value to use in the intensive care situation. Once more recourse had

to be had to the literature and during the process of reviewing the literature on this subject I personally learnt a great deal about the parameters and measurements which one can make to conduct such a study.

At the end of this period I had devised a set of investigations which I felt would fulfil these needs and which would, I hoped, provide some form of answer to the question.

I was entirely responsible for the organisation of the study when once we turned our attention to the patients. As we wished to study a consecutive group of patients, prospectively randomised to one method or the other, it was essential that no patients were missed and the organisation proved to be one of the most difficult problems of all since this work was being carried out in a busy cardiac surgical unit doing a large number of open-heart operations every week.

Each patient was studied serially and at each study a battery of determinations were carried out. I was responsible for carrying many of these determinations out myself and supervising each individual study as regards those investigations which were later carried out in the laboratory.

Each study generated data which I was responsible for collecting and recording on suitably prepared flow charts. The data was largely collected in code form for later use by the computer to evaluate the

results. The data collection lasted for a period of approximately five months.

When once the data had been collected, it was now necessary to pose the necessary questions of our statistician, in order to arrive at answers which would have meaning in relation to this study. This initially involved a large amount of data reduction to which I previously referred in my acknowledgement to Dr. Eugene H. Blackstone.

In conclusion, my involvement in this study was one of devising, organising, carrying out of the necessary determinations, collection of the raw data, data reduction and finally working out the methods of presentation so as to allow publication of this work.

CONTENTS

CHAPTER I

INTRODUCTION

The first operation on the aortic valve was carried out in 1912. Since 1947 these operations have been carried out regularly throughout the world. Cardiopulmonaey bypass was first used to facilitate operation on the aortic valve in 1958. This has, and still does, allow the aortic valve to be operated on through the aortic root. In order to do this the ascending aorta has to be cross-clamped between the site of arterial return of the perfusate and the coronary ostia, thus depriving the myocardium of its blood supply for the duration of the procedure. Myocardial preservation during aortic valve surgery has been, and still is, a problem which undoubtedly contributes to the mortality and morbidity of these operations to this day. The non-perfusion arrest, which was produced by this manoeuvre, was accepted by some surgeons as adequate and the necessary procedure carried out. Many surgeons will still use normothermic non-perfusion arrest today for short procedures, such as aortic valvotomy in congenital aortic stenosis and some even accept it as adequate for longer procedures, such as aortic valve replacement.

Three methods of myocardial preservation, used either singularly or in various combinations, have been developed for operations on the aortic valve using cardiopulmonary bypass.

Chemical cardioplegia using potassium chloride, potassium citrate or acetyl choline was one of the earliest used methods. It was soon abandoned, however, because the method was superseded by other methods thought to be more satisfactory and because of early reports of toxicity of the agents used. Of necessity it was used in conjunction with non-perfusion arrest of the heart and most surgeons used a variable degree of hypothermia as well.

Hypothermia has been used every since 1956. Mild hypothermia ($32^{o}C$) or moderate hypothermia ($28 - 31^{o}C$) was initially achieved by whole body surface cooling. At this time it was used as an adjunct to non-perfusion arrest of the heart. With the advent of cardiopulmonary bypass and coronary perfusion, mild or moderate hypothermia was usually induced by perfusion and it was used as an adjunct to non-perfusion arrest of the heart or coronary perfusion of the myocardium. Profound hypothermia (below $27^{o}C$) was either achieved using whole body cooling, or topical cooling of the heart and was and still is used as an adjunct to non-perfusion arrest of the heart.

Coronary perfusion was developed early in the history of aortic valve surgery. Oxygenated blood from the pump oxygenator is pumped into both main coronary arteries through catheters which had been inserted into them through their ostia from inside the opened aortic root. Ideally the perfusion pressures developed in each system,

together with the flows, should be controlled so as to keep these within the limits which would pertain under resting conditions in health. This method thus ensures that the myocardium is perfused with oxygenated blood for most of the procedure, in the same way that the rest of the body is being perfused.

Today myocardial preservation is achieved largely by two broad combinations of two of these methods.

The majority of surgeons use coronary perfusion either at normal temperature or together with whole body mild, or moderate hypothermia produced by core (perfusate) cooling on cardiopulmonary bypass. A few surgeons use non-perfusion arrest of the heart together with moderate or profound hypothermia. This is achieved either by core (perfusate) cooling or topical cooling of the heart. There is a large body of evidence that both methods have serious shortcomings in achieving their goal. Many of these shortcomings have been documented but are still unavoidable and must at present be accepted as contributing to the risks of the procedure irrespective of the method used.

The two methods are being used successfully throughout the world. The mortality and morbidity figures for operations on the aortic valve, using either method, have steadily fallen to the point where they themselves are no longer a sensitive indication of any advantages possessed by one or other of the methods. Comparisons are also

difficult since no prospective randomised studies comparing the two methods or any combination or permutation of the various methods have been reported to date.

AIM

The aim of the present study was to determine whether there were any differences, detectable by the methods used, between coronary perfusion at moderate hypothermia or profound myocardial hypothermic non-perfusion arrest, in their abilities to preserve the myocardium in patients undergoing aortic valve replacement.

CHAPTER II

HISTORY AND DEVELOPMENT

Surgery of the heart and great vessels is almost entirely a development of this century. It has come about in three phases, with periods of overlap between the first and second and the second and third and those features of value in each of the first two phases have been retained to contribute to the armamentarium of the cardiac surgeon as he is today.

The first phase in the development of cardiac surgery was characterised by carrying out operations on the heart and great vessels while the heart was still beating and supporting the patients circulation. There are many examples of this pioneering surgery and many of the operations still survive today, particularly those on the great vessels. In 1912 Tuffier (Tuffier, T. 1913) described a successful trans-aortic, aortic valvotomy. In 1923 Cutler and Levine reported the first successful case of transventricular mitral valvotomy (Cutler, E.C., Levine, S.A. 1923) followed in 1925 by Sir Henry Souttar's report of a similar operation from this country (Souttar, H. 1925). In 1939 Gross of Boston reported the first successful ligation of a patent ductus arteriosus (Gross, R.E. 1939): and in 1944 Crafoord performed the first successful resection of a coarctation of the aorta (Crafoord, C. 1945). Tetralogy of Fallot was also a condition which occupied the minds of cardiac surgeons during this period and in 1945 Blalock and Taussig described the use of the pulmonary artery to systemic artery anastomosis (Blalock, A.,

Taussig, H.B. 1945). In 1948 Lord Brock described his operation of pulmonary valvotomy for isolated pulmonary stenosis which he later developed as a useful operation for isolated infundibular stenosis, as well as infundibular resection in Tetralogy of Fallot. (Brock, Sir Russell 1951). Many other workers developed all these procedures which in their turn stimulated a considerably greater study of the disease conditions which were being treated.

The second phase in the development of cardiac surgery was brought about by the use and development of hypothermia as a means of allowing direct intracardiac operations to be carried out. A considerable body of experimental work preceded the first reported case of the use of hypothermia in the human to close an atrial septal defect by Lewis in 1952 (Lewis, F.J. 1953). This was accomplished using whole body surface cooling, a technique used by many surgeons from that point on, to carry out the simpler intracardiac repairs. In 1955 Sir Russell Brock described an ingenious system which he had developed for cooling. He inserted tubes into the right atrium through the appendage, and connected them with tubes running to a refrigerating apparatus (Brock, R.C. 1955). Draw and his colleagues developed the use of hypothermia even further by setting up a double circuit. Blood was withdrawn from the left atrium and passed through a cooling coil using a sygmamotor pump. The blood was returned through a cannula in the femoral artery.

At the same time blood was withdrawn from the right atrium and returned to the pulmonary circulation through a stab wound in the infundibulum of the right ventricle. This blood was not cooled. The technique allowed pround hypothermia to be induced and at the same time the patient's own lungs were acting as an oxygenator. (Drew, C. E., Keem, G., Benazon, D.B. 1959). The advent of hypothermia undoubtedly contributed enormously to the development of cardiac surgery, but it still possessed many serious limitations.

The third phase in the development of modern cardiac surgery was concerned with the development of the extracorporeal circulation, or cardiopulmonary bypass as it is now commonly known. Experimental work to bypass both the heart and the lungs had been going on for many years. Gibbon is attributed with developing the original concept as far back as 1931 and by 1934 he and his wife were carrying out active experiments on laboratory animals which proved that this was indeed a possibility. In 1937 he published his first paper on the subject. (Gibbon, J.H. 1937). The principle problem in the development of extracorporeal circulation lay in the development of the oxygenator. Gibbon in his experimental work used a rotating drum oxygenator, whereby a thin film of blood spread over the surface of the drum was exposed to an oxygen and carbon dioxide mixture in the surrounding chamber. Other workers, notably Bjork, (Bjork, V.O. 1948),

Melrose (Melrose, D.G. 1953) and Kay and Cross together with colleagues (Kay, E.B., Galjda, J.E., Lux, A., Cross, F.S. 1958) developed the disc oxygenator whereby rotating discs dipped into the blood and lifted a thin film of blood on each disc into the upper part of the chamber through which the mixture of oxygen and carbon dioxide were circulating. In 1956, Lillehei and his associates devised the first of many bubble oxygenators (Lillehei, C.W., Wall, R.A. 1958). In this apparatus bubbles of oxygen were fed directly into a column of blood, the large number of bubbles producing a large surface area from which oxygen could be absorbed into the blood itself.

During this time work was continuously going on to develop and improve tubing systems, heat exchanger systems and pump systems, so as when finally fully assembled the modern heart-lung machine of today was produced. Work is still going on to develop and improve this equipment and currently the membrane oxygenator is a source of widespread research and development.

Extracorporeal circulation was first successfully used in a human in 1953 to close an atrial septal defect. From that point on its use gre rapidly. Surgeons all over the world began doing more and more operations inside the heart and at present procedures are carried out with the aid of extracorporeal circulation which were

thought totally inoperable little more than twenty years ago.

The aortic valve was first operated upon under direct in 1958. Dye and his associates used hypothermia to achieve this (Dye, W.S., Julian, O.C., Grove, W.J., Moorehead, D.E., Prec, O. 1959). Bahson, and his associates in the same year carried out operations on congenital aortic stenoses using cardiopulmonary bypass (Bahson, H.T., Spencer, F.G., Neill, C.A. 1958).

Surgery on the aortic valve posed an immediate and unique problem as soon as cardiopulmonary bypass was used. The aortic valve could only be approached through the aortic root. This necessitated occlusion of the aorta by a cross-clamp between the site of the arterial perfusion into the femoral or iliac artery or upper end of the ascending aorta and the coronary ostia in the sinuses of valsalva. The result of this necessary manoeuvre was to leave the myocardium deprived of a blood supply for the duration of the procedure.

Various methods were developed, either to reduce the myocardial oxygen requirements of the heart, or to provide the myocardium with a blood supply during the operation.

CHEMICAL CARDIOPLEGIA

Various chemical agents were found to be effective in producing cardioplegia. Three, namely potassium chloride, (Lam, C.R., Geoghegan, T., Lepore, A. 1955); potassium citrate, (Melrose, D.G.

Dreyer, B., Bentall, H.H., Baker, J.B.E. 1955; Baker, J.B.E., Bentall, H.H., Dreyer, B., Melrose, D.G. 1957) and acetyl choline (Lam, C.R., Gahagan, T., Sergeant, C., Green, E. 1958) were extensively tested, first in the laboratory (Kolff, W.J., Effler, D.B., Groves, L.K., Peereboom, G., Aoyama, S., Sones, F.M.Jr. 1958; Nunn, D.D., Belisle, C.A., Lee, W.E.Jr., Parker, B.F. 1959) and later during cardiopulmonary bypass surgery in patients (Moulder, P.V., Thompson, R.G., Smith, C.A., Adams, W.E. 1956; Effler, D.B., Groves, L.K., Sones, F.M.Jr., Knight, H.F., Kolff, W.J. 1957; Sones, F.M.Jr. 1958; Lam, C.R., Georghegan, T., Sergeant, C., Green, E. 1958), where they were utilised with encouraging initial results.

Chemical cardioplegia produced a flaccid asystolic heart which greatly facilitated intracardiac procedures. The oxygen consumption of the chemically arrested heart was shown to be 20 to 30% of normal resting values (Willman, V.L., Neville, E.C., Hanlon, C.R. 1958; Beuren, A., Bing, R.J., Sparks, C. 1958; McKeever, W.P., Gregg, D.E., Canney, P.C. 1958; Bing, R.J. 1959; Clark, L.C.Jr., Berg, F., Lyson, C., Kaplan, S., Edwards, W.S. 1960) and the oxygen availability was also shown to be higher in these hearts. (Greenberg, J.J., Edmonds, L.H.Jr., Brown, R.B. 1960). Venting was also thought to be a useful adjunct as it reduced the transmyocardial wall tension to zero, in addition

to preventing accidental over-distension of the ventricle and reduced the incidence of air embolism (Miller, B.T., Gibbon, J.H.Jr., Greco, V.F., Cohen, C.H., Allbritten, F.F.Jr. 1954).

In 1971 Braunwald published a review that rationalised these observations (Braunwald, E. 1971). He clearly delineated isovolumetric and isotonic contraction of the myocardium as the major determinants of myocardial oxygen consumption. Chemical cardioplegia, by abolishing these determinants, thus lengthened the period that the heart would tolerate a non-perfusion arrest.

The mortality, during and following intracardiac procedures using chemical cardioplegia, remained high. At this early stage it was often difficult to separate those deaths due to faulty diagnosis, operative errors and post-operative problems, from those due to the method used (Effler, D.B., Groves, L.K., Sones, F.M.Jr., Knight, H.F., Kolff, W.F. 1957) but chemical cardioplegia itself undoubtedly contributed to this mortality. Many workers demonstrated experimentally that after the use of these agents a depression of left ventricular function occurred (Willman, V.L., Cooper, T., Zafiracopoulos, P., Hanlon, C.R. 1959; Greenberg, J.J., Edmonds, L.H.Jr., Brown, R.B. 1960; Waldhausen, J.A., Braunwald, N.S., Bloodwell, R.D., Cornell, W.P., Morrow, A.G. 1960; Kusunoki, T., Cheng, H.C., Maguire, H.H., Bosher, L.H. 1960). Other workers noted the invariable cardiac

dysrhythmias that occurred during operations in which chemical cardioplegia was used (Lam, C.R., Geoghegan, T., Lepore, A. 1955; Young, W.G.Jr., Sealy, W.C., Brown, I.W.Jr., Hewitt, W.C.Jr., Calloway, H.A.Jr., Merrit, D.H., Harris, J.S. 1956; Schramel, R.J., Ross, E., Morton, R.D., Creech, O.Jr. 1957; Weirich, W.L., Jones, R.W., Burke, M.F. 1960). A third group of workers demonstrated definite myocardial lesions which they attributed to the cardioplegic agents used (Helmsworth, J.A., Kaplan, S., Clark, L.C.Jr., McAdams, A.J., Matthews, C., Edwards, F.K. 1959; McFarland, J.A., Thomas, L.B., Gilbert, J.W., Morrow, A.G. 1960; Miller, D.R., Rasmussen, P., Kliionsky, B., Cossman, F.P., Allbritten, F.F.Jr., 1961; Hoelscher, B., Just, G.H., Merker, H.J. 1961; Miller, D.R., Rasmussen, P., Klionsky, B. 1964). Finally it was demonstrated that in fact the different agents had different effects on myocardial oxygen consumption, potassium chloride and acetyl choline were both shown to increase it, only potassium citrate was found to lower it consistently (Adachi, M. 1968). Potassium citrate was also found to result in an inability of the myocardial oxygen consumption to return to control values following the arrest, during which there was a consistent increase in lactic acid production by the heart, when the period of arrest was of sufficiently short duration to allow survival

of the animal (Greenberg, J.J., Edmonds, L.H.Jr., Brown, R.B. 1960).

As a consequence of these findings and because methods which appeared less harmful were being developed and assessed, chemical cardioplegia fell into disuse. Today, however, there is a renewed interest in chemical agents that can induce cardioplegia and a wide variety of substances and mixtures are being tried out in the experimental animal and in man (Nakae, S., Webb, W.R., Salyer, K.E., Unal, M.O., Cook, W.A., Dodds, R.P., Williams, G.T. 1967; Kirsch, U., Rodewald, G.B., Kalmar, P. 1972). It is also possible that some of the original conclusions which resulted in abandoning the agents then in use may have been erroneous and that agents like potassium citrate may still have a role to play, if it was re-evaluated (Bentall, H.H., Melrose, D.G. 1975; Hearse, D.J. 1976).

HYPOTHERMIA

Moderate hypothermia induced by immersing the entire patient in a waterbath at a suitably low temperature, has been in use to allow intracardiac repairs to be carried out since 1953. This technique was based on a large body of experimental work, principally by Gollan and his co-workers (Gollan, F., Blos, P., Shuman, H. 1952; Gollan, F. 1954; Gollan, F., Tysinger, D.S.Jr., Grace, J.T., Kory, R.C., Meneely, G.R. 1955; Gollan, F., Phillips, R., Grace, J.T. Jones, R.M. 1955; Gollan, F., Grace, J.T., Schell, M.W.,

Tysinger, D.S., Feaster, L.B. 1955; Gollan, F. 1959). This experimental work, confirmed in humans as soon as it was utilised, indicated that hypothermia reduced the oxygen demands of the heart, though to a lesser degree than in other tissues subjected to it (Edwards, W.S., Tuluy, S., Reber, W.E., Siegel, A., Bing, R.J. 1954; Tybjerg, H.A., Haxholdt, B.F., Husfuld, T.E., Lassen, N.A., Munck, O., Sorensen, H.R., Winkler, K. 1956; Jude, J.R., Haroutunian, L.M., Folse, R. 1957; Thauer, R., Brendel, W. 1962). Further studies quentitated this decrease in oxygen consumption as the temperature was lowered (Jordan, J., Lochner, W. 1962; Lochner, W. 1963; Arnold, G., Lochner, W. 1965). Hypothermia itself, in a heart that is being perfused, does not result in cardiac standstill only in cardiac slowing until very low temperature levels are reached, usually below those of practical clinical value, and even then electrical activity continues (Bernhard, W.F., Schwarz, H.F., Mallick, M.P. 1960; Bonhoeffer, K., Standfuss, K. 1964; Bretschneider, H.J. 1964; Kubler, W. 1964). There is now also evidence that the myocardial oxygen consumption per beat actually rises as the temperature is lowered (Archie, J. 1975). The effects of hypothermia on lowering myocardial metabolism are enhanced by the non-perfusion arrest, as this obligatory manoeuvre together with left ventricular venting removes the major determinants of myocardial oxygen

consumption, namely isovolumetric and isotonic contractions. This information provided a basis for using hypothermia to preserve the myocardium during aortic valve surgery.

Many terms relating to the degree of hypothermia have been and are currently in use. For the purpose of this discussion the following terms will be used and adhered to. Normothermia refers to a temperature of $37^{o}C$. Mild hypothermia indicates a temperature range of $32^{o}C$ to $36^{o}C$. Moderate hypothermia refers to a temperature range of $28^{o}C$ to $31^{o}C$. While profound hypothermia indicates a temperature below $27^{o}C$ ranging down to approximately $10^{o}C$. Temperatures lower than $10^{o}C$ have not been found useful in man.

Hypothermia was initially achieved using whole body surface cooling, as previously mentioned. Brock introduced the method of cooling by withdrawing the venous blood from the patient and passing it through a heat exchanger before returning it to the patient. This method of core cooling, as opposed to surface cooling, became standard practice with the advent of cardiopulmonary bypass. The venous blood, withdrawn from the patient to pass through the pump oxygenator would be passed through a heat exchanger so that any desired level of hypothermia could be induced before returning the blood to the patient via the arterial cannula. Core cooling developed as cardiopulmonary bypass methods were improved, both in efficiency and safety to the patient,

as a result of the development of heat exchangers and an understanding of the rates of coolings so as to avoid too large gradients of temperature from one part of the body, or from one tissue to another.

Regulation of the patient's temperature in this fashion required, and still does require, accurate control of the temperature of the water used both to cool the patient's blood in the heat exchanger and also to re-warm the blood and most perfusionists today maintain a temperature record of the perfusate temperature which is being returned to the patient. The effect of the cooling, or re-warming on the patient, also requires monitoring and it is now common in cardiac surgical practice to record one or more of four different temperatures in the patient, so as to form a picture of what is happening not only to the heart, but to the rest of the body as well. Brain temperature is most commonly monitored by a temperature probe placed in the nasopharynx; myocardial temperature is monitored indirectly in most cases by placing a temperature probe in the mid-oesophagus; and the splanchnic temperature is usually monitored with a suitable probe placed in the rectum.

Before the institution of coronary perfusion, myocardial hypothermia was achieved as part of the whole body core cooling, and had to reach the desired level before the aorta could be cross-clamped. Coronary perfusion permitted aortic cross-clamping to be

carried out early and myocardial cooling to be continued, either to the same temperature as the body or as in the practice of some surgeons to a lower temperature than the rest of the body (Urschel, H.C.Jr., Greenberg, J.J. 1959; Bernhard, W.F., Schwarz, H.F., Mallick, N.P. 1960). Coronary perfusion thus provided a greater range of myocardial hypothermia than was previously present.

During this time other groups of surgeons were working on the development of various methods of topical profound myocardial cooling. Crushed ice in saline placed in thepericardium around the heart was described to produce profound myocardial hypothermia by some groups of workers (Hufnajel, C.A., Conrad, P.W., Schanno, J., Pifarre, R. 1961; Hufnajel, C.A., Conrad, P.W. 1961; Sanger, P.W., Robicsek, F., Daugherty, H.K., Gallucci, V., Lesage, M.A. 1966). This method was largely abandoned, however, when other workers demonstrated cold injuries to the myocardium, pericardium and phrenic nerves (Speicher, C.E., Ferrigan, L., Wolfson, S.K.Jr., Yalav, E.H., Rawson, A.J. 1962). Shumway and his co-workers substituted cold normal saline at $4^{o}C$ to induce topical profound myocardial hypothermia, based on their own experimental work. (Shumway, N.E., Lower, R.R., Stoffer, R.C. 1959; Shumway, N.E., Lower, R.R. 1960; Hurley, E.J., Lower, R.R., Dong, E.Jr., Pilsbury, R.C., Shumway, N.E. 1964). This method possessed none

of the tendencies to produce the injuries previously described.when crushed ice in saline was used and is still in use today.

Myocardial hypothermia however induced, conferred many technical advantages to the surgeon in carrying out the required operation. The operative field was rendered bloodless and therefore facilitated accurate work, the heart was flaccid and immobile, enhancing accuracy, the aortic root was uncluttered by coronary catheters, a point of considerable value in small deeply placed aortic valve rings. Many surgeons have also felt that the use of one of the methods of hypothermic non-perfusion arrest resulted in a shorter period of aortic cross-clamping and a shorter period of cardiopulmonary bypass, although this latter fact is probably not true when topic myocardial hypothermia is employed as the heart requires a period in which to cool down and also a period of support during re-warming. The patient benefits from all these factors, as well as the fact that the amount of cardiotomy suction is considerably reduced during the procedure, thus reducing the extent of haemolysis and denaturation of plasma proteins with its attendant bleeding and renal problems (Lee, W.H.Jr., Krumhaar, D., Fonkalsrud, E.W., Schjeide, O.A., Maloney, J.V.Jr. 1961).

Hypothermic non-perfusion arrest of the heart suffers from two very serious drawbacks, however. Accidental over-distention of the

ventricles has been thought to cause serious disruption of the cellular architecture of the myocardium and therefore of inadequate myocardial function, following the discontinuation of cardiopulmonary bypass. There does not however appear to be any irrefutable evidence of this in the literature, presumably because of the difficulty in separating injury due to over-distension from that due to the methods themselves. The cooling heart in cases of aortic regurgitation has always been thought to be at risk of over-distension if myocardial cooling is carried out by the perfusate using the aortic root; before applying the aortic cross-clamp, because the aortic valve is unable to relieve the steadily failing ventricle of the perfusion pressure. The ventricles have also been thought to be at risk at the completion of the procedure, when the heart is being refilled, just prior to re-warming the heart. This risk should, however, be capable of abolition with adequate venting of the left ventricle.

The second and more serious problem is the length of time that can be allowed in which to complete the procedure. No definite time limits have as yet been clearly defined in the human heart, in spite of a considerable body of knowledge about the animal heart (Gollan, F., Blos, P., Shuman, H. 1952; Gollan, F., Grace, J.T., Schell, M.W., Tysinger, D.S., Feaster, L.B. 1955; Shumway, N.E., Lower, R.R., Stoffer, R.C. 1959; Helmsworth, J.A., Kaplan, S.,

Clark, L.C.Jr., McAdams, A.J., Matthews, C., Edwards, F.K. 1959; Gollan, F. 1959; Shumway, N.E., Lower, R.R. 1960; Greenberg, J.J., Edmonds, L.H. 1961; Lower, R.R., Stoffer, R.C., Hurley, E.J., Dong, E.Jr., Cohn, R.B., Shumway, N.E. 1962; Sato, R., Ogawa, K., Okada, M., Takeda, Y., Kimura, K. 1967). The tolerance of a given heart to non-perfusion arrest has been thought to depend on certain intrinsic factors, such as the degree of hypertrophy that exists, the presence of pre-existing myocardial disease, due to coronary artery disease, rheumatic fever or cardiomyopathies and to other degenerating changes attendant on aging (Vasko, J.S. 1967).

Hypothermia has now convincingly been shown to lengthen this time period and the degree to which it lengthens it is inversely proportional to the temperature at which the non-perfusion arrest is carried out (Tsifutis, A., Burton, R.M., Goldring, D. 1970). Most surgeons will accept that it is safe to use periods of non-perfusion arrest from about twenty minutes at 37^{o}C to about ninety minutes at 15^{o}C and even longer if the myocardial temperature is lowered to 10^{o}C. The reasons for this time limit at any given temperature are now well described (Braunwald, E. 1971). Irrespective of the myocardial temperature a greatly reduced cellular basal metabolism continues. The lesser determinants of oxygen consumption are not

abolished, these are the maintenance of the function and integrity of the cellular membrane, electrical activity and finally depolarisation changes which persist under these conditions. The basal oxygen consumption of the heart is about 20% of that of the contracting heart at normothermia. Depolarisation changes utilise only about 0.5% of the oxygen consumption of the normal beating heart.

In the absence of a supply of oxygen, glucose, lactate and fatty acids, the energy for these functions is provided anaerobically. Under hypothermic conditions, if total cessation of the coronary circulation occurs, as in accidental cardiac arrests, the following metabolic events occur; which can be divided into three time intervals. During the first or latency period the oxygen reserve of the heart is utilised (Bretschneider, H.J. 1964). This is about 0.8 volumes percent in room air (Opitz, E., Thews, G. 1952) or about 2.5 volumes percent during ventilation with pure oxygen at normal atmospheric pressure (Bretschneider, H.J. 1964). An average myocardial oxygen consumption of 0.1 millilitre per 100 grams of tissue per beat will suffice for a few contractions only. During the second period progressive functional deterioration occurs as the metabolism becomes anaerobic, in a heart that soon ceases to contract and does not therefore have to provide energy for isovolumetric and isotonic contration. The most important event, relating to the outcome, is

the decline of energy-rich phosphates. Creatine phosphate decreases first. It decreases from a normal value of 5 to 8 micromoles per gram to about 2 micromoles per gram within 3 to 4 minutes and it is no longer detectable after 6 or 7 minutes. Adenosine triphosphate next begins to decrease and has declined by about 15% after 3 to 4 minutes. In the third period adenosine triphosphate continues to decline and reaches 50% after 8 to 10 minutes, below which level it is no longer possible to resuscitate the heart (Opitz, E., Thews, G. 1952; Bretschneider, H.J. 1964; Kubler, W. 1964). Adenosine triphosphate breaks down to adenosince diphosphate then to adenosine monophosphate and finally gives rise to adenosine, inosine, hypoxanthine, xanthine and finally uric acid. All the end products from adenosine monophosphate onwards can pass through the cell membrane and therefore become lost to the cell for the purpose of regenerating adenosince triphosphate. In addition the degeneration process becomes irreversible between the stages of hypoxanthine and xanthine (Crowell, J.W., Jones, C.E., Smith, E.E. 1969). Adenosine monophosphate and adenosince are potent coronary vaso-dilators. This could potentially confer benefit by increasing coronary blood flow if there was blood flow at this time.

By the time these changes have occurred to the point beyond which the cell cannot recover, its glycogen content has only declined

to about 50% (Bretschneider, H.J. 1964). This highlights the fact that it is the decline of the energy-rich phosphates and not glycogen that determines the outcome for the cell and therefore the entire heart. These facts are a little difficult to correlate with most surgeons observations on the length of time a heart will tolerate a normothermic non-perfusion arrest; it is possible, however, that anaesthesia, pre-oxygenation, together with a degree of perfusion produced by the blood trapped between the aortic valve and the aortic cross-clamp and finally retrograde perfusion by blood in the right atrium passing backwards via the coronary sinus into the coronary circulation all contribute to account for this discrepancy.

Hypothermia prolongs these time intervals, but the same processes occur, only at a decelerated pace. They are never entirely abolished. Bretschneider and his co-workers renewed interest in combining chemical methods with hypothermia. They thought it likely that the residual oxygen demand of the cooled heart might be reduced by stabilisation of the cell membrane by means of extracellular sodium deprivation and the use of a local anaesthetic agent (Bretschneider, H.J. 1964; Kubler, W. 1964; Bonhoeffer, K., Standfuss, K. 1964). They tested their theory with a cold solution devoid of sodium but containing 5% Mannitol; 0.3% Procaine; 0.1% Glucose and 0.4% Potassium Chloride. They

found that the myocardial oxygen consumption was about ten times smaller than that obtained using hypothermia alone. This was confirmed by another group of workers (Bernhard, W.F., Schwarz, H.F., Malick, N.P. 1961). This combination of chemical cardioplegia and hypothermia has been used, but it has not been fully reported in the literature and has not been extensively tested.

In the laboratory animal the effects of non-perfusion arrest, both normothermic and hypothermic, were determined by direct measurement of adenosine triphosphate, creatine phosphate and glycogen, degradation and utilisation respectively, using a technique whereby samples of the myocardium were instantly frozen in liquid nitrogen (Wollenberger, A., Ristau, C., Schoffa, G. 1960). Adenosine triphosphate, formed in the mitochondria, is essential in high concentrations for the complex reactions between actin and myosin that results in myocardial contraction (Cain, D.F., Davies, R.E. 1962). For the sodium and potassium changes that occur in the sarcotubular system and the cell membrane which mediate the electrical activity of the cell (Hodgkin, A.L., Huxley, A.F. 1952; Hodgkin, A.L., Horowicz, P. 1959; Charnock, J.S., Rosenthal, A.S., Post, R.L. 1963; Post, R.L., Sen, A.L. 1964; Iselhard, W., Pohl, W. Berghoff, W.J.W., Scherbauch, D.S., Schüller, H.W. 1964; Krespi, V., Fazzard, A.A., Sleator, W. 1964) and for

many other energy requiring reactions in the cell. When the concentration of adenosine triphosphate falls due to hypoxia, there is an increased uptake of glucose, if this is available and a mobilisation of intravellular glucogen. Both are converted anaerobically to pyruvate (Lemley, J.M., Meneeley, G.R. 1952; Michal, G., Naegle, S., Danforth, W., Ballard, F.B., Bing, R.J. 1959; Regan, D.M., Davies, W.V., Morgan, H.E., Park, C.R. 1964), with the regeneration of adenosine triphosphate in the cytoplasm. This regeneration is however very inefficient by comparison. Thirty eight moles of adenosine triphosphate are produced by complete oxidative breakdown of 1 mole of glucose, via the respiratory chain and citric acid cycle (Figure 1), while only 2 moles are produced by anaerobic glycolysis (Lamprecht, W., Klarwein, M. 1962). Hypoxia also decreases the rate of pyruvate accumulates forcing the lactate-pyruvate reaction to shift towards lactate formation. Finally the cell ceases to take up lactate, if available, and commences to liberate both lactate and pyruvate because these substances can readily cross the cell membrane. The lactate-pyruvate relationship thus becomes an indirect method, whereby anaerobic metabolism can be detected in the human heart. They can both be quantitated in arterial and venous blood, either of

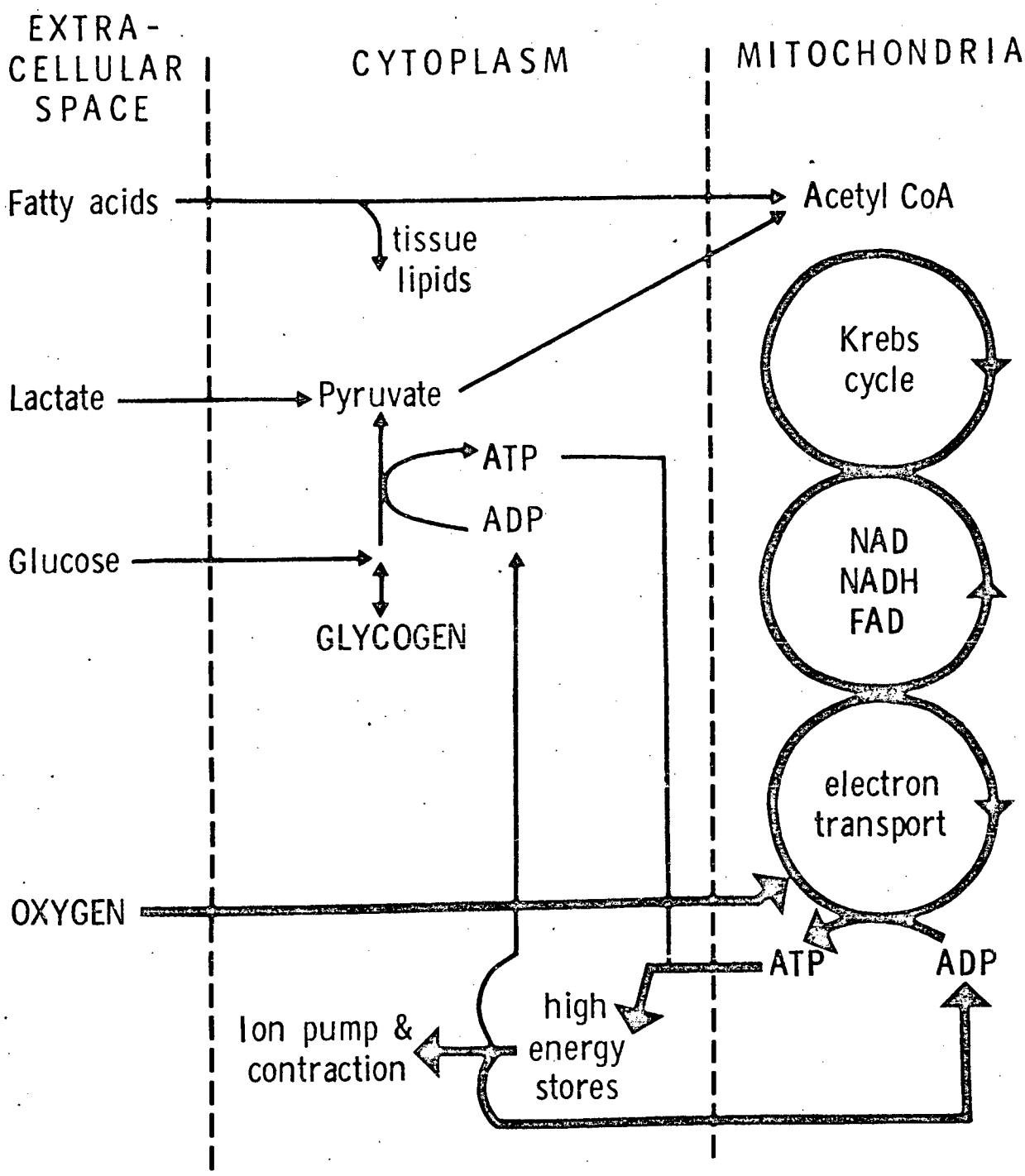

FIGURE 1

Schematic representation of the metabolic pathways in the normal myocardial cell.

(after Scheuer). Scheuer, J. Am. J. Cardiol. 19: 385, 1967.

the whole body, or different organs, and these values have in turn been used to calculate indices of anaerobic metabolism. These include the venous lactate concentration, the percentage lactate extraction, the percentage anaerobic metabolism (Huckabee, W.E. 1961); the excess lactate (Huckabee, W.E. 1961); the redox potential (Hakala, M.T., Glaid, A.J., Schwert, G.W. 1956; Jacey, M.J., Meiser, A.A., Schaefer, K.F. 1972; Jacey, M.J., Schaefer, K.F. 1972) and the electromotive force (Sigaard, O., Anderson, O. 1961; Gudbjarnason, S., Hayden, R.O., Wendt, V.E., Stock, T.B., Bing, R.J. 1962).

Doubt now exists as to the freedom with which lactate can cross the cell membrane, and it is probable that its extracellular concentrations are not a reliable guide to its intracellular concentrations, nor does it respond rapidly to intracellular changes (Glaviano, V.V. 1965). The same may apply to pyruvate. Therefore, measurements of blood lactate and pyruvate extraction by an organ are only indirectly related to the state of mitochondrial oxidative phosphorylation.

This evidence of anaerobic metabolism probably only occurs during that period when the cell and its membrane is viable and the situation is reversible. Some residual lactate and pyruvate liberation probably continues after cell necrosis, but it is probably

true to say that the presence of these indices under appropriate conditions, such as during an attack of angina pectoris (Krasnow, N., Gorlin, R. 1963; Cohen, L.S., Elliott, W.C., Klein, M.D., Gorlin, R. 1966), or during cardiac surgery, using cardiopulmonary bypass (Goldman, B.S., Trimble, A.S., Sheverini, M.A., Teasdale, S.J., Silver, M.D., Elliott, G.E. 1971; Goldschlager, N., Gerbode, F., Osborn, J.J., Cohn, K.E. 1972), represents a reversible state of anaerobic metabolism.

The fate of the myocardial cell depends on the duration of non-perfusion at any given temperature. Beyond a certain point the myocardium becomes incapable of immediately taking over its workload because of the low levels of available high energy phosphates. The individual cells, however, may not be irreversibly damaged and a period of further perfusion of the non-working heart, providing the necessary oxygen and substrates can result in regeneration of these high energy phosphate compounds and the replenishment of the intracellular glycogen.

During the latter stages of non-perfusion arrest, other changes occur which damage the cell structure, i.e. disrupt the anatomy of the cell by destroying the structure of the nuclear membrane, the cell membrane itself and the sarcotubular system, at the same time destroying their many complex functions. It is probable that

these changes are the consequency of a progressive intracellular acidosis brought about by anaerobic metabolism, which causes excess lactate production and accumulation. A proteolytic cathepsin with optimal activity at a low pH has been demonstrated in the anoxic rat heart (Dehaan, R.L., Field, J. 1959). It is probable, but not proven, that the intracellular acidosis can lower the pH to levels low enough to activate this enzyme which then destroys protein in the cell. The intracellular acidosis also partially inactivates many of the enzymes concerned with normal metabolic pathways, because they are no longer functioning within their optimum pH range. Hypoxia has also been demonstrated to release cardiac lysosomal enzymes, which act on a large variety of substrates (Brachfeld, N., Gemba, T. 1965) that may alter important chemical reactions and anatomic relations within the cell. The end products of anaerobic metabolism of many sorts are now liberated into the interstial fluid surrounding the cell where they may continue the process of destruction on neighbouring cells of all types including the cells of the capillary network related to the myocardial cells. The small molecules are largely removed via the venous effluent when once circulation has been re-established while the large protein molecules, which cannot readily cross the basement membrane of the capillaries into the venous effluent, are conveyed to the systemic venous system by the lymphatic drainage

of the myocardium (Roe, C.R. 1974).

Excessive quantities of large protein molecules, such as the detection of enzymes in the blood, is evidence of cell necrosis. If it is known that a given enzyme, or one or more of its isoenzymes come from a specific type of cell, the cells which have undergone necrosis can be identified. The human myocardial cell, amongst others, is now known to liberate the MB isoenzyme of creatine phosphokinase and isoenzymes 1 and 2 of lactic acid dehydrogenase (Roe, C.R., Limbird, L.E., Wagner, G.S. 1972).

Hypothermia is not without its problems for the rest of the body. Patients of all ages tolerate mild and moderate hypothermia, for the length of time required to carry out most intracardiac operation, very well. Profound whole body hypothermia, however, is only well tolerated by infants and small children, older patients are at risk from suffering cerebral damage and other complications if profound whole body is maintained for more than a short period (Sealy, W.C., Brown, I.W., Young, W.G., Stephen, C.R., Harris, J.S. 1957; Shields, T.W., Lewis, F.J. 1959; Drew, C.E., Anderson, I.M. 1960; Björk, V.O. 1961; Björk, V.O., Hultquist, G. 1962).

The value of hypothermia, irrespective of the method of achieving it, as a means of myocardial preservation is now beyond question,

and it is used as the only method of myocardial protection by some surgeons. The majority of surgeons, however, concerned about the time limit, the risk of over-distension of the ventricles, and the danger of cerebral injury and other complications, when profound hypothermia was used, readily adopted coronary perfusion either with or without hypothermia, when this was introduced (Kay, E.B., Head, L.R., Nogueira, C. 1958).

CORONARY PERFUSION

Coronary perfusion was a natural development to provide the myocardium with a blood supply during surgery on the aortic valve. It was thought that this would abolish all the limitations and dangers of non-perfusion arrest, and greatly extend the safe time period in which to carry out the procedure since the myocardium would be supplied with oxygen and the other necessary substrates. As it could also be used in conjunction with hypothermia of varying degree, the benefits acruing from the latter would thus increase the safety of the surgery.

Suitable cannulae were developed which could be inserted into the ostia of the right and left coronary arteris, through the aortic root. Originally these were rigid or maleable metal cannulae which were held in place by an assistant (Kay, E.B., Head, L.R.,

Nogueira, C. 1958; Gott, V.L., Woodson, R.D., Wong, D.M., Sellars, R.D., Lilleau, C.W. 1961; Bloomer, W.E., Anderson, R.M. 1962). Flexible catheters, however, soon replaced these and they were held in place by purse-string sutures placed around the coronary ostia and tightened around the catheter tip (King, B.J. 1963; Sprovier, L., Blondeau, P., Piwnica, A., Baculard, P., Dubost, C. 1965; McGoon, D.C., Pestana, C., Moffitt, E.A. 1965).

The coronary arteries were perfused via these cannulae or catheters, with oxygenated blood from the pump oxygenator. Many teams provided, and some still do provide, the perfusion simply by constructing a bifurcation in the arterial perfusate tubing and thus diverting some of the perfusate to the coronary arteries. Other groups developed methods to divert blood from the oxygenator to two separate calibrated roller pumps which then independently perfused each coronary system (Kay, E.B., Head, L.R., Nogueira, C. 1958; McGoon, D.C., Moffitt, E.A. 1963; Bosher, L.H., Edwards, J.F.Jr., Pois, A.J. 1964; McGoon, D.C., Pestana, C., Moffitt, E.A. 1965). Using this system the flows to each coronary artery system can be controlled and if suitable pressure monitoring gauges are included in the circuit the mean pressures in the tubing between the roller pump and the patient can be monitored.

The latter system is the more preferable, if the more complicated,

because perfusion to the coronary systems at too high, or too low flows, or pressures, can be more readily detected and corrected. One group of workers even devised a method for correcting flows and pressures automatically (Bosher, L.H., Edwards, J.F.Jr., Pois, A.J. 1964). Based on both experimental evidence and clinical experience (Gregg, D.E. 1950; Willman, V.L., Nevill, E.C., Hanlon, C.R. 1957; Littlefield, J.B., Lowicki, E.M., Muller, W.H. 1960) it is now widely accepted that the flows to the two coronary systems should be within the range of 75 to 200 mls/minute and the mean perfusion pressures should be within the range of 50 to 100 mmHg.

It fairly soon became apparent that coronary perfusion was not without its problems. In very young patients it could be impossible, simply because of the small size of the aortic root and the coronary ostia. It could also be impossible in patients with syphilitic aortitis and some advanced degenerating conditions because of ostial stenosis. The proper positioning of the catheters takes time, commonly in a normothermic heart or a heart that has been excluded from the circulation, by aortic cross-clamping before the desired degree of cooling is complete. This problem occurs most commonly in patients with severe aortic regurgitation where it proves difficult to maintain an adequate perfusion pressure from the pump oxygenator and the heart is also liable to damage by over-distension.

It not uncommonly proves to be impossible to cannulate one or other, usually the right coronary artery, either because they are congenitally small vessels, with the other vessel playing a dominant role, or because they arise from the aorta as two or more ostia. This latter anatomical variation is more common in the left system where the anterior descending branch and the circumflex branch come off the aorta separately (McGoon, D.C., Pestana, C., Moffitt, E.A. 1965). In the right coronary artery system, the artery to the sinus node occasionally arises separately from the main right coronary. In patients where one or other of the coronary artery systems do arise by separate branches from the aortic root it is usual that only one of these vessels can be cannulated and it has been the experience of many surgeons that there is a risk that the patient will sustain an infarction in the non-perfused territory when this is done.

A similar situation can occur where the catheter tip is advanced too far into the main coronary artery and in so doing excludes a major proximal branch (usually the circumflex branch of the left coronary artery) from the perfusion system (McGoon, D.C., Pestana, C., Moffitt, E.A. 1965; Green, G.E., Bernstein, S., Reppert, E.H. 1967). It is thought that the sinus node branch of the right coronary artery if excluded in this way may account for some of the post-operative atrial dysrhythmias encountered in patients who have undergone aortic

valve surgery.

Myocardial damage has been reported experimentally, to occur rapidly due to hypoxic low-flow perfusions (Redo, F., Porter, Y. 1959; Blackstone, E.H., Evans, R.H., Eckner, F.A.O., Drake, A., Moulder, P..V. 1968), which could inadvertently occur during any coronary perfusion. Other workers have demonstrated that high coronary perfusion pressures associated with diminished flow rates could produce histological evidence of myocardial infarction and intramyocardial haemorrhage (Fishman, N.H., Youker, J.E., Roe, B.B. 1968). Perfusions at high pressures with normal oxygenation and normal or high flows were also demonstrated by another group of workers to produce myocardial oedema and a diminution of left ventricular compliance. These features were worsened by fibrillation, hypothermia and defibrillation, amongst others (Brown, A.H., Braimbridge, M.V., Niles, N.R., Gerbode, F., Aguilar, M.J. 1969). They also reported some intramyocardial haemorrhage. This latter observation had previously been well documented (Shaw, R.F., Mosher, P., Ross, J.Jr., Joseph, J.I., Lee, A.S.J. 1962; Shaw, R.F., Baum, W.M., Joseph, J.I. 1962).

A variety of lesions consequent on catheterising the coronary ostia have been described. These include a perforation injury to the left main coronary artery itself, just inside the ostium with extravasation

of blood into the periarterial fat and obliteration of the lumen by extrinsic pressure exerted by the haematoma on the vessel. The extravasation caused extensive disruption of the adjacent myocardium and finally resulted in a full thickness tear along the left anterior descending artery with the death of the patient, due to uncontrollable haemorrhage (Sturridge, J.F. 1973). Others have reported medial dissection in the left coronary artery extending into the anterior descending branch, perforation of the left main coronary artery with compression of the lumen due to the surrounding haematoma and yet other fatal cases where ecchymoses were present in the periarterial tissue, usually around the left anterior descending branch of the left coronary artery which were thought to be due to the coronary perfusion (Fishman, N.H., Youker, J.E., Roe, B.B. 1968). Another group of authors described an intimal tear at the bifurcation of the left coronary artery with obliteration of the lumen due to a turning-in of the intima, resulting in the death of the patient (Heilbrunn, A., Zimmerman, J.M. 1965). Trimble and his co-workers described a case where coronary perfusion resulted in late ostial stenosis of the left coronary artery system following coronary perfusion for aortic valve replacement, as yet a further potential hazard using this method (Trimble, A.S., Bigelow, W.G., Wigle, E.D., Silver, M.D. 1969).

Coronary perfusion may give rise to considerable technical difficulty in performing aortic valve surgery. The heart continues to beat and thus the aortic root is constantly moving. The ventricles maintain their tone and therefore render the access to the valve ring more difficult because the valve ring cannot be drawn up into the aortotomy. The catheters themselves are in the aortic root and may in a small root make access to the valve very difficult. Leakage around the catheters through the purse-string is common and this blood may further obscure the operative field. The latter two facts result in the necessity to stop coronary perfusion intermittently, or even to remove the catheters periodically to facilitate vision and access.

Aortic valve surgery, requiring as it does cardiopulmonary bypass, exposes the myocardium to the perfusate during the performance of the procedure irrespective of the method of myocardial preservation to be used. Many workers have shown that the mixture of a patient's blood and the prime, which constitute the perfusate, contains large numbers of platelet, denatured protein and fibrin microaggregate emboli (Lee, W.H., Krumhaar, D., Fonkalsrud, E.W., Schjeide, O.A., Maloney, J.W. 1961; Swank, R.L. 1961; Bloom, A.L. 1962; Swank, R.L. 1962; Swank, R.L., Porter, G.A. 1963; Swank, R.L., Hirsch, H., Brauer, M., Nissen, W. 1963; Allardyce, D.R., Yoshida, S.H., Ashmore, P.G. 1966; Ashmore,

P.G., Svitek, V., Ambrose, P. 1968). These microaggregates are present in greatest numbers at the commencement of cardiopulmonary bypass and then decline steadily, presumably because they are filtered off by the capillary beds of the body, including the myocardium, and the filters used in the extracorporeal circuit. This shower of microemboli to the myocardium ceases when the aorta is cross-clamped, and is therefore not a continuing problem if non-perfusion arrest is used, but commences once more when the aortic cross-clamp is released and during this time may continue to harm the myocardium until cardiopulmonary bypass is discontinued.

Air embolisation is a particular hazard with coronary perfusion, particularly when the catheters are periodically removed, or come out on their own and have to be replaced. The harmful effects of repeated air embolisation have been well shown experimentally (Eguchi, S., Bosher, L.H. 1962; Goldfarb, D., Bahnson, H.T. 1963) and also in Man (Nichols, H.T., Morse, D.P., Hirose, T. 1958).

Calcific emboli are a well known problem which can occur during the excision of the valve, or debridement of the valve ring (Kavanaugh, G.J., Pruitt, R.D., Edwards, J.E. 1958; Glotzer, D.J., Shaw, R.S., Scannell, J.G. 1962). This problem can occur with either method if the left coronary ostium is open during the time when the

valve is being excised or the valve ring debrided. If coronary perfusion is set up before these procedures are carried out the risks from calcific embolisation are less than with non-perfusion arrest where the left coronary ostium is likely to be open through the entire procedure.

Cardiotomy suction, usually via the left ventricular vent, can be considerable when coronary perfusion is used, because the coronary sinus return to the right atrium can be pumped to the lungs by the beating, unvented, right ventricle and thus produce a continuous pulmonary venous return which must be removed by the left atrial or left ventricular vent. This exposes the patient to the consequences of haemolysis which excessive suction has been shown to cause (Osborn, J.J., Cohn, K., Hait, M., Russi, M., Salel, A., Harkins, G., Gerbode, F. 1962).

From the foregoing it is clear that both hypothermic non-perfusion arrest and coronary perfusion have definite advantages and equally they each have serious drawbacks. It is my impression that the majority of surgeons doing aortic valve surgery at present use coronary perfusion as the principal means of myocardial preservation. Some do so under normothermic conditions, but perhaps a larger number use moderate hypothermia in addition. The moderate hypothermia is usually induced by whole body perfusate cooling of the patient, cooling the heart at the same time and allowing this to

become complete to the desired temperature before cross-clamping the aorta. The remainder of the surgeons use hypothermia alone and nearly all of these use profound topical cooling of the heart, usually with saline at 4°C as described by Shumway (Shumway, N.E., Lower, R.R. 1960).

Mention must be made at this point of electrically induced ventricular fibrillation. The fibrillating heart has been shown by many workers to have a reduced oxygen consumption of the order of 50% (Senning, A. 1952; Berglund, E., Monroe, R.G., Scheiner, G.L. 1957; Stoney, R.J., Zanger, L.C.C., Roe, B.B. 1962). This fact, together with the fact that it has always been used as a useful manoeuvre to prevent accidental systemic air embolisation, in those procedures where coronary perfusion is maintained by the perfusate via the intact aortic root with a competent aortic valve, such as in mitral valve replacement, have made it popular with many surgeons. A small group of surgeons use it together with coronary perfusion in aortic valve surgery. This, however, is not common practice. It is known that ventricular fibrillation either electrically induced or spontaneously occurring, results in an increased amount of myocardial oedema as demonstrated by studies of lymphatic drainage of the heart following cardiopulmonary bypass in which ventricular fibrillation has been used (Jowett, A.W. 1971).

Recent work has indicated that in addition to its rather poor ability to reduce the myocardial oxygen requirements it is also potentially harmful as a direct cause of subendocardial ischaemia (Hottenrott, C., Buckberg, G., Maloney, J.V. 1974) in the normal dog heart and that these effects are even worse in the hypertrophied heart (Hottenrott, C.E., Tower, B., Kurrji, H.J., Maloney, J.V. Buckberg, G. 1974), or in over-distended ventricles (Hottenrott, C., Buckberg, G. 1974). These workers have clearly defined the reasons for this damage to the myocardium (Buckberg, G., Fixler, D.E., Archie, P., Hoffman, J.I.E. 1972; Hottenrott, C., Maloney, J.V., Buckberg, G. 1974). Spontaneous ventricular fibrillation is a common event during aortic valve surgery, irrespective of whether coronary perfusion or hypothermic non-perfusion arrest of the heart is used. It is clear from these workers (Hottenrott, C., Maloney, J.V., Buckberg, G. 1974) that it is less harmful than electrically induced fibrillation. It is also however clear that any form of ventricular fibrillation is less desirable than the empty beating heart, if coronary perfusion is used, or the cold, nearly arrested heart which can be produced if profound hypothermic non-perfusion arrest is used. There has recently been a renewed interest in combining cardioplegia with profound topical hypothermia and one group of workers are arresting the heart at the commencement

of profound topical cooling using potassium citrate (Caves, P., Davidson, K. 1976) while others are using Bretschneider's solution to achieve this end (Lauridsen, P. 1976) so as to prevent any myocardial contraction from occurring during the period of cooling and thusgreatly reduce its oxygen requirements during this time.

CHAPTER III

PATHOLOGY

Careful macroscopic histopathological and electron microscopic studies have been carried out on patients who have died at operation, or in the post-operative period following cardiac operations utilising cardiopulmonary bypass. These studies have shown that similar characteristic pathological changes can be found in the hearts of patients who have had their valve surgery carried out using either hypothermic non-perfusion arrest, or coronary perfusion.

The "stone heart", or ischaemic contracture of the heart, (Cooley, D.A., Reul, G.J., Wukasch, D.C. 1972) has been described. This phenomomen refers to an entity in which the ventricles of the heart are hard in consistency, they appear to be fully contracted and are unable to contract when called upon to do so. The "stone heart" has most often been described at the end of a period of normothermic, non-perfusion arrest. It has, however, also been observed at the termination of hypothermic non-perfusion arrest and coronary perfusion, both at normal and low temperatures. It has also been observed confined to the territory of an excluded left anterior descending branch of the left coronary artery (personal experience) in a patient in whom the two branches of the left coronary artery arose by separate ostia from the aortic root. Only the circumflex branch was perfused during the procedure. The condition has to date proved to be irreversible.

No clearly defined histopathological changes, except interstitial oedema, have been described in this lesion probably because the death of the patient supervenes too soon after myocardial cell death occurs to produce recognisable changes. A biochemical basis for the lesion has been postulated (Katz, A.M. 1968; Katz, A.M., Tada, M. 1972) to explain the one constantly observed fact in this condition, that is that the sarcomere length is as short as it is possible to be, i.e. the actin and myosin fibrils are locked together in a maximally contracted state. These workers suggest that the depletion of adenosine triphosphate, consequent on the anoxia, is responsible. This is, however, not enough on its own to explain the phenomenon. It is well known that an infarcted area of myocardium is flaccid and relaxed (Katz, A.M. 1968). Adenosine triphosphate has a dual role on the contractile proteins of the heart in vitro (Nimura, Y., Tada, M. 1967; Katz, A.M. 1970) under different experimental conditions, it is probable that different conditions in the ionic and chemical environment of the myocardial cell prevail, to explain the differences in behaviour of the heart to these two situations. This condition has also only been observed in hypertrophied ventricles and it is very probable that this is major contributing factor, since it is known that the hypertrophied and the failing ventricle have depleted stores of high energy phosphate compounds (Fox, A.C. 1971; Pool, P.E. 1971).

Other groups of workers have described a series of changes, which are detectable histologically, provided the patient survives the injury which produces myocardial cell necrosis for twelve to twentyfour hours, as this is the length of time that is required for the structural changes in the cell to take place, which are recognisable as diagnostic of myocardial necrosis using standard staining techniques such as haemtoxylin and eosin (Mallory, G.K., White, P.D., Salcedo-Salgar, J. 1939; Lodge-Patch, I. 1951; Titus, J.L. 1969). Persistence of these changes allows their detection up to a few weeks later. Henson and his co-workers clearly described four changes which occurred in patients dying after open-heart surgery or cardiopulmonary bypass. These changes consist of intracellular contraction bands, interstitial haemorrhages, coagulative necrosis of the myocardial cells and finally, calcification (Henson, D.E., Najafi, H., Callaghan, R., Coogan, P., Julian, O.C., Eisenstein, R. 1969). The earliest changes to occur are the contraction bands. In the mildest form of myocardial injury they may be the only changes observed and are usually transient in nature. The contraction bands may be accompanied by one, two, or all three of the other changes and the number of additional changes that exist reflects the severity of a given lesion. Thus a spectrum of severity can be found, ranging from a lesion where only contraction bands are seen, to one in which all four changes are

found. The size of the lesions are another indication of their severity. In their mildest form they are present as diffusely scattered microscopic, subendocardial foci, which are much more common in the left ventricle than the right. When the damage is more severe the lesions are larger due to coalescence of the individual microscopic lesions and reach a stage where they can be seen macroscopically. The distribution, however, remains diffuse and does not conform to the anatomical areas of supply of the coronary arteries. The entire circumference as well as the length of the left ventricle is most commonly involved. A further indication of the severity of the lesions is the extent to which they have extended from the subendocardial towards the subepicardial surface of the myocardium. In the mildest form the lesions are confined to the subendocardial myocardium, while in its severest form the entire ventricular wall thickness may be involved and the involvement is almost entirely circumferential.

Taber and his co-workers have related these findings to the post-operative low output syndrome (Taber, R.E., Morales, A.R., Fine, G. 1967). They found that in those patients who underwent cardiac surgery on cardiopulmonary bypass and who later died following a low output state, that usually not less than 30% of the left ventricle was involved by this process. Coronary artery disease was carefully excluded in their cases by post-mortem coronary arteriography. They found evidence of

platelet-protein microaggregate emboli, antifoam microemboli, and probably air emboli, but these were not thought sufficient to account for the widespread distribution and density of the lesions. It is probable that the aetiology of this pathology is to be found in the work of Buckberg and his co-workers (Buckberg, G., Fixler, D.E., Archie, P., Hoffman, J.I.E. 1972; Hottenrott, C., Maloney, J.V., Buckberg, G. 1974).

These lesions have also been thought to be the precursor of left ventricular subendocardial fibrosis found at autopsy in patients who died months or years later, after aortic valve surgery in which either coronary perfusion or hypothermic non-perfusion arrest had been used. Roberts and Morrow, however, found that this condition appeared to be confined to patients who underwent isolated mitral valve replacement, or mitral valve replacement combined with aortic or tricuspid valve replacements, and postulated an entirely different pathogenesis (Roberts, W.C., Morrow, A.G. 1968).

The coronary arteries may, or may not, be entirely normal, but almost certainly do not contribute to the pathogenesis of this condition (Horn, H., Field, L.E., Dack, S., Master, A.M. 1950). Seriously diseased vessels can, however, give rise to typical myocardial infarctions in addition to the pathology already described.

Electron microscopic studies have contributed further to our

understanding of the pathology that occurs in the myocardium, irrespective of the method of preservation used. Chief attention has been focused on the mitochondrium and five general types of mitochondrial degeneration have been described. These consist of clearing of the matrix with fragmentation of the crests, loss of the large granules, lamellar degeneration, granular degeneration and chondrosphere formation. Mitochondrial oedema has been noted as well and invariable accompanies these degenerations (Burdette, W.J., Ashford, T.P. 1963; Miller, D.R., Rasmussen, P., Klionsky, B. 1964; Kottmeier, C.A., Wheat, M.W. 1966). Although many enzymes have been found to operate in the mitochondria, three major processes are carried out by this organelle in the myocardium. These are the Kreb's tricarboxylic acid cycle (Burdette, W.J. 1952), terminal electron transport and oxidative phosphorylation. These processes are the principle source of high energy phosphate compounds in the normal aerobically metabolising heart. The observed mitochondrial degenerations probably represent the deleterious effects of anaerobic metabolism on the sites of these complex large molecule chemical reactions, or more probably the disintegration of the chemical reactions themselves, which are the structures observed in the mitochondrion. The result of these degenerations is a rapid depletion of the high energy phosphate bonds which are necessary for the function

of the contractile elements, namely actin and myosin, until finally a point is reached where the degenerations are so far advanced that regeneration is impossible (Burdette, W.J., Ashford, T.P. 1963).

CHAPTER IV

PATIENTS, METHODS AND MATERIALS

All adult patients who underwent elective, aortic valve surgery for the first time, in the Department of Surgery, the University of Alabama, Birmingham Alabama, between 2nd February 1973 and 24th July 1973 were included in the study.

Two methods of myocardial preservation were in use in the Department prior to February 1973. The methods were coronary perfusion and profound hypothermic non-perfusion arrest (the methods will be described in detail later). Both methods were believed to be acceptable by the surgeons working in the Department, based on their own experience and on the published experience of others, which had indicated that good results could be obtained with either method. Up to the time of commencing the study no differences had emerged from the mortality and morbidity figures in the Department (Kirklin, J.W. 1973).

Two facts emerged from a study of these publications. Firstly it appeared that no properly controlled prospectively randomised comparisons had been carried out and secondly it was apparent that mortality and morbidity figures were now no longer sensitive enough to provide answers to the question. We attempted to overcome these difficulties by setting up a controlled prospective randomised study using statistically comparable measured parameters which we hoped would be sensitive enough to demonstrate any differences if there

were any. The parameters chosen were, however, restricted to those that were practical and safe to use in patients in the Intensive Care Unit in the first fortyeight hours post-operatively.

Randomisation

The randomisation was carried out in pairs per surgeon. Random digit tables were used, according to the methods recommended for their use (Wallis, W.A., Roberts, H.V. 1956). There were four surgeons whose patients were used in the study. The first patient of each surgeon was randomly allocated to one of the two methods which should be used to preserve his or her myocardium during the procedure. The next patient of a given surgeon was automatically allocated the other method. The third patient of that surgeon was again randomly allocated a method, and so forth. If a patient was rejected from the study, the following patient was allocated the method that should have been used during the rejected patient's operation. This method of randomisation was used because it was beyond criticism on statistical grounds, it would give two reasonably equal sized groups, it would allow statistical determinations of surgeon-to-surgeon differences and surgeon change with time differences to be made and adjusted for, if these differences were found to bias the results. It would also prevent any surgeon from favouring one method or the other, because

any change of method instituted by the surgeon, from that allocated, would result in the rejection of the patient from the study, and that the surgeon's next patient would be allocated the same method. Persistent favouring of a method would, in fact, result in rejection of the surgeon from the study. This did not occur.

The randomisation was carried out by the author, at a time when he had no prior knowledge of the patient, except that he or she was scheduled to have aortic valve surgery the following day. Since the scheduling of the patient was usually carried out well in advance, the surgeon also had no prior knowledge of the method he would be asked to employ for any particular patient. All inadvertently missed patients were obviously not in the study. Patients who had their valves replaced as an emergency were excluded. All patients in whom homograft aortic valves were inserted were also rejected because the current view in the Department was that this operation was usually too long to justify the risks of profound hypothermic non-perfusion arrest. If any additional procedure, such as an aorto-coronary vein bypass graft, or a mitral valve replacement, was carried out in a previously randomised patient, that patient was rejected, even if the allocated method was adhered to, as it was thought that these additional procedures could introduce unknown variables into the assessment of the patient in relation to the others.

Methods of Myocardial Preservation

1 Coronary Perfusion

Those allocated to have their valve surgery carried out using coronary perfusion were done using the following procedure:

The arterial perfusate temperature was adjusted to 32°C prior to cannulation of the heart. When this was complete bypass was commenced and the pre-calculated flow (based on 2.2 litres/min/M^2) was reached in approximately 30 seconds. The perfusate temperature was then maintained at this level until rewarming was commenced. The aorta was cross-clamped as soon as convenient. The right and left coronary arteries were cannulated with suitable sized catheters, through their ostia, via the open aortic root as soon as possible and perfusion commenced. The coronary perfusate temperature was maintained at 32°C until cooling was no longer required.

Coronary perfusion was carried out using separate roller pumps (Sarn's Model 2000) for each coronary system and each system contained a pressure gauge on which the mean perfusion pressure could be monitored. After establishing coronary perfusion, the flows and pressures in each system were adjusted so that the flows fell within the range of 75 - 200 mls/min and the pressures within the range of 50 - 100 mmHg. An attempt was made to ensure that coronary perfusion in both systems was maintained for the maximum percentage

of the time that the aorta was cross-clamped, i.e. the surgeons inserted the coronary catheters just as soon after opening the aorta as possible, coronary perfusion was not interrupted unless absolutely vital and then for the shortest possible time, catheter displacement was corrected as speedily as possible and the catheters were left in situ until the last possible moment during the closing of the aortotomy incision. Rewarming of the patient and the heart was commenced usually just before completing the valve replacement, or when the aortic cross-clamp was released. The rewarming was usually complete by the time cardiopulmonary bypass was no longer required and did not in itself lengthen the total period of time that the patient spent on cardiopulmonary bypass.

2 Profound Hypothermic Non-Perfusion Arrest

The procedure used in those patients allocated to have their valve surgery carried out using this method was as follows:

The arterial perfusate temperature was adjusted to 25^{o}C before cannulation. When this was complete cardiopulmonary bypass was started and the calculated flow reached in 30 - 60 seconds. The perfusate temperature was maintained at this level for four minutes. It was then lowered to 15^{o}C, this usually took about 30 seconds. This new level was maintained for two minutes, at the end of which time

the aorta was cross-clamped. The perfusate temperature was then raised to 28°C where it was maintained until rewarming was commenced. Following aortic cross-clamping the aorta was opened and the surgery proceeded with. Rewarming of the body was commenced when the valve replacement was nearing completion. Rewarming of the heart, however, could only commence when the aortic cross-clamp was released. Rewarming was once more usually complete when cardiopulmonary bypass was no longer required and did not lengthen the time of total cardiopulmonary bypass.

Cardiopulmonary bypass was in all other respects identical for the two methods. The extracorporeal circuit was primed with 500 mls of acid citrate dextrose blood, obtained the day prior to surgery, 7.5 mls of heparin, 60 mls of 1.4% sodium bicarbonate, 1500 mls of 0.4% saline in 5% dextrose and 5 mls of 10% calcium chloride. Losses from the circuit were replaced with acid citrate dextrose blood or a buffered electrolyte solution. Oxygenation was achieved using a Temptrol Q100 bubble oxygenator (Bentley Laboratories Inc., Irvine, California). Perfusion was established and maintained using a roller pump (Sarn's Model 2000) and the temperature control was achieved using a Sarn's heat exchanger.

The cannulations to effect cardiopulmonary bypass were identical for the two methods. Venous drainage was carried out using a

common right atrial basket fitted to the end of a $\frac{3}{8}$ inch venous catheter. Drainage was affected by gravity. Arterial perfusion was achieved through a suitable sized Bardic cannula inserted high up in the ascending aorta. The internal diameter of this cannula was determined by the total flow required for any particular patient (see Table I). Left ventricular venting was carried out across the left atrium and through the mitral valve. The vent drainage and any additional cardiotomy suction was filtered through micropore filters before being returned to the oxygenator. Venting and cardiotomy suction were both achieved using reversing roller pumps provided for the purpose on the Sarn's console.

TABLE I

BARDIC ARTERIAL CANNULAE FLOW CHART

PRESSURE GRADIENT IN MM.HG

Cannula Size in French Scale	Flow in Litres Per Minute							
	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0
10	60	175	350					
12	40	100	225	325				
14	25	60	140	240	350			
16		25	50	90	150	200	260	
18		20	40	60	80	120	150	200
20			25	40	60	80	100	120
22			25	40	50	60	75	90
24				40	50	60	70	80

The table of internal diameter arterial cannulae (French Scale) used for aortic valve replacement according to the required flows.

CHAPTER V

OBSERVATIONS AND DATA

1 Clinical Data

The age, sex and race of every patient in the study was recorded.

Pertinent clinical data was obtained in every patient. Particular note was made of a previous history of rheumatic fever, subacute bacterial endocarditis or syphilis. A history of any other associated conditions was noted. The patients' symptoms were carefully recorded. The presence or absence of the following was noted in every patient:

(a) Dyspnoea on exertion. This was further qualitatively sub-divided into those who had no dyspnoea on exertion; those who had dyspnoea only on severe exertion (running, playing sports etc.); those who had dyspnoea on moderate exertion (walking fast, or up a hill); those who had dyspnoea on minimal exertion and those who had dyspnoea at rest.

(b) Paroxysmal nocturnal dyspnoea.

(c) Orthopnoea.

(d) Angina.

(e) Syncope.

(f) Palpitations or documented dysrhythmias.

(g) Any other relevant symptoms.

The patients' clinical signs were recorded. The following were noted in all patients:

(a) The quality of the pulse, i.e. whether the patient had a normal pulse, a plateau pulse or a collapsing pulse.

(b) The position and quality of the apex beat, so that this fact could be used to determine whether there was clinical evidence of left ventricular hypertrophy.

(c) The signs on auscultation were noted and used to determine, together with the other evidence, whether the patient's predominant lesion was aortic stenosis or aortic regurgitation.

The following radiological features were recorded where this data was available:

(a) Calcification in the aortic valve and/or the aortic valve root.

(b) Changes in the patients' lungs due to their aortic valve disease.

(c) Any other relevant changes.

The pre-operative electrocardiogram was evaluated by an experienced observer who had no prior knowledge of the patients, to record the following:

(a) The rhythm.

(b) The P wave configuration.

(c) Evidence of left ventricular hypertrophy.

(d) Repolarisation changes.

(e) Ischaemic changes.

(f) Old myocardial infarctions.

These electrocardiograms were later used to blindly compare with the 7 - 10 day post-operative electrocardiograms to determine whether any significant changes with reference to rhythm, ischaemic features or new infarctions had occurred.

Many patients in the study were not submitted to cardiac catheterisation and angiography. Where these diagnostic procedures had been carried out, the data so obtained was recorded. The amount of data provided for each patient varied so no definite facts could be recorded for all the patients, either haemodynamically or angiographically. Coronary arteriography was, however, carried out in all patients where there existed a suspicion that the patient's coronary arteries could be diseased. It was therefore possible to document accurately the existence of coronary artery disease and its distribution in the patients' coronary arteries, but patients who had coronary artery disease of milder severity who had not been submitted to this diagnostic procedure were undoubtedly missed.

2 Operative Data

At operation in all patients, the left ventricular wall thickness and the left ventricular diameter was measured. The left ventricular wall

thicness was measured by passing a 22 gauge hollow needle slowly through the wall, to the right of the anterior descending branch of the left coronary artery at the junction of the proximal artery and middle thirds of the long axis of the ventricle. The length of the needle which had penetrated the ventricle when blood was seen to enter its lumen was taken to be the wall thickness at that point. The left ventricular diameter was measured with a caliper constructed for the purpose (Fig. 2) and the measurement was made around the base of the ventricular mass, an attempt was made to make this measurement around the same portion of the ventricles in all the patients.

When cardiopulmonary bypass was established, the myocardial temperature was recorded just after the aortic cross-clamp was applied using a termistor needle probe (Model 524, Yellow Springs Instrument Co., Inc., Yellow Springs, Ohio). The actual temperature to which the myocardium had been cooled was therefore recorded in all patients, irrespective of the method which was to be used. This temperature was repeated either just before rewarming was commenced or just before the aortic cross-clamp was released, whichever occurred first. These measurements gave an accurate record of the myocardial temperature and also indicated how well the myocardial temperature was maintained during the procedure.

FIGURE 2

The caliper used to measure the external diameter of left ventricle in centimeters.

Careful note was made of the length of time that the aorta was cross-clamped in both groups and the total cardiopulmonary bypass time was recorded.

Spontaneous episodes of ventricular fibrillation were noted and the number of electrical defibrillations required were recorded.

Calcification of the aortic valve and / or the aortic valve ring was noted to compare with the radiological findings. Similarly macroscopic coronary artery disease was noted to compare with the angiographic findings. The route of left ventricular venting was recorded. The type of prosthetic valve used or the procedure carried out was noted.

Patients who had their aortic valve surgery carried out using coronary perfusion were observed so as to record the following points pertinent to the method:

(a) The number of coronaries perfused during the procedure.

(b) Whether there were any difficulties encountered in catheterising either the right or the left coronary arteries, or both.

(c) The internal diameter of the coronary catheters used.

(d) The average flow rates that were used in both the left and right coronary artery systems. These figures were the ones that pertained after the flows had been adjusted at the onset of coronary perfusion. Little variation occurred during the perfusion.

(e) The mean perfusion pressures that pertained in each system. Once more little variation was found after the initial adjustments had been made.

An attempt was made to determine, accurately, what the difference was between the aortic cross-clamping time and the coronary perfusion time. The values obtained, however, were thought to be unreliable and were therefore not used in the analysis. It appeared, however, that the coronary perfusion time was 10 - 15 minutes shorter than the aortic cross-clamping time.

Patients who had their valve surgery carried out using profound hypothermic non-perfusion arrest were observed to see whether any episodes of over-distension of the left ventricle occurred, either during the period of cooling or after the aortic cross-clamp was released.

CHAPTER VI

INSTRUMENTATION

At the conclusion of cardiopulmonary bypass, while final haemostasis was being secured the heart was instrumented in those patients in whom it was deemed logistically possible, so as to allow the studies to be carried out in the post-operative period.

This instrumentation consisted of:

(a) A Millar micro-tip catheter pressure transducer model PC - 350A with TCB - 100 control, 5 French gauge (Millar Instruments, Inc., Houston, Texas). (Figures 3 and 4). The catheter was zeroed outside the heart immediately prior to insertion. It was then introduced into the left atrium through a stab wound in the right superior pulmonary vein which was controlled by a double purse-string suture. It was advanced across the left atrium, through the mitral valve and into the left ventricle. The position of the catheter tip in the left ventricle was verified by a micro-ampere meter modified to indicate pressure changes by its needle deflection. The inertia in this system was such as to be rather insensitive, but sensitive enough to indicate when the tip was in the left ventricle. The catheter itself was then brought out through the lower end of the median sternotomy wound.

(b) A coronary sinus sampling catheter. (C.R. Bard, Inc., Murray Hill, New Yersey). A 24 inch Bardic inside needle catheter

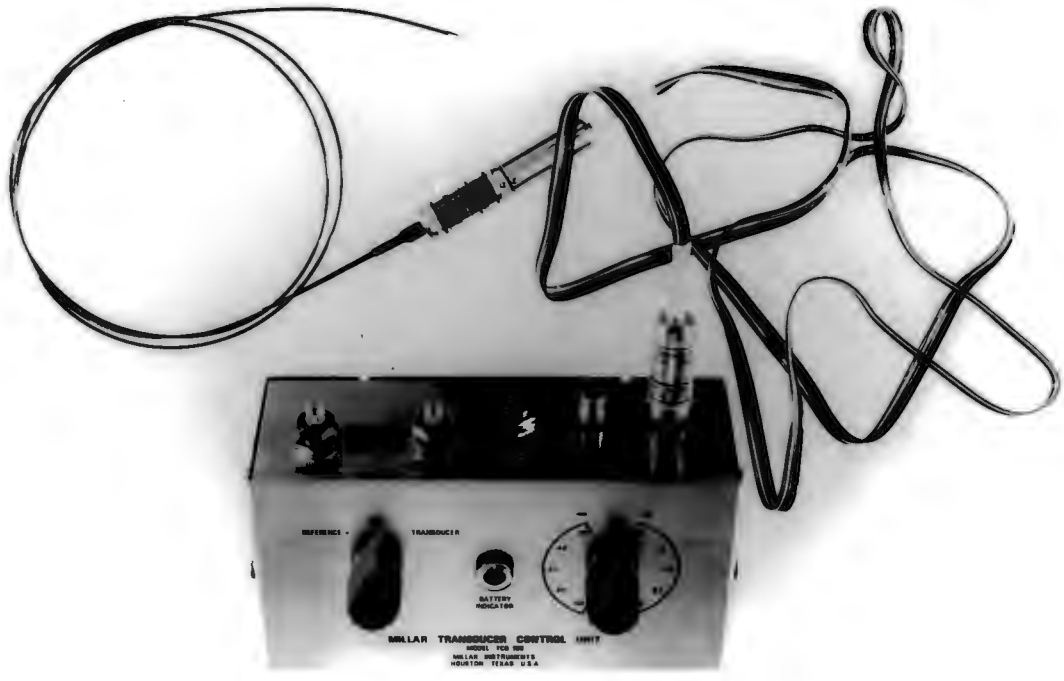

FIGURE 3

The Millar micro-tip catheter transducer PC - 350A (5F) with cable and transducer control unit TCB - 100.

FIGURE 4

Detailed view of the tip of the Millar micro-tip catheter pressure transducer PC - 350A (5F).

(No. 1914R) with stylet was used for this purpose. (Figure 5). Four side holes were drilled into it within a centimetre of its end. (Figure 6). The catheter with stylet in situ was introduced into the right atrium through a stab wound controlled by a double purse-string at the inferior cavo-atrial junction. Under digital control the tip was guided into the coronary sinus ostium. The left atrio-ventricular groove was then palpated and the catheter advanced until its tip and side holes were situated to the left of the middle cardiac vein, thus ensuring as far as possible that the left ventricular venous effluent alone was sampled (Hood, W.B. 1968; Giannelli, S.Jr., Conklin, E.F., Ayres, S.M., Mueller, H., Gregory, J. 1968).

(c) Routine monitoring catheters. All patients undergoing aortic valve surgery in the Department had a radial artery catheter inserted after the induction of anaesthesia, a left atrial catheter inserted before the commencement of cardiopulmonary bypass, and a right atrial, and pulmonary artery catheter inserted after cardiopulmonary bypass. These catheters were all used to obtain the other data necessary to complete the studies.

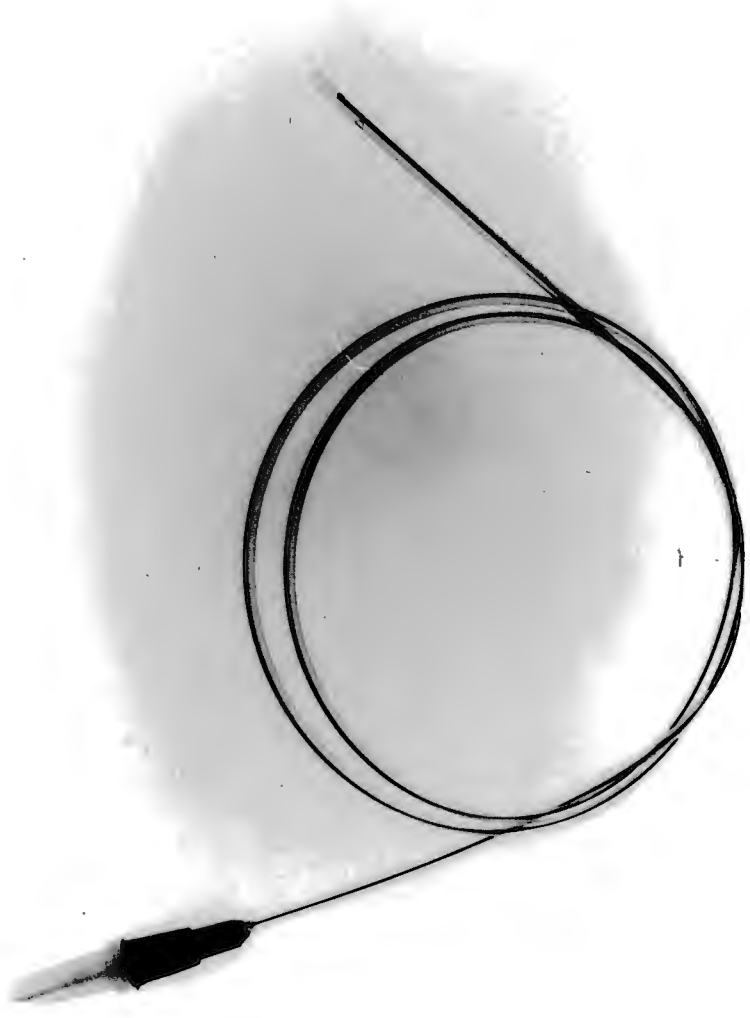

FIGURE 5

The 24 inch Bardic inside needle catheter (No 1914R) with stylet used as a coronary sinus sampling catheter.

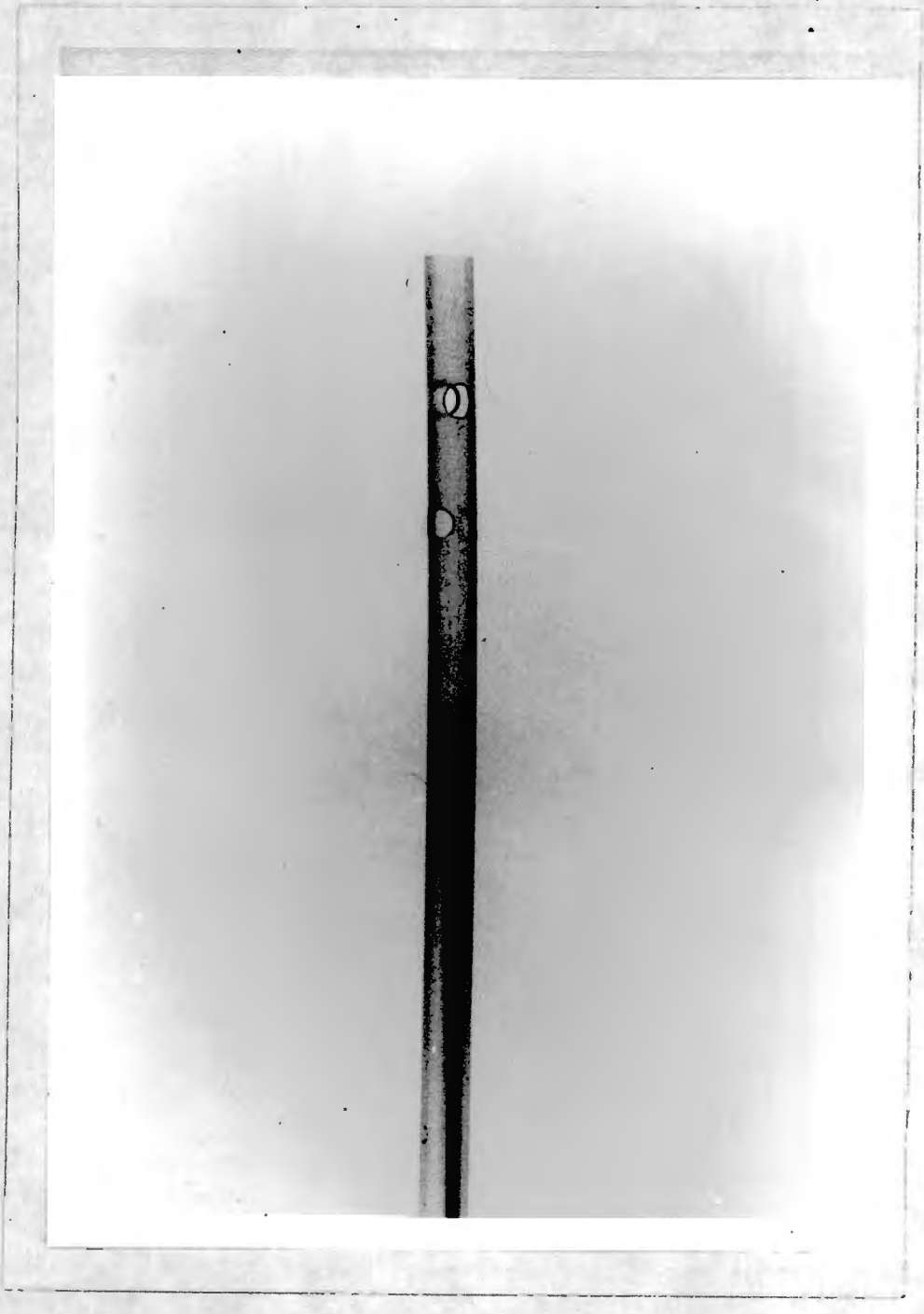

FIGURE 6

Detailed view of the tip of the coronary sinus sampling catheter to show the four side holes.

CHAPTER VII

THE STUDIES

All patients who were instrumented in the operating theatre and in whom the instrumentation was found to be functioning satisfactorily on return to the cardiac intensive care unit had a group of haemodynamic, a group of metabolic and a group of enzyme isoenzyme studies carried out serially during the following 54 hours.

A study consisted of the measurement and/or computation of the haemodynamic parameters, obtaining the blood samples for the blood gas analyses, and for the metabolic, enzyme and isoenzyme determinations.

A sample of venous blood was withdrawn from all patients after the induction of anaesthesia, but before commencing cardiopulmonary bypass. This sample was used only for enzyme and isoenzyme determinations. Full studies were then carried out about 5 hours, 10 hours, 22 hours, 26 hours, 31 hours and 45 hours after the commencement of cardiopulmonary bypass. A final venous sample was obtained at about 54 hours after the commencement of cardiopulmonary bypass once again just for enzyme and isoenzyme determinations.

The haemodynamic parameters

(a) The cardiac output (litres/min)

This was obtained using the indigo-cyanine green dye dilution technique (Sekelj, P., Tait, G.R., Nathanson, M.M. 1966).

Calibration was carried out using a concentration of 12.5 mgms of the dye to be injected per litre of heparinised blood, freshly drawn from the patient. Three determinations were carried out by injecting 5 mgs of dye in one ml Boluses into the right atrium and sampling from the pulmonary artery. If it was not possible to use this route, usually for technical reasons, the dye was injected into the left atrium and the sampling carried out from the radial artery. Sampling was carried out by a Harvard infusion-withdrawal pump running at 7.64 mls/min, through a Waters Cuvette oximeter (XC 250) connected to a suitable densitometer. Computation of the cardiac output was either carried out on-line by an IBM 1800 computer, or manually from the curve obtained on a Honeywell visicorder strip chart recorder. (Figure 7). The mean of the three values obtained was then used as the cardiac output. Any value which was not within 10% of the other two was rejected and the procedure repeated so as to ensure close reproducibility at each estimation.

(b) The cardiac index (litres/min/M^2)

This value was derived from the mean cardiac output in litres/min and the patient's body surface area in square metres which had previously been calculated from the patient's weight and height.

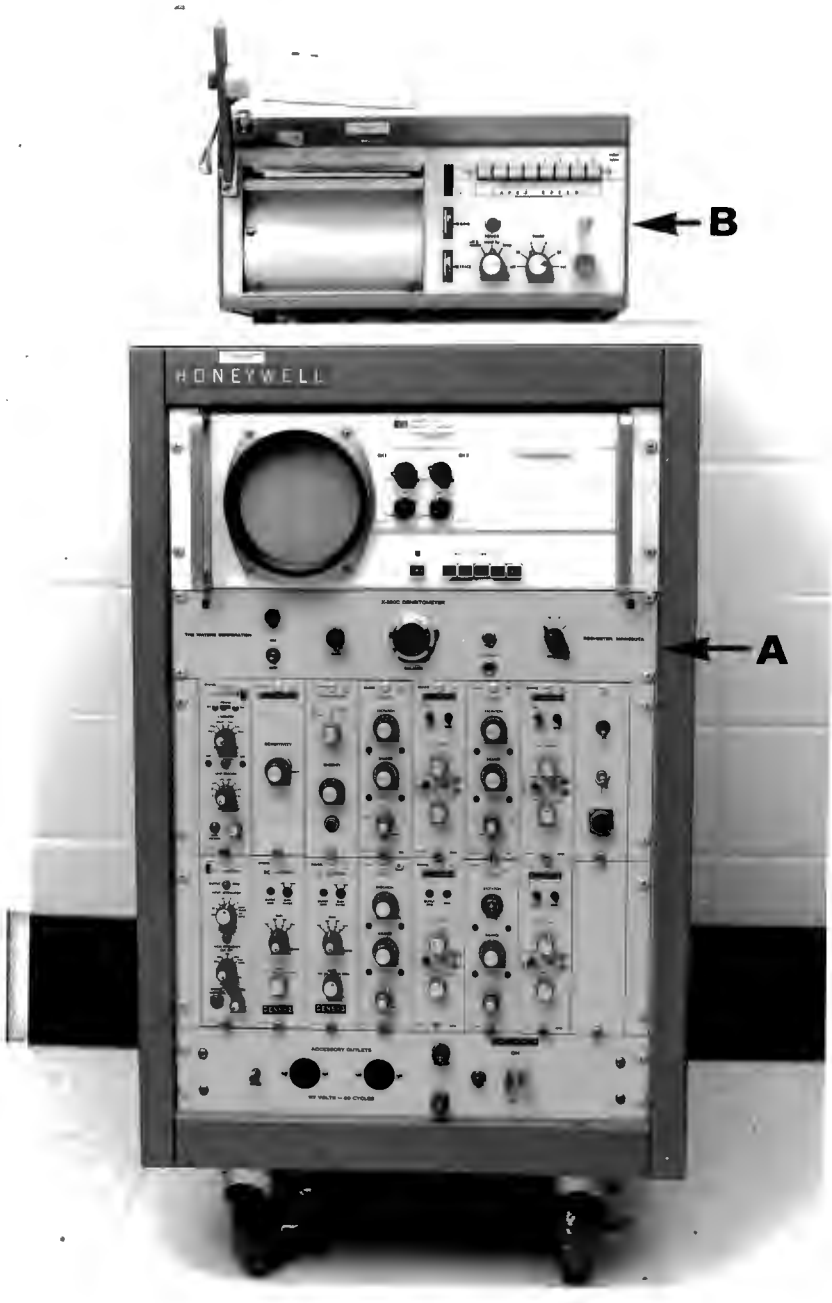

FIGURE 7

The Honeywell visicorder strip chart recorder

A = Waters X - 250C densitometer

B = Strip chart

(c) The stroke volume (mls/beat)

This was obtained from the mean cardiac output and a mean heart rate which pertained at the time that the cardiac output was estimated.

(d) The stroke index (mls/beat/M^2)

The stroke volume was divided by the patient's body surface area to provide this value.

A simultaneous record of the patient's dynamic radial artery pressure in mmHg (scale 0 - 200 mmHg), mean left atrial pressure in mmHg (scale 0 - 40 mmHg) and dynamic left ventricular pressure in mmHg (scale 0 - 200 mmHg), was made on the Honeywell visicorder strip chart recorder. (Figure 8). A passive differentiating circuit in the left ventricular recording circuitry allowed the first derivative of the left ventricular pressure to be recorded on the same strip chart in $mmHg/sec^{-1}$ (scale -1000 to +1000 $mmHg/sec^{-1}$). The mean right atrial pressure in mmHg was recorded at the time of doing the study and the strip chart recording was completed by obtaining a record of the electrical mean radial artery pressure in mmHg. All the pressures recorded, with the exception of the left ventricular pressure, were zeroed and calibrated before each study, and the differentiating circuit was adjusted using a standard triangular wave form and its square wave

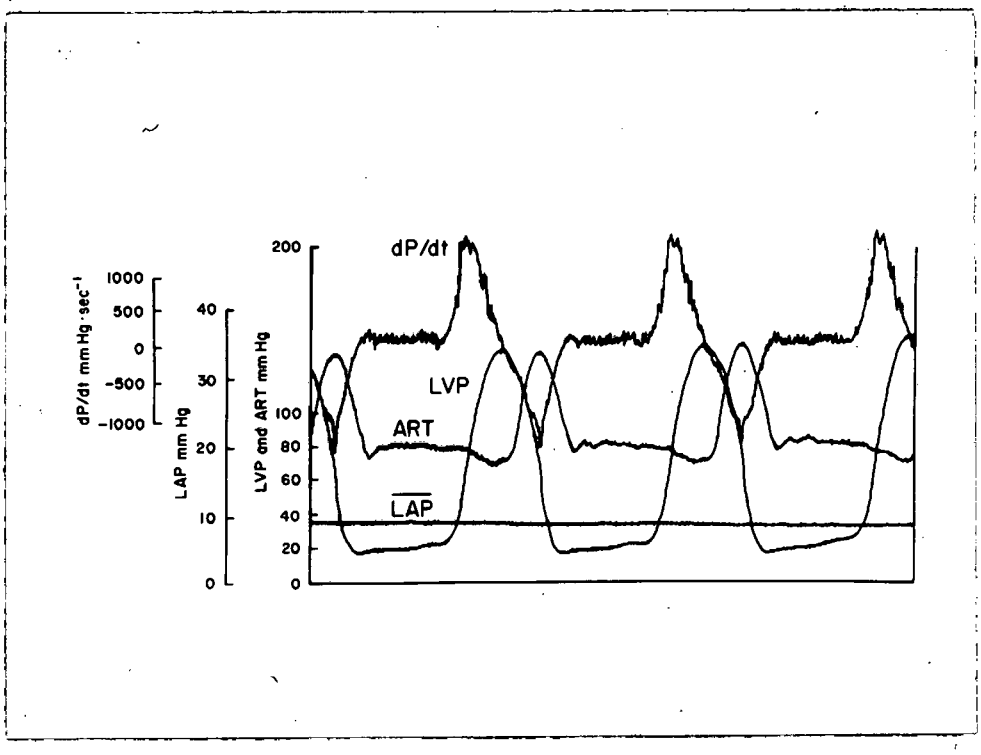

FIGURE 8

The strip chart recording containing a simultaneous record of:

a) The left ventricular dP/dt

b) The dynamic left ventricular pressure (LVP)

c) The dynamic radial artery pressure (ART) and

d) The mean left atrial pressure (LAP)

The scales and units of measurement used for each are shown on the left of the figure.

derivative to allow direct reading of its value to be made from the chart. From these strip chart records and other observed parameters, all obtained under stable conditions, the following haemodynamic parameters were determined as well:

(e) The stroke work (mmHg/ml)

This value was obtained using the formula S.W. = (A.P. - L.A.P.) x S.V. where S.W. = the stroke work in mmHg/ml, A.P. = mean radial artery pressure in mmHg. L.A.P. = mean left atrial pressure in mmHg and S.V. = the stroke volume in mls/beat.

(f) The stroke work index (mmHg/ml/M^2)

This was obtained from the stroke work and the patient's body surface area.

(g) The peripheral vascular resistance (resistance units)

The following formula was used to obtain this parameter:

$$P.V.R. = \frac{(A.P. - R.A.P.)}{C.O.}$$

, where P.V.R. = peripheral vascular resistance in resistance units. A.P. = mean radial artery pressure in mmHg. R.A.P. = mean right atrial pressure in mmHg. C.O. = cardiac output in litres/min.

(h) The peak left ventricular dp/dt (mmHg/sec)

This was obtained by reading the value directly off the strip chart. Three values were obtained on each occasion and the mean of the three was used.

(i) The peak left ventricular dp/dt/P ($secs^{-1}$)

This value was obtained by normalising the peak left ventricular dp/dt for developed pressure. Developed pressure was obtained by dropping a perpendicular $A-A^1$ (Figure 9) from the peak dp/dt (on the strip chart), onto the upslope of the left ventricular pressure trace and subtracting from this pressure the end diastolic pressure B (Figure9) in the ventricle. This pressure was the pressure developed in the ventricle during isovolumetric contraction. The point on the left ventricular pressure trace obtained by the perpendicular corresponded well with the pressure on the arterial trace at which the radial artery pressure began to rise at the commencement of arterial systole A^1 - C (Figure 9).

(j) The ratio of the diastolic pressure time index to the tension time index (DPTI/TTI)

Perpendiculars were dropped to the zero line from (1) the point of commencement of arterial systole A - A^1 (Figure 10). (2) the dicrotic notch B - B^1 (Figure 10). It must be borne in mind that all these patients, with one exception, had prosthetic aortic valves in place during the study, so the dicrotic notch could be abnormally placed. (3) the point of commencement of arterial systole C - C^1 (Figure 10). These perpendiculars were dropped in three successive cycles on the strip chart recording of the arterial pressure trace.

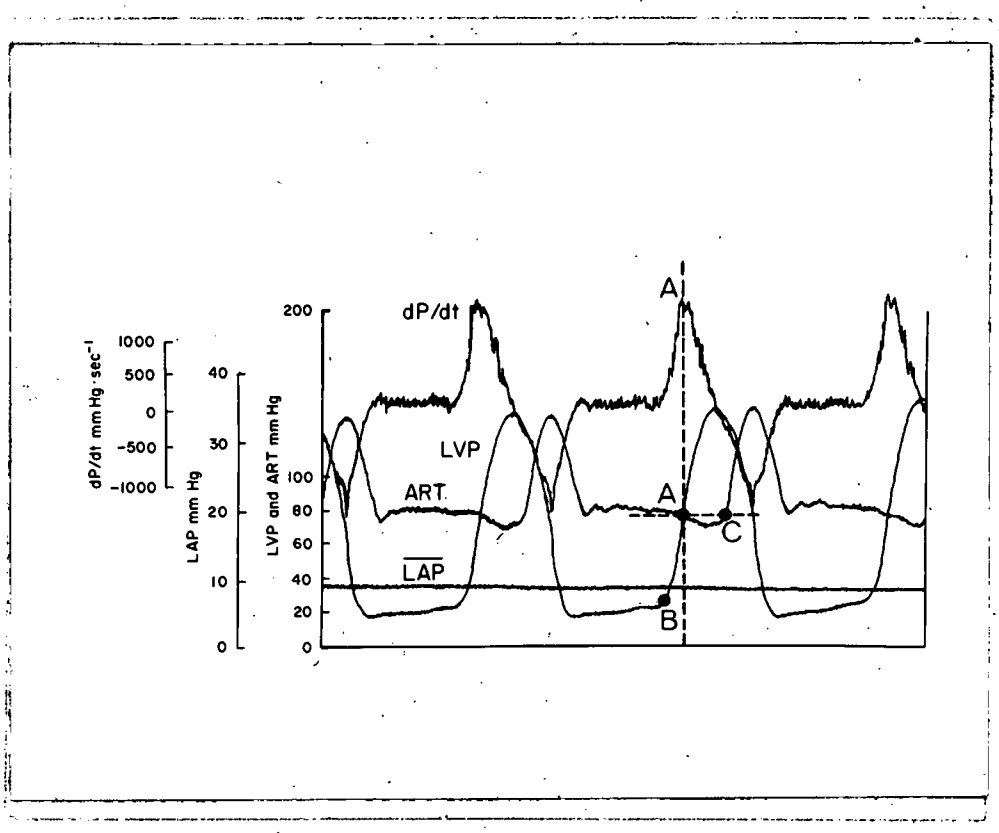

FIGURE 9

The method employed for determining developed pressure (p) A - A^1 = the perpendicular dropped from A (the peak dP/dt) onto the upstroke of the left ventricular pressure trace meeting it at A^1. B = the end diastolic pressure in the left ventricle. C = the point of pressure rise on the radial artery pressure trace. A^1 - C = a horizontal connecting these two points confirming the end point of isovolumetric contraction.

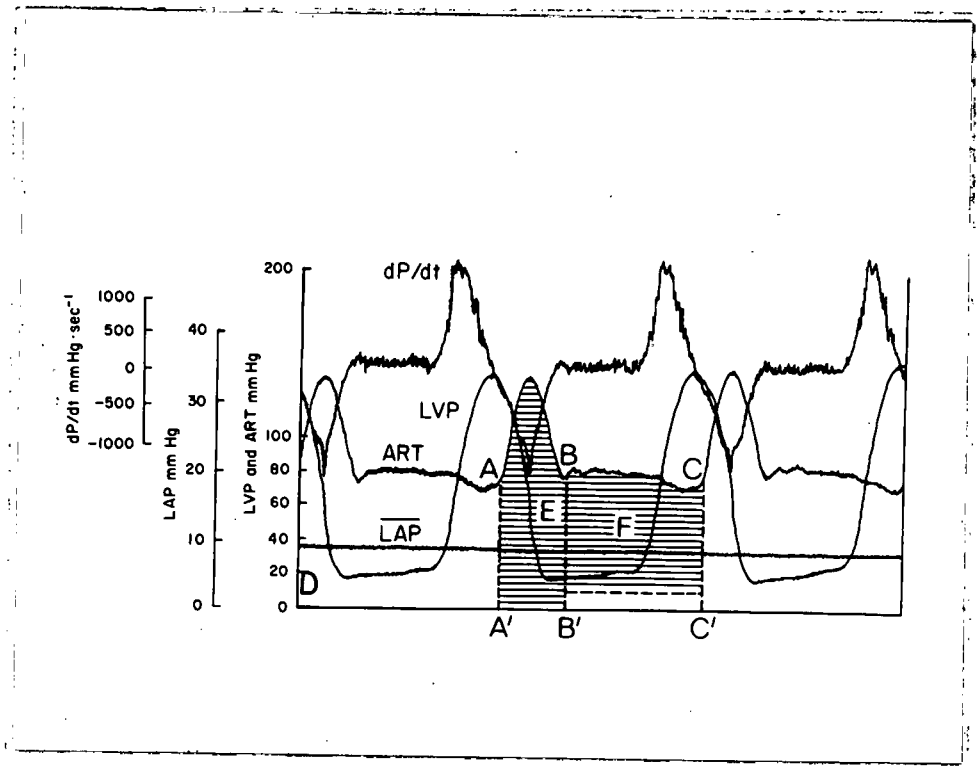

FIGURE 10

The method used to determine the ratio between the diastolic pressure time index and the tension time index DPTI/TTI. A - A^1 = the perpendicular from the commencement of arterial systole (A) to the zero line (A^1). B - B^1 = the perpendicular from the dicrotic notch (B) to the zero line (B^1). C - C^1 = A - A^1 in the following cycle D - D^1 = the mean left atrial pressure on the same scale as the arterial pressure. E = the area under arterial systole and F = the area under diastole minus the mean left atrial pressure.

The mean left atrial pressure at that time was drawn onto the trace using the same scale as the arterial pressure D - D^1 (Figure 10). The area under arterial systole and the area under diastole minus mean left atrial pressure were now obtained by planimetry. The two areas were then expressed as a ratio and used as an index of coronary blood flow as described by Buckberg and co-workers (Buckberg, D.G., Towers, B., Paglia, D.E., Mulder, D.G., Maloney, J.V. 1973), who postulated that this ratio related the amount of blood supplied to the myocardium during diastole (proportional to the diastolic pressure time index) to the demands of the myocardium, generated during systole (proportional to the tension time index).

The metabolic determinations

These studies were all carried out utilising simultaneously obtained arterial and coronary sinus blood samples.

The position of the coronary sinus catheter was checked before each study by comparing the pO_2 of the blood obtained from the coronary sinus catheter with that obtained from the pulmonary artery or, where not available, the right atrium (Wisheart, J.W., Archie, J.P., Kirklin, J.W., Tracy, W.G. 1974). The coronary sinus catheter was considered to be in situ if the difference between the two pO_2s exceeded 5 mmHg. If the difference was found to be below this figure at the commencement, or

fell below this level at any time during the fifty-four hour period, the metabolic studies were either not done, or were terminated.

Full arterial and coronary sinus blood gas analyses using an Instrument Laboratory Inc. Model 313 Analyser and haematocrit were obtained at the time of every study so as to ensure that the patients were not hypoxic, hypercapnic or acidotic due to respiratory or metabolic causes as any of these conditions could have serious effects on the transmyocardial lactate and pyruvate estimations that were carried out (Lundsgaard-Hansen, P. 1966).

The arterial blood gas analyses were utilised to derive other metabolic parameters which were in turn used in their own right to compare the two methods under study and also to ensure that there were no significant differences between the two groups of patients, which could be the cause of any differences between them in their lactate and pyruvate levels and the parameters derived from them.

The following values and determinations were obtained either by direct measurement or assay, or were computed from these levels:

(a) <u>The arterial oxygen contents in volumes percent</u>

These values were obtained in this study by computation rather than direct measurement according to the algorithms of L.J. Thomas Jr. (Thomas, L.J.Jr. 1972), using the pertinent blood gas figures, haematocrit and temperature values required.

(b) The arterial to coronary sinus oxygen extraction in volumes percent

The arterial oxygen contents were used together with the coronary sinus oxygen contents calculated in identical fashion to provide these values using the formula: $O.E. = \frac{(a\ O.C. - c.s.\ O.C.)}{a\ O.C.}$

where O.E. = arterial to coronary sinus oxygen extraction in volumes percent, a O.C. = arterial oxygen content in volumes percent and c. s. O.C. = coronary sinus oxygen content in volumes percent.

(c) Arterial buffer base in M. Equivs/litres

Arterial buffer base values were calculated from the blood gas analyses, again according to the algorithms of L.J. Thomas Jr. (Thomas, L.J.Jr. 1972).

(d) Arterial to coronary sinus buffer base extraction in M. Equivs/litre

Coronary sinus buffer base values were calculated in the same way as the arterial levels and both were then used to calculate the arterial to coronary sinus buffer base extraction using the formula: $B.B.E. = \frac{a.\ B.B. - c.s.\ B.B.}{a\ B.B.}$ where B.B.E. = arterial to coronary sinus buffer base extraction in M. Equivs/litres. a B.B. = arterial buffer base in M. Equivs/litre. It was felt that this value would give a true index of the hydrogen ion uptake or release from the myocardium because it eliminated the influence of the pCO_2 on the hydrogen ion concentration.

(e) The arterial potassium in M. Equivs/litre

Arterial potassium levels were obtained using a flame photometer (Instrument Laboratories Inc. Model 143).

(f) The arterial to coronary sinus potassium extraction in M. Equivs/litre

The arterial and coronary sinus potassium levels obtained in identical fashion were then used to obtain the arterial to coronary sinus extraction using a similar formula, namely: $K.E. + \frac{a(K) - c.s.(K)}{a(K)}$

where K.E. = arterial to coronary sinus extraction in M. Equivs/litre. a(K) = arterial potassium in M. Equivs/litre. c.s. (K) = coronary sinus potassium in M. Equivs/litre. These estimations were used to determine whether there was any significant losses of potassium from the myocardium and whether one method caused significantly more loss than the other.

(g) Lactate and pyruvate metabolism

Arterial and coronary sinus levels of lactate and pyruvate were estimated spectrophotometrically using the enzymatic method of Marbach (Marbach, E.D., Weil, M.H. 1967) and a Beckman Du Spectrophotometer. From these simultaneously obtained arterial and coronary sinus levels of lactate and pyruvate the following were computed:

(h) The arterial to coronary sinus percent lactate extraction

These levels were obtained using the formula: $\%L.E. = \frac{aL - c.s.L.}{a.L.} \times 100$

where %L.E. = arterial to coronary sinus percent lactate extraction, a.L. = arterial lactate in m.Mol/litre, c.s.L. = coronary sinus lactate in m.Mol/litre.

(i) The arterial to coronary sinus excess lactate (m.Mol/litre)

The arterial and coronary sinus levels of lactate and pyruvate were now used to calculate the excess lactate using a simplified version of Huckabee's formula (Huckabee, W.E. 1961), namely:

$$X.L. = c.s.L. - C.S.P. \times \frac{aL}{ap}$$, where S.L. = arterial to coronary sinus excess lactate in m.Mol/litre, c.s.L. = coronary sinus lactate in m.Mol/litre, a.L. = arterial lactate in m.Mol/litre, c.s.p. = coronary sinus pyruvate in m.Mol/litre, and a.p. = arterial pyruvate in m.Mol/litre.

(j) The percentage anaerobic metabolism

These values for each patient at each study period were obtained using the formula of Huckabee (Huckabee, W.E. 1961). The arterial to coronary sinus percent lactate extraction, the arterial to coronary sinus excess lactate and the percentage anaerobic metabolism are all measurements of myocardial anaerobic metabolism, which has been shown to occur during operations on the heart using cardiopulmonary bypass (Goldschlager, N., Gerbode, F., Osborn, J.J., Cohn, K.E. 1972; Goldman, B.S., Trimble, A.S., Sheverini, M.A., Teasdale, S.J., Silver, M.D.

Elliott, G.E. 1971), but it is less well documented as to whether it persists into the post-operative period and if so for how long and to what extent.

CHAPTER VIII

ENZYME AND ISOENZYME STUDIES

As previously mentioned the enzyme and isoenzyme studies differed from the other studies in that a sample was obtained prior to the commencement of cardiopulmonary bypass, but after the induction of anaesthesia and an additional sample was obtained at about fifty-four hours. These two samples were venous blood. The intervening samples obtained at the time of the other studies were obtained from the coronary sinus, in all cases where this catheter was functional. They were obtained from the right atrium or pulmonary artery in those patients in whom the coronary sinus catheter was non-functional. This was done (a) to ensure that the maximum number of patients were studied with reference to their enzyme and isoenzyme levels and because (b) experimental work currently being carried out at Duke University, Durham, North Carolina indicated that it did not make any difference where the sampling was carried out since these enzymes and isoenzymes reached the systemic venous blood via the cardiac lymphatics and not via the myocardial effluent (Roe, C.R. 1973). Since this work was still in the process of being carried out at the time of the present study and had not yet been published, we carried out a simple assessment of the validity of this claim in a few of our patients. Samples were simultaneously withdrawn from the coronary sinus and systemic vein at each study period

in order to compare them. This comparison was carried out in sixteen patients. There were no differences in the levels of total creatine phosphokinase, creatine phosphokinase MB isoenzyme, total lactic acid dehydrogenase and the five isoenzymes of lactic dehydrogenase which could not be explained by the limits of experimental error of the method. We were thus re-assured with reference to the claim and as a consequence were able to study the enzyme and isoenzyme levels in the maximum number of patients possible.

The enzyme and isoenzymes utilised in this study were chosen because (a) they were known to be liberated by necrotic myocardial cells (Wroblewski, F., Gregory, K.F. 1961; Coodley, E.L. 1966; Roe, C.R., Limbird, L.E., Wagner, G.S. 1972; Dixon, S.H.Jr., Limbird, L.E., Roe, C.R., Wagner, G.S., Oldham, H.N.Jr., Sabiston, D.C.Jr. 1973) and (b) because they could be expected to appear in the patients' blood within the time span of the studies (Coodley, E.L. 1966). Both these points need, however, to be further considered.

All enzymes are large molecule proteins that catalyse specific biochemical reactions within the cell. The myocardial cell possesses many enzymes which are also to be found in many other cell types in the body. Myocardial cell necrosis thus liberates all the enzymes which are at present estimated in routine biochemistry laboratories, some in

greater quantity than others. If the sole source of enzyme release is the myocardium, as occurs early in acute myocardial infarction, a diagnosis which can be substantiated by clinical and electrocardiographic evidence, then it is safe to assume that the abnormal serum enzyme patterns are due to myocardial cell necrosis. Four enzymes are commonly used to support the diagnosis of acute myocardial infarction. They are creatine phosphokinase, lactic acid dehydrogenase, serum glutamic oxaloacetic acid transaminase and hydroxy butyrate dehydrogenase (Coodley, E.L. 1968).

Cardiopulmonary bypass surgery differs from the patient who has sustained an acute myocardial infarction because bypass itself results in injury to many different cells in the body, notably skeletal muscle, liver, smooth muscle, gastro-intestinal mucosa and the erythrocyte. All these cell types liberate the same group of enzymes in varying quantities, thus reducing their specificity as an indication of myocardial cell necrosis when they are used in patients who have undergone cardiac surgery utilising cardiopulmonary bypass. Their sensitivity, however, remains unchanged.

Creatine phosphokinase and lactic acid dehydrogenase exist in more than one form with reference to certain physical properties. They can both be fractionated into isoenzymes using electrophoresis (Wroblewski, F., Gregory, K.F. 1961; Nerenberg, S.T., Pogojeff, G. 1969;

Roe, C.R., Limbird, L.E., Wagner, G.S. 1972). The electrophoresis is carried out in Agar Gel and when complete the appropriate chemical reagents are added, thus allowing the isoenzymes to be recognised and identified by the distance they have migrated from their point of origin (Roe, C.R., Limbird, L.E., Wagner, G.S. 1972).

Creatine phosphokinase separates electrophoretically into three isoenzymes (Figure 11). The predominant fraction migrates to the cathode and is known as the M.M. isoenzyme. This isoenzyme constitutes the only detectable form in health as a result of the method used for this study and equals the total creatine phosphokinase found within the normal range (0 - 130 I.U.) in healthy people. It is liberated principally from skeletal muscle, but a certain amount also comes from the myocardium. The other two isoenzymes only occur in the blood of a patient in abnormal states in Man. They both migrate to the anode. The M.B. isoenzyme does not migrate as far as albumin and has only been found in patients suffering from a few conditions. It is liberated from necrotic myocardial cells and from skeletal muscle cells in certain of the progressive muscular dystrophies, dermatomyositis, polymyositis and conditions associated with myoglobinura (Roe, C.R., Limbird, L.E., Wagner, G.S. 1972). The only other condition that gives rise to elevated serum levels of M.B. isoenzyme are infants and children with congenital biliary atresia where it is thought to be liberated from

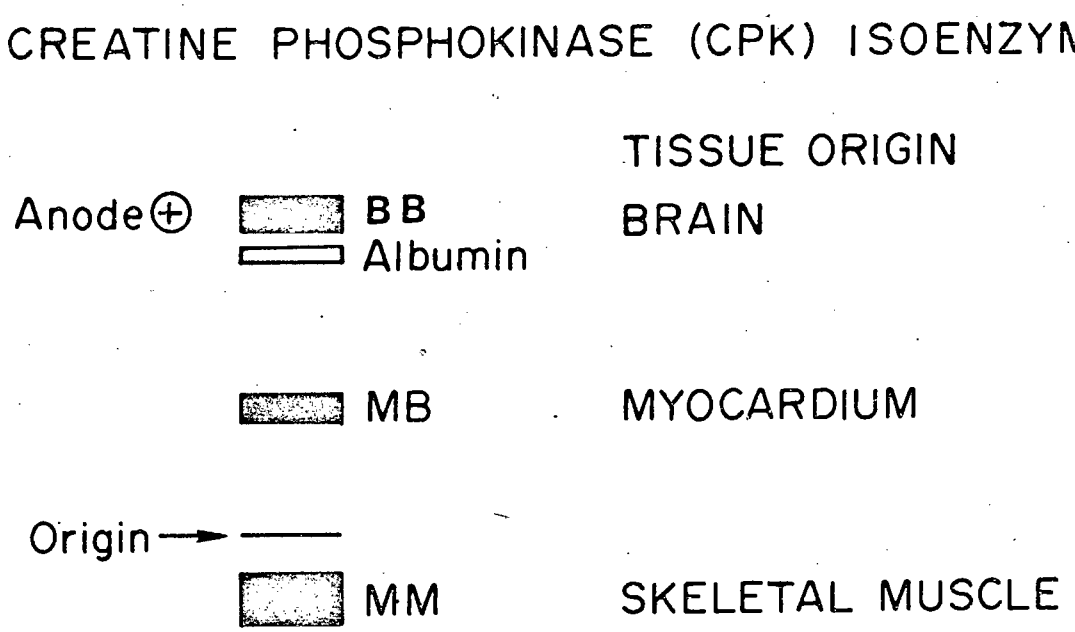

FIGURE 11

A diagrammatic representation of the electrophoretic separation of the isoenzymes of creatine phosphokinase and their principle tissues of origin. Note the position of albumin in relation to the isoenzymes.

the cells of the gall bladder mucosa (Roe, C.R. 1973). The B.B. isoenzyme migrates further than albumin and is only liberated by certain disease states involving the brain (Roe, C.R., Limbird, L.E., Wagner, G.S. 1972).

Lactic acid dehydrogenase fractionates electrophoretically into five isoenzymes which in this discussion are numbered according to the method used for their determination in this study (Figure 12) (Roe, C.R., Limbird, L.E., Wagner, G.S. 1972). Lactic acid dehydrogenase 1, 2 and 3 all migrate to the anode, but not as far as albumin. Lactic acid dehydrogenase 4 and 5 migrate to the cathode. Lactic acid dehydrogenase 1 and 2 are found in the myocardium, the erythrocyte and the renal cortex. Lactic acid dehydrogenase 3 is found in the lung and intestine and lactic acid dehydrogenase 4 and 5 is liberated from skeletal muscle and liver. Total lactic acid dehydrogenase within the normal range (26 - 186 I.U.) in health is made up of the sum of all its isoenzymes. Lactic acid dehydrogenase 2 is usually the predominant fraction followed by lactic acid dehydrogenase 1, 3, 4 and 5 in that order. Commonly lactic acid dehydrogenase 4 and 5 are not detected or are present in such small amounts as to preclude quantitation. From the foregoing it is obvious that the lactic acid dehydrogenase isoenzymes are not as specific for myocardial cell necrosis as creatine phosphokinase - MB isoenzyme is. However,

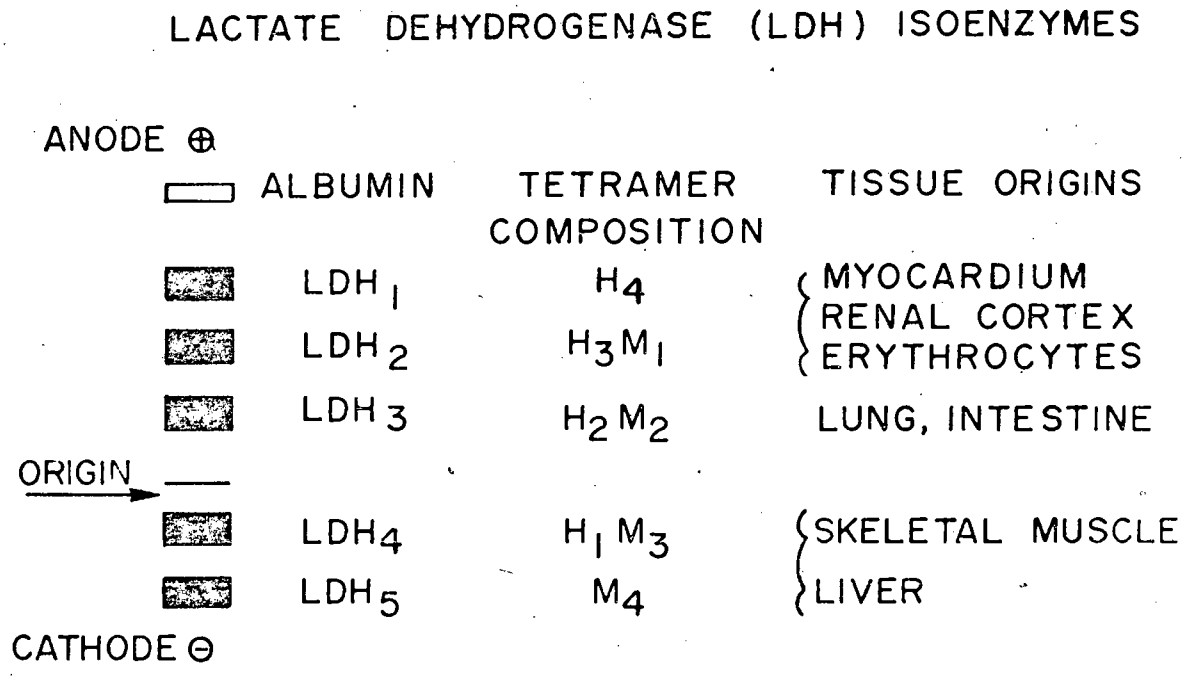

FIGURE 12

Diagrammatic representation of the electrophoretic separation of the isoenzymes of lactic acid dehydrogenase, (numbered according to the method used by C.R. Roe) and their principle tissues of origin. The corresponding tetramers are also shown. The position of albumin is once more shown.

experience has shown that when myocardial cell necrosis occurs total lactic acid dehydrogenase levels rise. This rise is due to a rise in lactic acid dehydrogenase 1 and 2, the others hardly rising at all. In addition lactic acid dehydrogenase 1 rises faster and more substantially than lactic acid dehydrogenase 2, thus the ratio of lactic acid dehydrogenase 1 to lactic acid dehydrogenase 2 approaches, reaches and exceeds unit (Wroblewski, F., Gregory, K.F. 1961; Roe, C.R., Limbird, L.E., Wagner, G.S. 1972). This abnormal pattern of lactic acid dehydrogenase isoenzyme levels is presumptive evidence of myocardial cell necrosis. Because lactic acid dehydrogenase 1 and lactic acid dehydrogenase 2 are both liberated from the erythrocyte as well, haemolysis seriously vitiates the use of these isoenzymes and it is essential that the haemolysis levels in any given patient should be checked if these isoenzymes are to be used to study patients during or after cardiopulmonary bypass surgery (Roe, C.R., Limbird, L.E., Wagner, G.S. 1972; Dixon, S.H.Jr., Limbird, L.E., Roe, C.R., Wagner, G.S., Oldham, H.N.Jr., Sabiston, D.C.Jr. 1973).

Lactic acid dehydrogenase can also be fractionated into tetramers (Figure 12) and the figure shows the correlation between the isoenzyme and the tetramers.

The tissue origins of the isoenzymes were determined by studying the isoenzyme patterns of tissue extracts submitted to the same process

of electrophoresis and specific chemical identification of the isoenzymes by their migration from the point of origin. Figure 13 is a representative photograph of the Agar Gel in which a tissue extract of skeletal muscle (slot 1), myocardium (slots 2 and 5) and brain (slot 7) have been submitted to electrophoresis and the appropriate reagents then added. Only the M.M. isoenzyme appears is slot 1, the M.M. and M.B. appear in slots 2 and 5 while only the B.B. isoenzyme appears in slot 7. No other tissue extract, with the exception of those already mentioned, have been found in this way to produce the same pattern as that in slots 2 and 5. These findings are a little misleading and are entirely related to the concentration of the tissue extract. If the tissue extract is made sufficiently concentrated all three isoenzymes of creatine phosphokinase can be found in almost any tissue (Ogunra, E. 1974). It is therefore only true to say that creatine phosphokinase - M.B. and B.B. isoenzymes are present in much greater quantity in their respective tissues than in others and that the method for detection and quantitation of these isoenzymes has to be adjusted with regard to sensitivity to ensure that they will detect the presence of these isoenzymes only when present in a tissue or in blood at levels above the extremely low levels which can be found if the sensitivity is made too great. The lactic acid dehydrogenase isoenzyme content of all tissues has similarly been determined (Wroblewski, F., Gregory, K.F. 1961). Note should

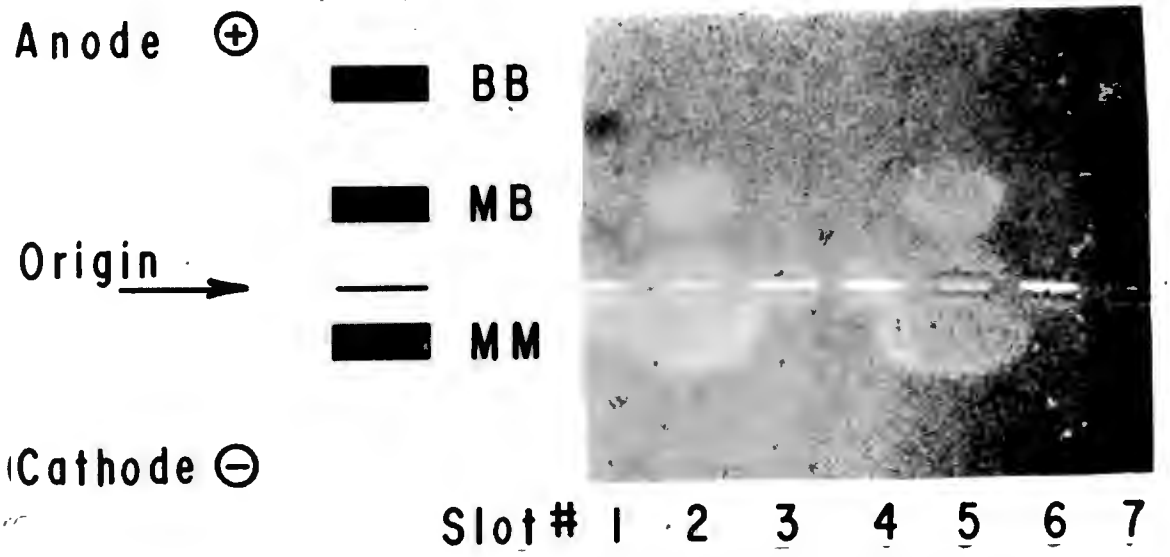

FIGURE 13

The electrophoretic separation of various tissue extracts

Slot 1 contains skeletal muscle, slots 2 & 5 contain myocardium,

Slot 7 contains brain, slots 3, 4 and 6 are empty.

be made of the different numbering system used by this group of workers when compared with the numbering system used in this study.

The methods have also been tested to ensure that false positives do not occur in the laboratory. Figure 14 is a photograph of an Agar Gel in which paired plasma samples from a patient who has sustained an acute myocardial infarction are in slots M.I. and M.I.^{1} and paired plasma samples from a patient suffering from a muscular dystrophy are in M.D. and M.D.^{1}. The reagents have only been added to slots M.I. and M.D. Note that no reaction occurs in slots M.I.^{1} and M.D.^{1}. This photograph also highlights the pattern obtained from one of the exceptions to the myocardium as a source of creatine phosphokinase - M.B. isoenzyme.

The isoenzymes of creatine phosphokinase and lactic dehydrogenase can be quantitated spectrophotometrically from the Agar plates after adding the necessary reagents in accurately measured amounts (Roe, C.R., Limbird, L.E., Wagner, G.S. 1972). The amounts of reagents used are critical because it is possible to make the assay so sensitive that creatine phosphokinase - M.B. and B.B. isoenzymes can be detected in health as previously mentioned. The sensitivity of the method of detection was adjusted in this study so that (a) the patterns already described pertained in health, (b) the same patterns that pertained in health could be found in patients during an attack of angina, i.e. that

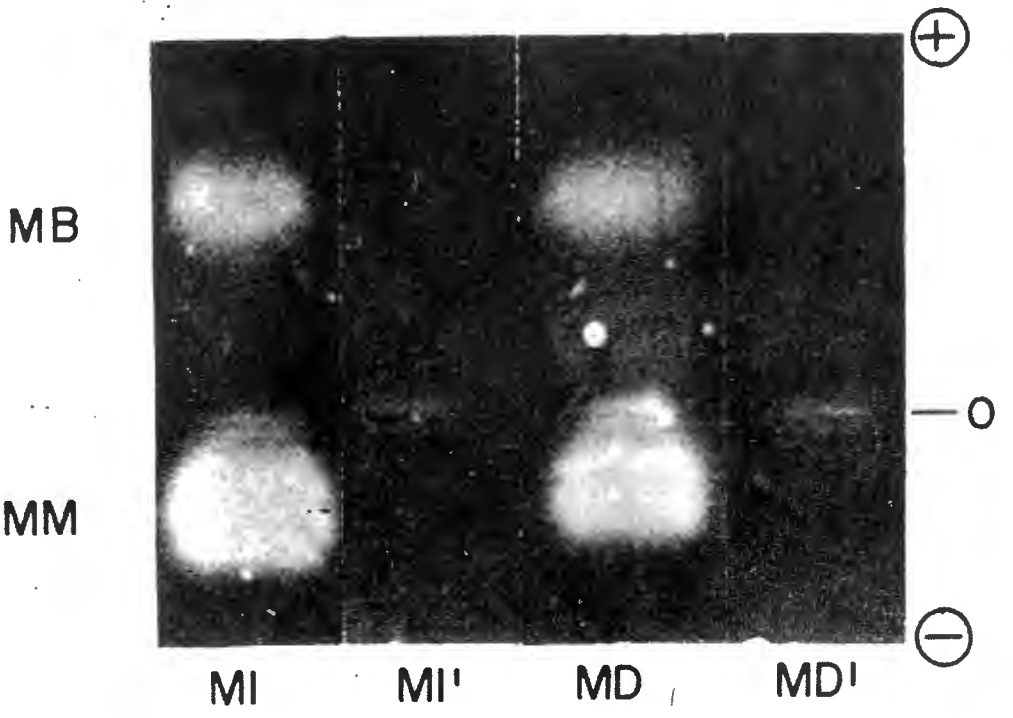

FIGURE 14

An assessment of the method to exclude false positive results. Slots MI and MI^1 contain serum from a patient who has suffered an acute myocardial infarction. Slots MD and MD^1 contain serum from a patient with muscular dystrophy. The chemical reagents have only been added to slots MI and MD. No reactions are present in slots MI^1 and MD^1.

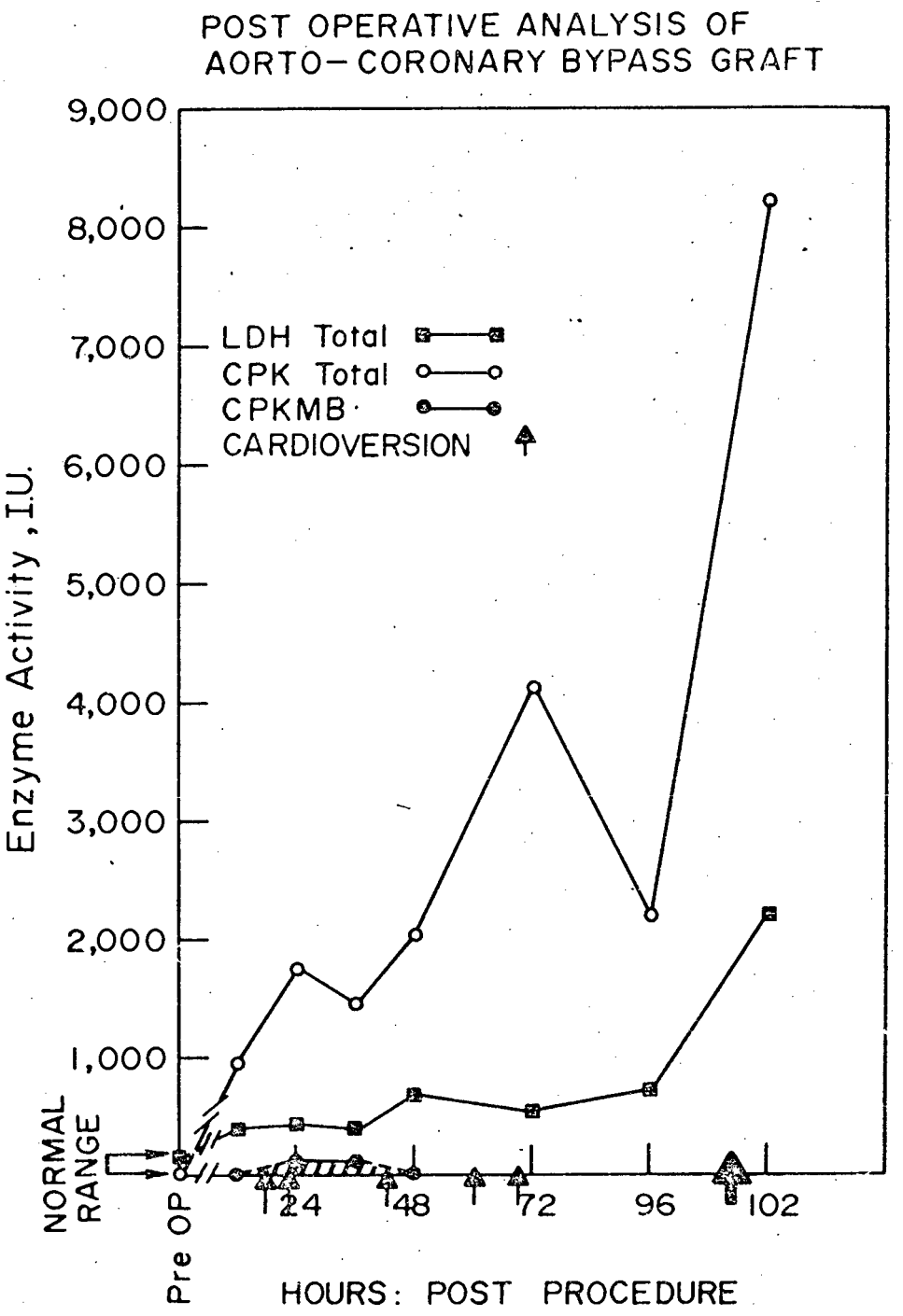

FIGURE 15

A graphic display of total CPK, total LDH and CPK - MB in a patient who has undergone aorto-coronary bypass grafting utilising cardiopulmonary bypass. The lack of correlation of CPK - MB and multiple cardioversions is clearly shown.

myocardial ischaemia as opposed to myocardial cell necrosis did not produce abnormal patterns and (c) that needle punctures of the myocardium, venting of the left ventricle through its wall or multiple defibrillation attempts did not produce patterns of isoenzyme release diagnostic of myocardial cell necrosis (Oldham, H.N.Jr., Roe, C.R., Young, W.G.Jr., Dixon, S.H.Jr. 1974). Figure 15 is a representative graphic display of the enzyme and isoenzyme release before, during and after aorto-coronary bypass graft surgery utilising cardiopulmonary bypass. Multiple defibrillation attempts in the post-operative period clearly have no effect on the levels of creatine phosphokinase - M.B. The isoenzymes of lactic acid dehydrogenase were not assayed in this patient because haemolysis occured, which vitiated these values.

Creatine phosphokinase has been shown for a long time to appear in the blood about six hours after the onset of pain in patients who have sustained an acute myocardial infarction. It reaches peak levels at about twenty-four hours and has usually disappeared by forty-eight hours. Elevated blood levels of lactic acid dehydrogenase are also known to appear between six to twelve hours, they tend to reach a peak around forty-eight hours and then gradually subside, but often still being abnormally elevated by four to five days (Coodley, E.L. 1966). The isoenzymes of both creatine phosphokinase and lactic acid dehydrogenase produce their characteristic abnormal patterns within these time spans.

Creatine phosphokinase - M.B. appears at about the same time as the total creatine phosphokinase starts to rise, but it has commonly disappeared before the total creatine phosphokinase has returned to the normal range (Figure 15), (Roe, C.R., Limbird, L.E., Wagner, G.S. 1972). The ratio of lactic acid dehydrogenase 1 and lactic acid dehydrogenase 2 commonly reaches and exceeds unity around twelve to twenty-four hours after the onset of an acute myocardial infarction, and remains this way for twenty-four to forty-eight hours, before returning to normal in those patients who survive (Cohen, L., Djordjevich, J., Ormiste, V. 1964).

Studies carried out during and after operations on the heart, utilising cardiopulmonary bypass, have further indicated that the abnormal patterns of isoenzyme release may occur much earlier than those seen in acute myocardial infarctions (Oldham, H.N.Jr., Roe, C.R., Young, W.G.Jr., Dixon, S.H.Jr. 1974). This is particularly true of creatine phosphokinase - M.B. where detectable levels have been observed while still on cardiopulmonary bypass. These levels have varied in amount and in their duration. In some patients the levels have not been high and they have been of short duration, i.e. no longer detectable three to four hours later. The probable explanation for this phenomenom in patients undergoing cardiac surgery is two-fold. Firstly the non-perfused myocardium, in which myocardial necrosis may have occurred,

is always re-perfused a half to one and a half hours later, as opposed to an infarcted area of myocardium where no re-perfusion occurs because of the basic lesion in the coronary arteries which caused the infarction. Secondly, the lymphatic return from the heart is greatly increased under conditions where non-perfusion is followed by re-perfusion (Jowett, A.W. 1971). This fact raises a very important consideration which may explain why some post-surgical patients have no detectable creatine phosphokinase - M.B., but do have a reversed lactic acid dehydrogenase 1 to lactic acid dehydrogenase 2 ratio. These patients may in fact have elevated creatine phosphokinase - M.B. levels, but because they were so early and so transient they were missed by a sampling schedule which was only commenced at about six hours as was used in this study.

With these considerations in mind it was decided to carry out the following enzyme and isoenzyme estimations in the two groups of patients post-operatively:

(a) The total creatine - phosphokinase (I.U.)

These were estimated spectrophotometrically using the method of Rosalki (Rosalki, S.B. 1967). The levels of creatine phosphokinase obtained were not however used in the statistical comparison of the two groups of patients because of the relatively low specificity of this estimation in patients who have sustained necrosis of many

different cell types during cardiopulmonary bypass. The levels obtained were, however, used to ensure that the sum of the isoenzyme levels obtained equalled the total value of creatine phosphokinase.

(b) The isoenzymes of creatine phosphokinase (I.U.)

An aliquot of the plasma used for the total creatine phosphokinase estimation was submitted to electrophoresis in Agar Gel and quantitated spectrophotometrically (Roe, C.R., Limbird, L.E., Wagner, G.S. 1972). The values of creatine phosphokinase - M.B. obtained were used in the comparison of the groups, since we felt that this isoenzyme in this population of patients indicated myocardial cell necrosis which must have occurred during the procedure (Oldham, H.N.Jr., Roe, C.R., Young, W.G.Jr., Dixon, S.H.Jr. 1974).

(c) The total lactic acid dehydrogenase (I.U.)

Total lactic acid dehydrogenase was determined spectrophotometrically using the method of Henry (Henry, R.J., Chiamori, N., Golub, O.J., Berkman, S. 1960), using aliquots of the samples which were used for creatine phosphokinase and its isoenzymes. As with total creatine phosphokinase, total lactic acid dehydrogenase was not used in the group comparisons because of its low specificity in patients who have undergone cardiopulmonary bypass surgery, but was merely

used as a check on the sum of its isoenzymes.

(d) The isoenzymes of lactic acid dehydrogenase (I.U.)

The aliquot used to determine the total lactic acid dehydrogenase levels was submitted to electrophoretic separation and once more spectrophotometrically quantitated for all five isoenzymes as described by Nerenberg and co-workers (Nerenberg, S.T., Pogojeff, G. 1969). Only the values of isoenzymes 1 and 2 were used to compare the groups, however, and this was done by using the ratio of lactic acid dehydrogenase 1 and lactic acid dehydrogenase 2 rather than using their values independently.

The diagnosis of myocardial cell necrosis in this study and the comparisons that were carried out between the two groups of patients were based on combined myocardium specific isoenzyme analyses, i.e. creatine phosphokinase - M.B. and the ratio of lactic acid dehydrogenase 1 to lactic acid dehydrogenase 2 as described by Roe and co-workers (Roe, C.R., Limbird, L.E., Wagner, G.S. 1972).

CHAPTER IX

THE ELECTROCARDIOGRAM STUDY

Standard 12-lead electrocardiograms, recorded two to three days pre-operatively and seven to ten days post-operatively, were obtained on every patient.

The pre-operative electrocardiogram was used to document the rhythm, the P wave configuration quantitatively and the presence of left ventricular hypertrophy. Repolarisation changes detectable by the presence of T wave inversion in the left chest leads. The presence of features suggestive of ischaemia using pre-determined criteria, of ST elevation or depression assuming that the ischaemia could be diagnosed if the J point was depressed 2 mm or more in the left chest leads (Hultgren, H.N., Miyagawa, M., Buck, W., Angell, W.W. 1971). The presence of previous infarctions, based on accepted criteria for the diagnosis of old and healed infarcts and any other significant abnormalities were recorded.

The pre-operative and post-operative electrocardiograms were assessed by an unbiased, independent, but experienced assessor in a blind fashion, i.e. he had no prior knowledge of the patient and he was not aware whether any particular electrocardiogram was a pre-operative or a post-operative electrocardiogram. He only knew that they were all electrocardiograms of patients with aortic valve disease, and whether

the particular electrocardiogram was obtained from a patient on Digoxin or not.

As a result of this blind assessment it now became possible to compare the pre and post-operative electrocardiogram for changes in rhythm, ischaemic features, new infarctions, or any other significant changes. Since the post-operative electrocardiogram was taken seven to ten days post-operatively, myocardial infarctions could not with certainty be ascribed to the methods used at operation, as they might have occurred in the post-operative period. It was, however, hoped that any infarction patterns would not have resolved within this time period, but that the known specific electrocardiographic changes associated with cardiopulmonary bypass would have resolved, as these changes can often cause confusion in making a diagnosis of an intra-operative or post-operative myocardial infarction (Hultgren, H.N., Miyagawa, M., Buck, W., Angell, W.W. 1971).

CHAPTER X

STATISTICAL METHODS AND DATA ANALYSIS

The process of randomisation led to two populations of patients, each assigned to have his or her aortic valve replaced by one of the two methods under study. The recorded facts about each patient, such as vital statistics, age, sex, etc., symptoms, signs, diagnosis, radiological features, electrocardiographic data, pre-operative haemodynamic data, left ventricular wall thickness and diameter measured at operation, could be divided into quantitative and qualitative data. The former were all stated as a range (where applicable) and a mean $\pm$ one standard error of the mean. The student T test was then used to compare the populations. The latter were tested by chi square for a two way contingency table.

The data recorded about the two methods, namely the myocardial temperatures at the time of aortic cross-clamping and release, the aortic cross-clamping times and the total cardiopulmonary bypass times were stated as a range and a mean $\pm$ one standard error of the mean, and the methods were compared using the student T test.

Each post-operative haemodynamic, metabolic and isoenzyme variable was tested in three separate ways against the hypothesis that the mean value for all patients in whom coronary perfusion was used, was the same as that for those in whom profound myocardial hypothermic non-perfusion arrest had been used.

The three separate ways were:

(1) The difference between the two groups (a population in whom one of the two methods was used) means at each study period was tested by student's T test.

(2) The difference between the two groups means, averaged over all study periods, obtained by least squares analysis, was tested by the F ratio of variation between groups to the variation between patients in the groups.

(3) The difference between the two group means was tested against experimental error as in (2) using as experimental error the variability within patients within each group.

For (2) and (3) a least squares, rather than a standard analysis of variance, was employed, because of unequal group sizes and incomplete data for some patients. Averaging over periods to obtain a best unbiased estimate of population means was permitted because the group period interaction term used in the analysis was never significantly different from zero.

An estimate of reproducibility for those haemodynamic and metabolic variables measured in duplicate or tripicate was carried out. The ratio of the standard deviation of these repeated measurements at each study period to the overall mean was calculated using a nested analysis of variance and expressed as a coefficient of variation.

When departures from a normal distribution were encountered, data transformations were selected to equalise as nearly as possible the variation within each group. All isoenzyme data were log transformed since the normal value for creatine phosphokinase - M.B. in health is zero and the reciprocal of $dp/dt/P^{-1}$ was employed.

Trends over the five month study were examined by regressing each variance against the order in which the patients were treated. In like manner surgeon-to-surgeon differences were examined by regressing each variable against each surgeon.

Interrelations among certain variables were examined by regression and correlation. Age, sex, race, orthopnoea, angina, syncope, diagnosis of stenosis or incompetence of the aortic valve, cardiothoracic ratio, left ventricular wall thickness and diameter, macroscopic coronary artery disease, aortic cross-clamping time and total cardiopulmonary bypass times and additionally in the patients who had their aortic valves replaced using coronary perfusion, average flows and pressures in the right and left perfusion catheters were regressed against cardiac index, creatine phosphokinase - M.B., the ratio of lactic acid dehydrogenase 1 to 2 and excess lactate.

A forward stepwise regression procedure was used both for the patient population as a whole using "group" as a regression variable and separately by groups. Only those variables which had a $p < 0.1$

remained in the model.

The following variables were studied for correlation of each with all the others in the patient population as a whole: cardiothoracic ratio, left ventricular wall thickness and diameter, two myocardial temperatures, the aortic cross-clamp and total cardiopulmonary bypass times, the cardiac index (time intercept and slope obtained by least squares), creatine phosphokinase - M.B. and the ratio of lactic dehydrogenase 1 to 2 (magnitude and rates of rise and disappearance fit with a gamma function), excess lactate (intercept and rate of return to zero).

CHAPTER XI

RESULTS

POPULATION ANALYSIS

Eighty-one adult patients underwent elective isolated aortic valve surgery for the first time in the Department of Surgery, The University of Alabama in Birmingham Alabama, between the second of February 1973 and the twenty-fourth of July 1973. Four patients were inadvertently missed and thus not randomised, leaving seventy-seven patients who were prospectively and randomly allocated to have their operations carried out using one or the other methods of myocardial preservation under study. Seven patients had homografts inserted. The practice in the Department at the time was to use coronary perfusion while inserting a homograft, but the decision to insert a homograft was only made at operation and thus these patients were necessarily rejected from the study. The surgeon elected to change the method of myocardial preservation to which six patients had been allocated, believing that the allocated method was not in the patients' best interests. It is interesting that in every case the change was from coronary perfusion to profound hypothermic arrest. These patients were rejected from the study.

Sixty-four patients remained in whom the randomisation was adhered to. Thirty-one or 48.4% of these patients had their valves replaced using coronary perfusion and thirty-three or 51.6% had their valves

replaced using profound myocardial hypothermic non-perfusion arrest.

The age range in the population was twenty-two to seventy-seven years with a mean $\pm$ 1 standard error of the mean of 50.8 $\pm$ 1.621 years. The range and mean in the coronary perfusion group was twenty-four to seventy-seven years with a mean of 50.6 $\pm$ 2.457 years and for the profound hypothermic non-perfusion arrest was twenty-two to seventy-two years with a mean of 51.0 $\pm$ 2.170 years.

There were fifty-one males and thirteen females in the entire population. The coronary perfusion group consisted of twenty-six males and five females while the profound hypothermic non-perufsion group consisted of twenty-five males and eight females.

The population consisted of fifty-six whites and eight negroes. Twenty-eight whites and three negroes formed the coronary perfusion group, twenty-eight whites and five negroes formed the profound hypothermic non-perfusion arrest group.

Statistical analysis of these figures indicated a high similarity between the groups with reference to these vital statistics (Table II).

A history of underlying conditions and/or other associated problems was sought in each patient. Twenty-two patients in the population had a previous history of rheumatic fever. Eleven of these were included in the coronary perfusion group and eleven in the profound hypothermic non-perfusion arrest group. Five patients gave a history compatible

TABLE II

		TOTALS		CORONARY PERFUSION		NON-PERFUSION ARREST		SIGNIFICANCE	
AGE	(YEARS)	RANGE 22-77	MEAN ± SE 50.8 ± 1.621 (n = 64)	RANGE 24-77	MEAN ± SE 50.6 ± 2.457 (n = 31)	RANGE 22-72	MEAN ± SE 51.0 ± 2.170 (n = 33)	N/S	
		No.	%	No.	%	No.	%	Prob $>X^2$	DF
SEX	MALES	50	78.1	26	83.9	24	72.7		
	FEMALES	14	29.9	5	16.1	9	27.3		
	TOTAL	64	100.0	31	100.0	33	100.0	0.28	1
RACE	WHITE	57	89.1	28	90.3	29	87.9		
	NEGRO	7	10.9	3	9.7	4	12.1		
	TOTAL	64	100.0	31	100.0	33	100.0	0.75	1

Statistical analysis and comparison of the vital statistics in the total population and between the two groups

with subacute bacterial endocarditis. Three of these had their valves replaced using coronary perfusion and two using profound hypothermic non-perfusion arrest.

An assortment of associated conditions were recorded, including hypertension in ten patients, diabetes in three patients, asthma, pleural calcification, carcinoma of the breast previously treated by surgery and radiotherapy and alcoholism in four additional patients.

Statistical analysis revealed a high degree of similarity between the two groups of patients (Table III).

The presenting symptoms of each patient were carefully noted. The symptom list included dyspnoea on exertion, paroxysmal nocturnal dyspnoea, orthopnoea, angina, syncope, a history of palpitations and/or documented dysrhythmias, a history of previous episodes of left ventricular or biventricular failure, a history of dependent oedema, and a history of haemoptysis. Dyspnoea on exertion was divided into five grades related to severity, namely no dyspnoea on exertion, dyspnoea on severe exertion, dyspnoea on moderate exertion, dyspnoea on minimal exertion, and dyspnoea at rest.

The two groups of patients were highly similar except for two symptoms. A significantly greater number of patients who had a history of paroxysmal nocturnal dyspnoea and episodes of dependent

TABLE III

		Total		Coronary Perfusion		Non-Perfusion Arrest		Significance	
		No.	%	No.	%	No.	%	Prob $>X^2$	DF
Rheumatic Fever	Positive History	22	34.4	11	35.5	11	33.3		
	Negative History	42	65.6	20	64.5	22	66.7		
	Total	64	100.0	31	100.0	33	100.0	0.83	1
Sub-Acute Bacterial Endo-Carditis	Positive History	5	7.8	3	9.7	2	6.1		
	Negative History	59	92.2	28	90.3	31	93.9		
	Total	64	100.0	31	100.0	33	100.0	0.60	1
Associated Conditions	Diabetes	3	4.7	2	6.5	1	3.0		
	Hypertension	10	15.6	3	9.7	7	21.2		
	Asthma	1	1.6	0	0	1	3.0		
	Pleural Calcification	1	1.6	0	0	1	3.0		
	Carcinoma of Breast	1	1.6	0	0	1	3.0		
	Alcoholism	1	1.6	1	3.2	0	0		
	None	47	73.3	25	80.6	22	66.7		
	Total	64	100.0	31	100.0	33	100.0	0.42	1

Statistical analysis and comparison of the underlying and associated conditions in the total population and between the two groups.

oedema (probability $>X^2$ was 0.0085 and 0.0198 respectively) were allocated to have their valves replaced using profound hypothermic non-perfusion arrest. Since the randomisation had been carried out before these facts were known the stiatistically significant differences, with reference to these two symptoms, came about purely by chance. (Table IV).

The physical signs pertinent to the valve pathology in each patient was recorded. This allowed a diagnosis of the predominant haemodynamic lesion to be made. Fourty-six patients in the entire population had aortic stenosis, while eighteen had aortic regurgitation. Twenty-one patients with aortic stenosis and ten patients with aortic regurgitation had their valves replaced using coronary perfusion, while twenty-five patients with aortic stenosis and eight patients with aortic regurgitation had their valves replaced using profound hypothermic non-perfusion arrest. There was no significant differences between the groups (Table V).

Relevant radiological features were recorded in most patients. These included the cardiothoracic ratio, a range of 0.40 - 0.66 with a mean of 0.50 ± 0.014 (n = 25) was found in the coronary perfusion group and a range of 0.35 - 0.71 with a mean of 0.51 ± 0.015 (n = 30) was found in the hypothermic non-perfusion arrest group. There was no significant difference between the groups ($p > 0.1$). Calcification

TABLE IV

		Total		Coronary Perfusion		Non-Perfusion Arrest		Significance	
		No.	%	No.	%	No.	%	Prob>X^2	DF
Dyspnoea	None	10	15.6	5	16.1	5	15.2		
	On severe exertion	12	18.8	6	19.4	6	18.2		
	On moderate exertion	39	60.9	19	61.3	20	60.6		
	On minimal exertion	3	4.7	1	3.2	2	6.1		
	At rest	0	0	0	0	0	0		
	Total	64	100.0	31	100.0	33	100.0	0.96	1
Paroxysmal Nocturnal Dyspnoea	Positive history	18	28.1	4	12.9	14	42.4		
	Negative history	46	71.9	0	87.1	19	57.6		
	Total	64	100.0	31	100.0	33	100.0	0.0085	1
Orthopnoea	Positive history	18	28.1	6	19.4	12	36.4		
	Negative history	46	71.9	25	80.6	21	63.6		
	Total	64	100.0	31	100.0	33	100.0	0.13	1
Angina	Positive history	31	48.4	17	54.8	14	42.4		
	Negative history	33	51.6	14	45.2	19	57.6		
	Total	64	100.0	31	100.0	33	100.0	0.32	1
Syncope	Positive history	22	34.0	12	38.7	10	30.3		
	Negative history	42	65.5	19	61.3	23	69.7		
	Total	64	100.0	31	100.0	33	100.0	0.49	1
Dys-rhythmias	Positive history	11	17.2	5	16.1	6	18.2		
	Negative history	53	82.8	26	83.9	27	81.8		
	Total	64	100.0	31	100.0	33	100.0	0.81	1
Left Ventricular or Biventricular Failure	Positive history	20	31.3	10	32.3	10	30.3		
	Negative history	44	68.7	21	67.7	23	69.7		
	Total	64	100.0	31	100.0	33	100.0	0.8419	1
Other Symptoms	None	50	78.1	28	90.3	22	66.7		
	Oedema	7	10.9	0	0.0	7	21.2		
	Haemoptysis	7	10.9	3	9.7	4	12.1		
	Total	64	99.9	31	100.0	33	100.0	0.0198	1

Statistical analysis and comparison of the presenting symptoms in the total population and between the two groups.

TABLE V

		Total		Coronary Perfusion		Non-Perfusion Arrest		Significance	
		No.	%	No.	%	No.	%	Prob $>X^2$	DF
Pulse Character	Normal	5	7.8	3	9.7	2	6.1		
	Plateau	42	65.6	19	61.3	23	69.7		
	Collapsing	17	26.6	9	29.0	8	24.2	0.75	2
	Total	64	100.0	31	100.0	33	100.0		
Apex Beat	Normal	11	17.2	6	19.4	5	15.2		
	Left Ventricular in Type	53	82.8	25	80.6	28	84.8		
	Total	64	100.0	31	100.0	33	100.0	0.66	1
Diagnosis	Aortic Stenosis	46	71.9	21	67.7	25	75.8		
	Aortic Regurgitation	18	28.1	10	32.3	8	24.2		
	Total	64	100.0	31	100.0	33	100.0	0.48	1

Statistical analysis and comparison of the physical signs in the total population and between the two groups.

of the aortic valve, pulmonary changes due to aortic valve disease, and the presence of coronary artery disease, documented by selective coronary arteriography, was compared between the two groups. No difference were found (Table VI).

The pre-operative electrocardiograms of the patients in both groups, when compared, showed no significant difference with reference to rhythm, P wave configuration, P-R interval, degree of left ventricular hypertrophy and St-T wave changes. One patient allocated to the coronary perfusion group had the changes diagnostic of a previous myocardial infarction present in his pre-operative electrocardiogram.

Table VII sets out a statistical comparison of the haemodynamic data obtained at cardiac catheterisation, in those patients who had this investigation carried out pre-operatively. The cardiac index varied between 1.4 and 3.6 litres/min/M^2 (n = 12) with a mean of 2.36 $\pm$ 0.190 litres/min/M^2 in the coronary perfusion group and between 1.74 and 4.11 litres/min/M^2 (n = 10) with a mean of 2.74 $\pm$ 0.231 litres/min/M^2 in the profound hypothermic non-perfusion arrest group. The left atrial mean pressure had a range of 4 - 45 mmHg (n = 14) with a mean of 13.5 $\pm$ 3.04 mmHg in the coronary perfusion group and a range of 2 - 28 mmHg (n = 9) with a mean of 13.3 $\pm$ 2.93 mmHg in the profound hypothermic non-perfusion arrest group. The

TABLE VI

		Total		Coronary Perfusion		Non-Perfusion Arrest		Significance	
		No.	%	No.	%	No.	%	Prob $>X^2$	DF
Valve Calcification (Radiological)	Present	34	53.1	16	51.6	18	54.5		
	Absent	30	46.9	15	48.4	15	45.5		
	Total	64	100.0	31	100.0	33	100.0	0.80	1
Lung Changes Due to Aortic Valve Disease	Present	10	15.6	4	12.9	6	18.2		
	Absent	54	84.4	27	87.1	27	81.8		
	Total	64	100.0	31	100.0	33	100.0	0.57	1
Coronary Artery Disease (Angiography)	No Angiography	29	45.3	13	41.9	16	48.5		
	Present	7	10.9	4	12.9	3	9.1		
	Absent	28	43.8	14	45.2	14	42.4		
	Total	64	100.0	31	100.0	33	100.0	0.82	1

Statistical analysis and comparison of some of the radiological features in the total population and between the two groups.

TABLE VII

	Coronary Perfusion			Non-Perfusion Arrest			Significance
	Range	Mean $\pm$ SE	N	Range	Mean $\pm$ SE	N	
Cardiac Index ($L/min/M^2$)	1.4 - 3.6	2.36 $\pm$ 0.19	12	1.74 - 4.11	2.74 $\pm$ 0.231	10	$p > 0.1$
Left Atrial Mean Pressure (mmHg)	4 - 45	13.5 $\pm$ 3.04	14	2.0 - 28.0	13.3 $\pm$ 2.93	9	$p > 0.1$
Left Ventricular End-Diastolic Pressure (mmHg)	5 - 37	21.9 $\pm$ 3.69	10	5 - 37	21.0 $\pm$ 3.08	11	$p > 0.1$

A statistical comparison of pre-operative haemodynamic parameters obtained at cardiac catheterisation in those patients who had this investigation carried out.

left ventricular end-diastolic pressure varied between 5 - 37 mmHg (n = 10) with a mean of 21.9 $\pm$ 3.69 mmHg in the coronary perfusion group and between 5 - 37 mmHg (n = 11) with a mean of 21.0 $\pm$ 3.08 mmHg in the profound hypothermic non-perfusion arrest group. There were no significant differences between the groups with reference to any of these parameters.

Four surgeons operated on the patients in the study. No significant trend of any variable over the five month study period and no significant interaction of a surgeon with the two groups was found (see 'Statistical Methods'). Each surgeons did an evenly matched number by each method.

The prosthetic valve types used were not significantly differently distributed between the groups.

The valve pathology found was likewise similar. Valve calcification found at operation was of note as it was found in many more patients than the radiological study revealed (Table VIII).

Macroscopically diseased coronary arteries were noted equally in both groups. Macroscopic coronary artery disease found at operation was compared with coronary artery disease demonstrated angiographically using X^2 for a two-way contingency table in each group. There was a significantly greater number in the former group, there was a

significantly greater number of patients in whom macroscopic coronary artery disease was found at operation than had been demonstrated arteriographically (probability $>X^2 = 0.0139$). This is of interest since more patients had angina as a presenting symptom (see Table VI) than were demonstrated to have coronary artery disease arteriographically, suggesting that either this investigation was not used frequently enough, or alternatively, that more angina in patients with aortic valve disease is due to concomitant coronary artery disease than is usually assumed.

Spontaneous ventricular fibrillation occurred significantly more frequently in the profound hypothermic non-perfusion arrest group (probability $>X^2 = 0.02$), Table VIII.

Quantitative variables obtained at operation are set out in Table IX. The left ventricular wall thickness was 2.2 - 4.8 cms with a mean of 3.10 ± 0.1100 cms in the coronary perfusion group and 2.10 - 4.00 cms with a mean of 3.20 ± 0.08300 in the profound hypothermic non-perfusion arrest group. There was no significant differences between the two. The left ventricular diameter was 7.5 - 13.0 cms with a mean of 9.60 ± 0.2540 cms in the coronary perfusion group and 7.0 - 12.5 cms with a mean of 9.50 ± 0.2700 cms in the profound hypothermic non-perfusion arrest group. Again there was no significant difference. The left ventricular diameter and the cardiothoracic ratio had a correlation

TABLE VIII

		Total		Coronary Perfusion		Non-Perfusion Arrest		Significance	
		No.	%	No.	%	No.	%	Prob $>X^2$	DF
Surgeon	Karp	24	37.5	10	32.3	14	42.4		
	Kirklin	18	28.1	10	32.3	8	24.2		
	Kouchoukos	8	12.5	3	9.7	5	15.2		
	Pacifico	14	21.9	8	25.8	6	18.2		
	Total	64	100.0	31	100.0	33	100.0	0.66	3
Valve Type Used	Starr-Edwards	58	90.6	29	93.5	29	87.9		
	Braunwald-Cutter	2	3.1	1	3.2	1	3.0		
	Bjork-Shiley	3	4.7	1	3.2	1	6.1		
	Valvotomy	1	1.6	0	0	1	3.0		
	Total	64	100.0	31	100.0	33	100.0	0.74	3
Valve Pathology	Unknown	1	1.6	1	3.2	0	0		
	Rheumatic	13	20.3	8	25.8	5	15.2		
	Congenital	40	62.5	18	58.1	22	66.7		
	S B E	7	10.9	2	6.5	5	15.2		
	Others	3	4.7	2	6.5	1	3.0		
	Total	64	100.0	31	100.0	33	100.0	0.46	4
Valve Calcification (Operation)	Present	48	75.0	23	74.2	25	75.8		
	Absent	16	25.0	8	25.8	8	24.2		
	Total	64	100.0	31	100.0	33	100.0	0.86	1
Macroscopic Coronary Artery Disease	Not Recorded	1	1.6	1	3.2	0	0		
	Present	14	21.9	7	22.6	7	21.2		
	Absent	49	76.6	23	74.2	26	78.8		
	Total	64	100.0	31	100.0	33	100.0	0.58	2
Spontaneous Ventricular Fibrillation	Not Recorded	2	3.1	2	6.5	0	0		
	Did Occur	47	73.4	18	58.1	29	87.9		
	Did Not Occur	15	23.4	11	35.5	4	12.1		
	Total	64	100.0	31	100.0	33	100.0	0.02	2

Statistical analysis and comparison of qualitative variables related to the operations in the total population and between the groups.

TABLE IX

	Coronary Perfusion			Non-Perfusion Arrest			Significance
	Range	Mean ± SE	N	Range	Mean ± SE	N	
Left Ventricular Wall Thickness (cms)	2.2 - 4.8	3.10 ± 0.1100	30	2.1 - 4.0	3.20 ± 0.0830	31	p >0.1
Left Ventricular Diameter (cms)	7.5 - 13.0	9.60 ± 0.2540	29	7.0 - 12.5	9.50 ± 0.2700	32	p >0.1
Myocardial Temperature at Aortic Cross-Clamp (^{o}C)	28.1 - 34.4	31.36 ± 0.3332	26	15.7 - 28.1	22.4 ± 0.6439	26	p <0.0001
Myocardial Temperature at Cross-Clamp Release (^{o}C)	24.7 - 35.6	29.6 ± 0.4637	24	16.1 - 28.8	24.6 ± 0.7121	26	p <0.0001
Aortic Cross-Clamp Time (mins)	42.0 - 100.0	68.3 ± 2.544	31	31.0 - 74.0	49.7 ± 1.576	33	p <0.0001
Cardiopulmonary Bypass Time (mins)	58.0 - 119.0	82.4 ± 2.712	30	45.0 - 100.0	65.1 ± 2.135	33	p <0.0001

A statistical comparison of operative quantitative variables between the two groups.

coefficient of 0.625.

The myocardial temperature at the time that the aortic cross-clamp was applied was 28.1 - 34.4°C with a mean of 31.0 $\pm$ 0.4620 (n = 26) in the coronary perfusion group and 15.7 - 28.1 with a mean of 22.4 $\pm$ 0.6439 (n = 26) in the profound hypothermic non-perfusion arrest group. These values were significantly different ($p < 0.0001$).

The myocardial temperatures recorded when the aortic cross-clamp was released, or re-warming commenced (whichever occurred first) was 24.7 - 35.6 with a mean of 29.6 $\pm$ 0.4637 (n = 24) and 16.1 - 28.8 $\pm$ 0.7121 (n = 24). Again a significant difference was found ($p < 0.0001$). These values were expected to be significantly different since the temperature was designed to be different between the two methods. It is of interest that the mean temperature rose in the profound hypothermic non-perfusion arrest group by 2.2°C and fell in the coronary perfusion group by 1.4°C during the course of the procedure.

The aortic cross-clamp times were 42.0 - 100.0 minutes (n = 31) with a mean of 68.3 $\pm$ 2.544 minutes in the coronary perfusion group and 31.0 - 74. 0 minutes (n= 33) with a mean of 49.7 $\pm$ 1.576 (n = 33) in the profound hypothermic non-perfusion arrest group. These times were significantly different ($p < 0.0001$).

The total cardiopulmonary bypass times were also significantly different in the two groups ($p < 0.0001$). It was 58.0 - 119.0 minutes ($n = 30$) with a mean of 82.4 ± 2.712 minutes in the coronary perfusion group and 45.0 - 100.0 minutes ($n = 33$) with a mean of 65.1 ± 2.135 minutes in the profound hypothermic non-perfusion arrest group. Hypothermic non-perfusion arrest resulted in an aortic cross-clamp time that was 27% and a total cardiopulmonary bypass time that was 21% shorter than coronary perfusion.

Four significant individual surgeon differences were found and are presented here as departures from the means of the other three surgeons. One surgeon had a significantly lower mean temperature at the time of aortic cross-clamping ($-4.32^{\circ}C$, $p < 0.006$). Another surgeon had a higher mean temperature at the time of release of the aortic cross-clamp ($+4.55^{\circ}C$, $p < 0.001$). A third surgeon had a shorter mean aortic cross-clamping time (-7.04 minutes, $p < 0.04$) and the second-mentioned surgeon had a longer mean total cardiopulmonary bypass time (+9.27 minutes, $p < 0.05$).

Table X sets out the data relevant to the coronary perfusion used in the coronary perfusion group. This includes the number of coronaries perfused in each patient. Both coronaries were perfused in all but one patient and this patient had only the left coronary perfused because the right coronary arose as two small vessels, neither of which would admit

TABLE X

		Coronary Perfusion	
		No.	%
Number of Coronaries Perfused	1 Coronary	1	3.2
	2 Coronaries	30	96.8
	Total	31	100.0
Difficulties with Cannulation (Right)	No Difficulties	28	90.3
	Small Right	2	6.5
	Double Right	1	3.2
	Total	31	100.0
Difficulties with Cannulation (Left)	None		
Cannula Size (Right)	3.3 mms	29	93.5
	4.0 mms	1	3.2
	Not Recorded	1	3.2
	Total	31	100.0
Cannula Size (Left)	3.3 mms	27	87.1
	4.0 mms	3	9.7
	Not Recorded	1	3.2
	Total	31	100.0

Operative data relevant to the method of coronary perfusion in the coronary perfusion group.

tip of a coronary catheter. There were no other difficulties encountered apart from two further patients who had small right coronary orifices which made cannulation difficult. There were no difficulties encountered in dealing with the left coronary.

A coronary perfusion catheter with an internal diameter of 3.3 mm was used in twenty-nine (93.5%) of the patients to perfuse the right coronary. A catheter of 4.0 mm internal diameter was used to perfuse the right coronary in one patient (3.2%) and in one the catheter size was not recorded. The left coronary orifice was cannulated in twenty-seven patients (87.1%) with a 3.3 mm internal diameter catheter, in three patients (9.7%) with a 4.0 mm internal diameter catheter, and in one patient (3.2%) the catheter size was not recorded. There were no patients in whom the coronary orifices were noticed to have been damaged, either by the purse-string sutures or the catheters themselves. At the time of writing no known late sequelae, such as ostial stenoses, had been recorded.

Coronary artery flows and pressures are set out in Table XI. The range of flows delivered to the right coronary arteries was 25.0 - 175.0 mls/min (n = 30) with a mean of 109.0 $\pm$ 7.54 mls/min and it was 100.0 - 250.0 (n = 31) with a mean of 138.0 $\pm$ 6.472 mls/min to the left.

The mean pressure range in the right coronary perfusion system was 90.0 - 140.0 mmHg (n = 30) with a mean of 108.0 $\pm$ 2.276 mmHg

TABLE XI

	Coronary Perfusion		
	Range	Mean $\pm$ SE	N
Coronary Flow Rate (Right)	25 - 175	109.0 $\pm$ 7.54	30
Coronary Flow Rate (Left)	100 - 250	158.0 $\pm$ 6.472	31
Perfusion Pressure (Right)	90 - 140	108.0 $\pm$ 2.276	30
Perfusion Pressure (Left)	90 - 150	111.0 $\pm$ 2.684	31

Operative data relevant to the method of coronary perfusion in the coronary perfusion group.

and it was 90.0 - 150.0 mmHg (n = 31) with a mean of 111.0 $\pm$ 2.684 mmHg in the left coronary artery system.

The average flow to the left coronary artery was significantly less for those patients with thicker left ventricular walls (regression coefficient for left coronary flow = -281.0 $\pm$ 10.4, $p < 0.025$.)

Two patients suffered minor episodes of acute over-distension of the left ventricle during their operations using profound hypothermic non-perfusion arrest. In neither case did these episodes appear to produce any deleterious effects.

MORTALITY

There was one death in the series. This patient had his aortic valve replacement carried out using coronary perfusion. Very shortly after setting up a satisfactory coronary perfusion, ventricular fibrillation occurred which proved very resistant to defibrillation, which either failed to defibrillate the heart, or proved effective for only a very short time before ventricular fibrillation once more occurred. Cardiopulmonary bypass could not be discontinued on this account. No obvious cause was evident, macroscopically or metabolically at the time, and unfortunately consent for a post-mortem was not given by the relatives. No statistical significance could be attached to this death and the cause could only be surmised, it is probable that the ventricular fibrillation was a feature of a myocardial infarction, whose cause remains obscure. There certainly was no evidence that the coronary perfusion could have caused it.

HAEMODYNAMICS

Cardiac index, stroke index, heart rate, mean left atrial pressure, mean right atrial pressure, mean arterial pressure, total systemic peripheral vascular resistance, stroke work index, peak left ventricular dp/dt/p and the coronary blood flow index (DPTI/TTI) were measured or computed serially for every patient in each group. The haemodynamic data is set out graphically in figure 16 to 25 . The variable under discussion is plotted on the vertical axis and the time in hours after commencing cardiopulmonary bypass is plotted on the horizontal axis.

The crosses connected by an unbroken line represent the group mean $\pm$ 1 standard error of the mean, at each study period for those patients who had their valves replaced using coronary perfusion. The squares connected by a dotted line are used to indicate the group mean $\pm$ standard error of the mean for those patients who had their valves replaced using profound hypothermic non-perfusion arrest.

Cardiac Index (litres/min/M^2) Figure 16)

Analysis of the three cardiac outputs obtained from each patient at each study period, from which the cardiac indices were computed showed an overall mean of 5.27 litres/min. The mean patient-to-patient

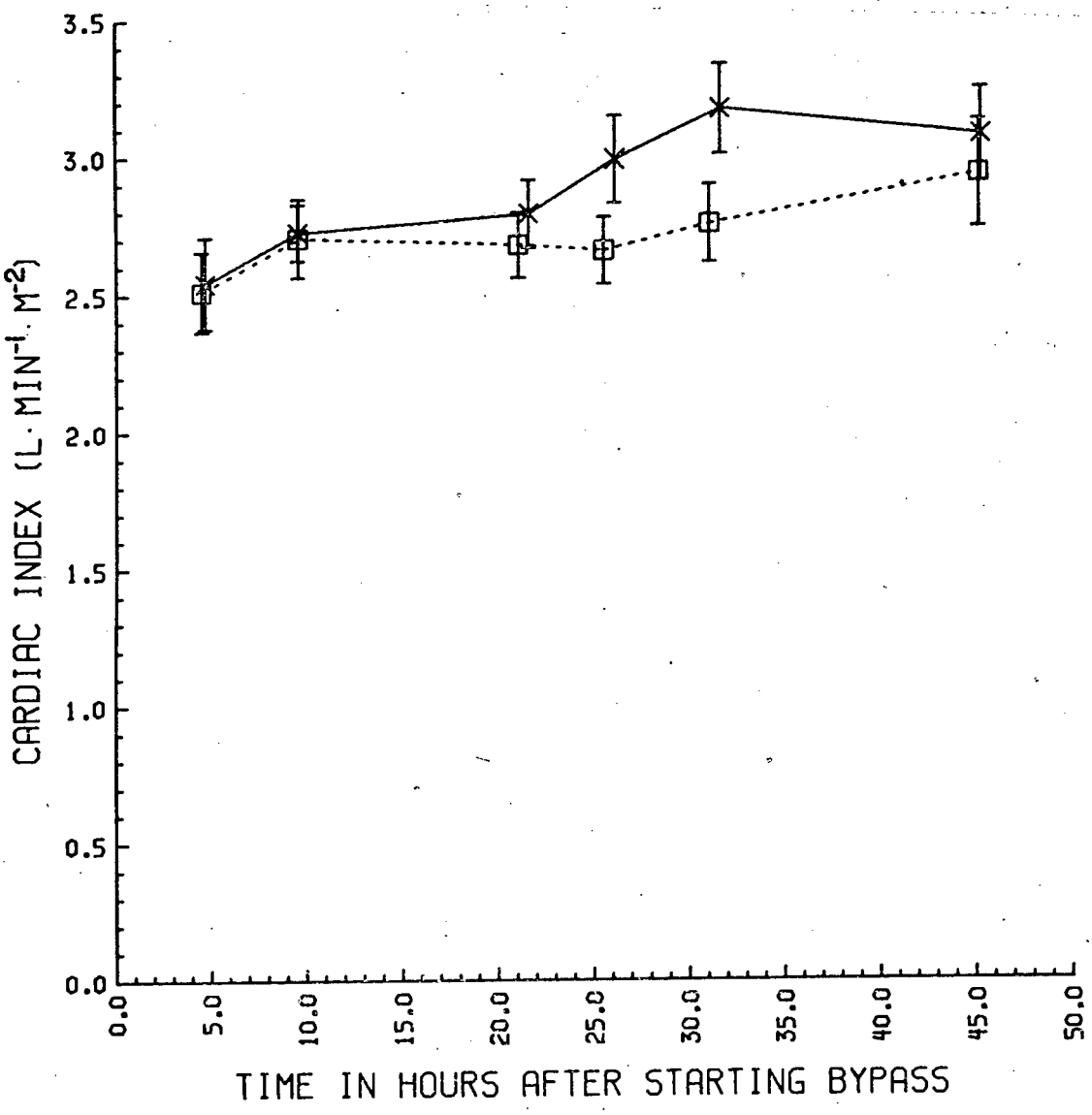

FIGURE 16

The cardiac index plotted against time in hours after the commencement of cardiopulmonary bypass for each study period (mean $\pm$ 1 S.E.). The coronary perfusion group is represented by the crosses joined by the solid line and profound hypothermic non-perfusion arrest group is represented by the squares joined by the dotted line (this format is used in Figures 16 to 25).

variation was 4.5 litres/min; the mean variation between study periods was 1.54 litres/min and the residual variation was 0.370 litres/min. The coefficient of variation percentage was 7.02 percent.

The two group means at each study period for the cardiac index was not significantly different at any study period. There was no significant difference between the two group means averaged over all study periods, 2.87 litres/min/M^2 for the coronary perfusion group and 2.69 litres/min/M^2 for the profound hypothermic non-perfusion arrest group ($p > 0.1$). However, a difference between the two group means, significantly greater than experimental error, was found ($p < 0.006$). The cardiac indices in those patients in whom coronary perfusion was used was higher.

Two of the variables studied for interrelations with the cardiac index (see 'Statistical Methods') for the study population as a whole and for each group separately were found to influence it significantly. For the study population as a whole the patients with larger cardiothoracic ratios had smaller cardiac indices, i.e. the intercept of the cardiac index (roughly equivalent to the first post-operative measurement) was negatively correlated with the cardiothoracic ratio ($r = -0.336$, $p < 0.05$). Older patients had lower cardiac indices (intercept regression coefficient for age = 0.025 ± 0.0061, $p < 0.001$; slope regression coefficient for age = 1.00045 ± 0.000199, $p < 0.05$).

When the two study groups were examined separately, these same two influencing variables were found.

There was a significant individual surgeon difference noted as well. One surgeon's patients had a higher cardiac index intercept (0.44 litres/min/M^2, $p < 0.005$) when this was assessed and expressed as departure from the mean of the other three surgeons.

In the group in whom coronary perfusion was used, one additional influencing variable was found. The intercept of cardiac index was higher in those patients in whom the average flow to the left coronary artery was higher (regression coefficient for left coronary artery flow = 0.0125 ± 0.00470, $p < 0.05$).

The stroke index (mls/beats/M^2) (Figure 17)

There was no statistically significant differences between the group means at any study period, nor in the overall group mean, 30.5 mls/beats/M^2 for the coronary perfusion group and 29.9 mls/beats/M^2 for the profound hypothermic non-perfusion arrest group ($p > 0.1$). Likewise there was no significant differences which could be accounted for by experimental error.

The heart rate (beats/min) (Figure 18)

There was no significant difference between the two groups means

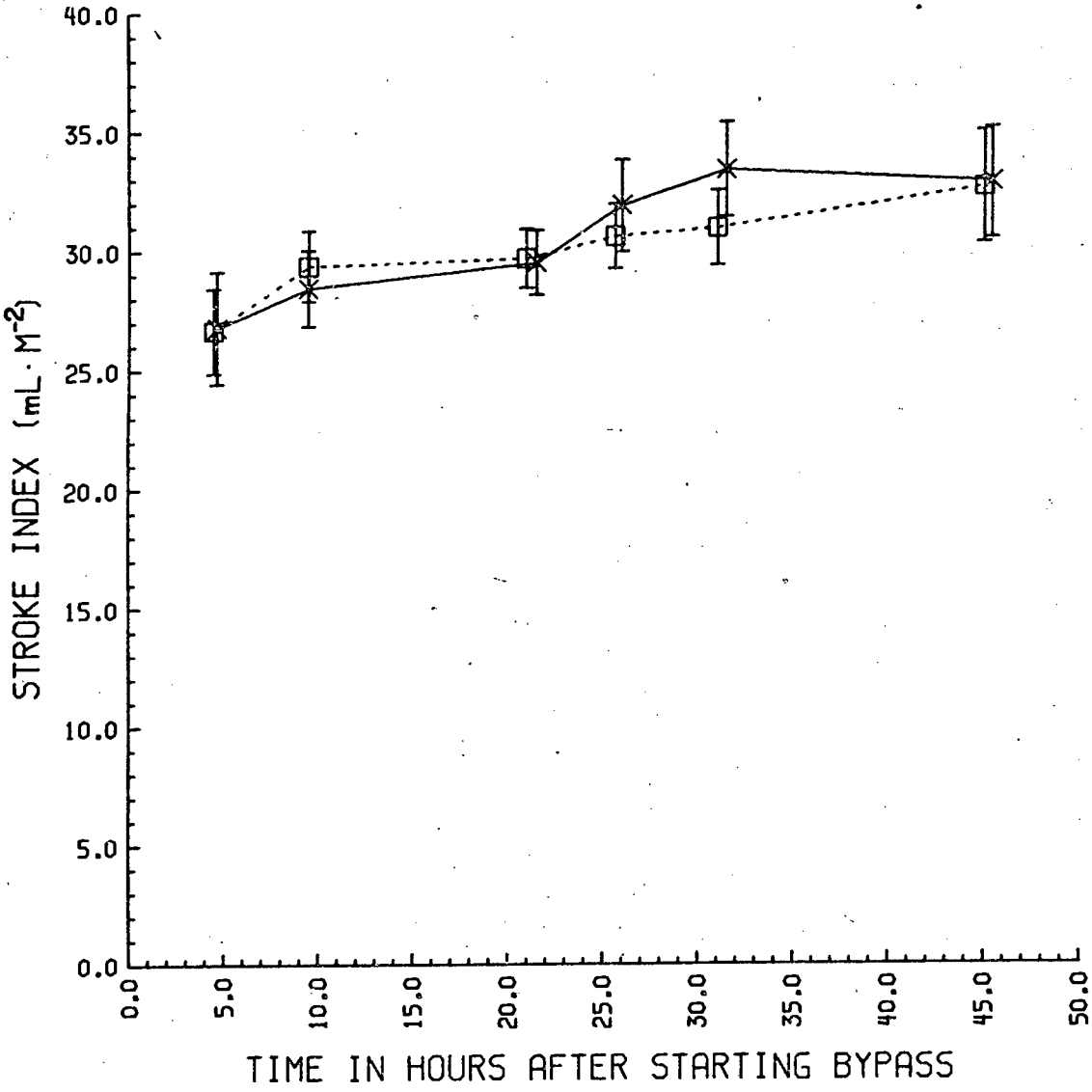

FIGURE 17

The stroke index plotted against time in hours after commencing cardiopulmonary bypass.

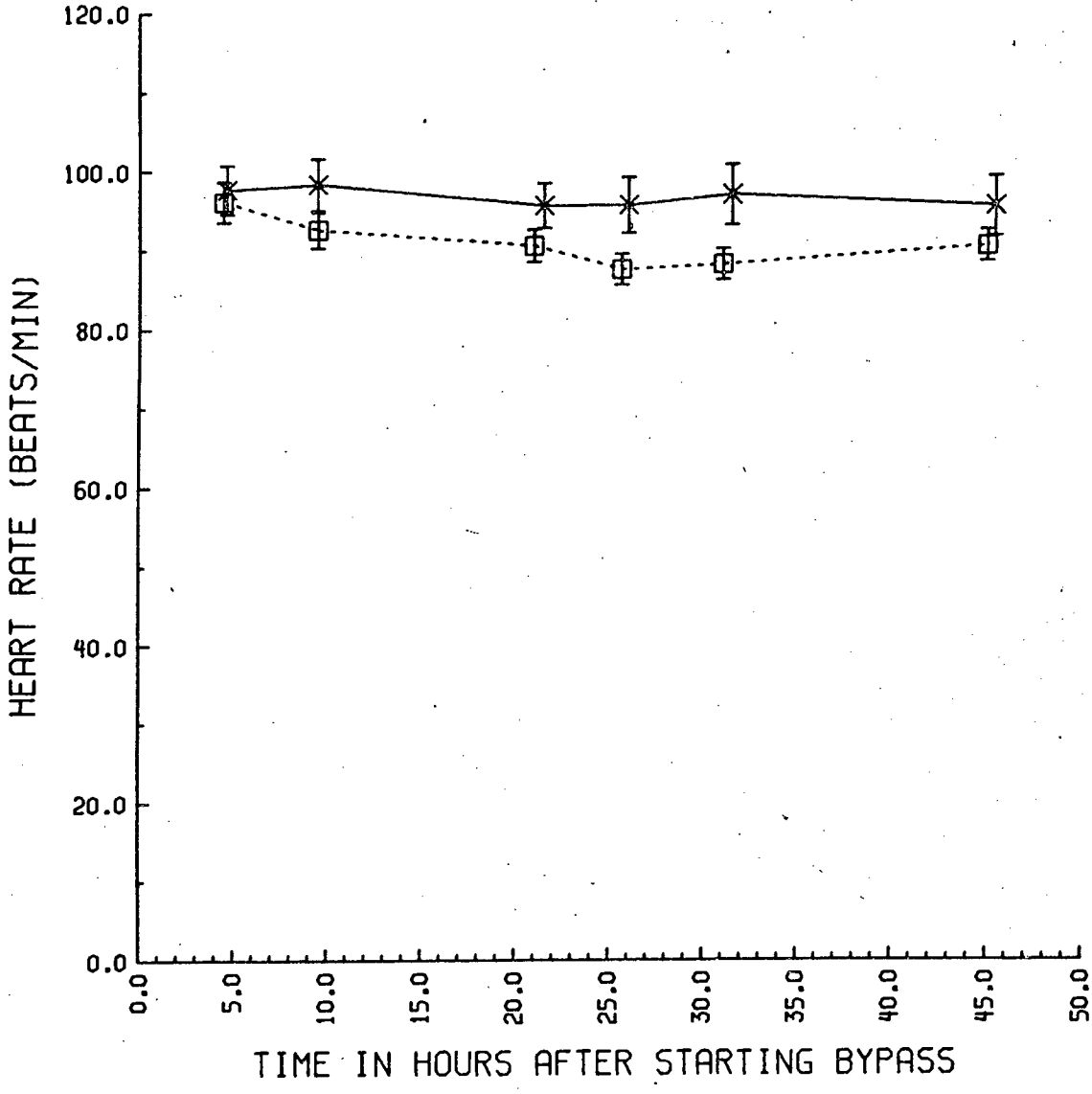

FIGURE 18

The heart rate is plotted against time in hours after commencing cardiopulmonary bypass.

averaged overall study period, 96.6 beats/min for the coronary perfusion and 90.9 beats/min for the profound hypothermic non-perfusion arrest group ($p > 0.1$). The heart rates at thirty-one hours after the commencement of cardiopulmonary bypass was significantly higher in the group of patients in whom coronary perfusion had been used ($p < 0.04$). Heart rate was also significantly higher than could be explained by experimental error in those in whom coronary perfusion was used ($p < 0.001$). These significant differences in the heart rate, coupled with the absence of any differences in the stroke index, probably account for the differences noted in the cardiac index, which could not be accounted for by experimental error.

The mean left atrial pressure (mmHg) (Figure 19)

No differences between the groups was found, either with reference to the averaged overall mean, 11.3 mmHg for the coronary perfusion group and 11.7 mmHg for the profound hypothermic non-perfusion arrest group ($p > 0.1$), or the means at each study period, and there were no differences found, other than those that could be explained by experimental error. It was anticipated that this would be so, because the mean left atrial pressure was used as an index of the preload and this was adjusted by volume replacement if below 12 - 14 mmHg, or inotropic stimulation of the left ventricle if above 12 - 14 mmHg when

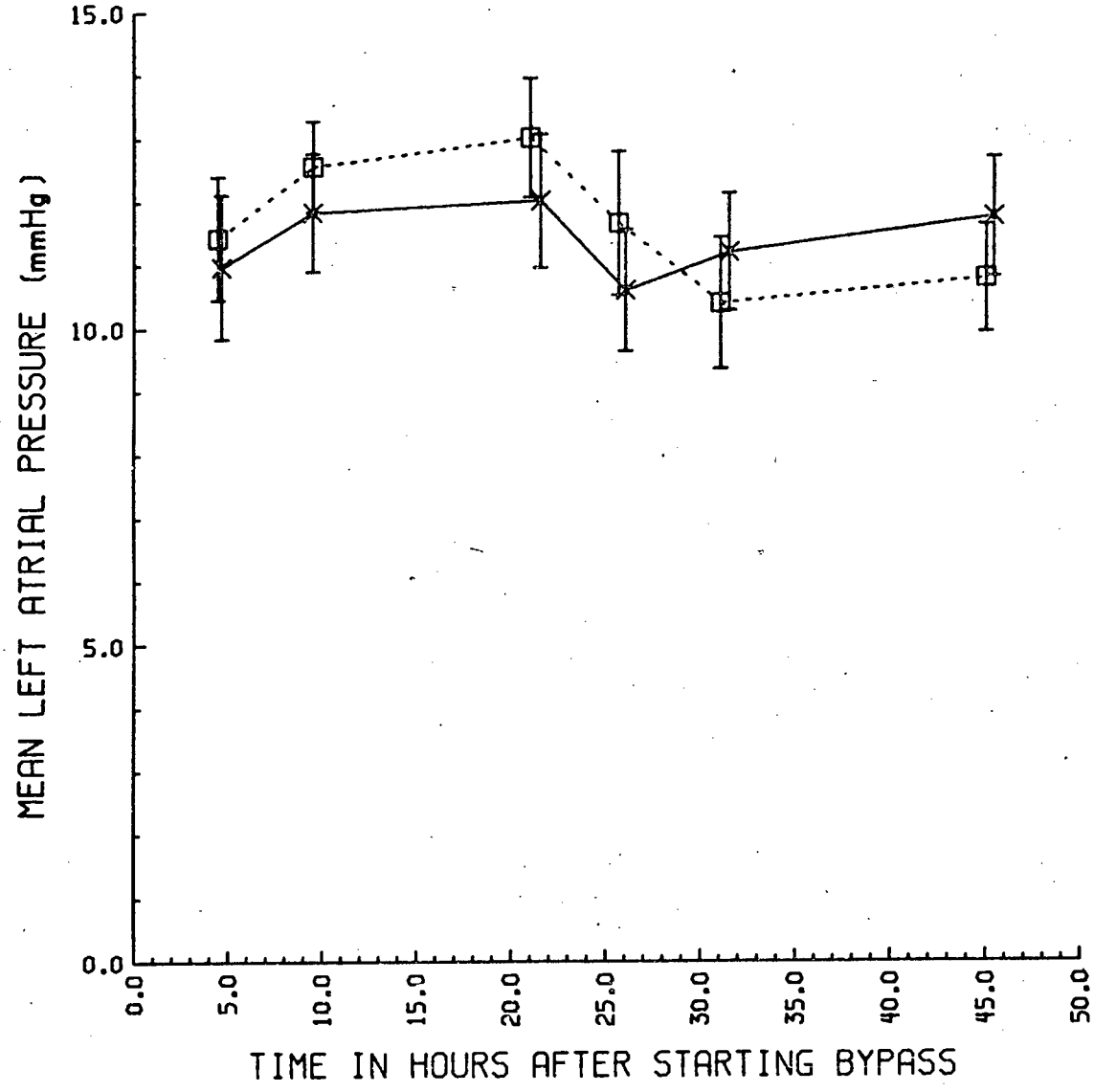

FIGURE 19

The mean left atrial pressure plotted against time in hours after the commencement of cardiopulmonary bypass.

the cardiac index was below 1.8 lites/min/M^2, according to the protocol of patient management employed in the Department of Surgery, The University of Alabama.

The mean right atrial pressure (mmHg) (Figure 20)

There were no differences between the averaged overall means, 7.3 mmHg for the coronary perfusion group and 8.5 mmHg for the profound hypothermic non-perfusion arrest group ($p > 0.1$), or the means for the individual study periods between the groups. There was, however, a statistically significantly higher mean pressure in the group who had their valves replaced using coronary perfusion than could be explained by experimental error alone ($p < 0.002$).

The mean arterial pressure (mmHg) (Figure 21)

There was no significant difference between the averaged overall means, 88.5 mmHg for the coronary perfusion group and 93.5 mmHg for the profound hypothermic non-perfusion arrest group ($p > 0.1$). The mean arterial pressure was significantly higher in the profound hypothermic non-perfusion arrest group at the twenty-six hour mark after the commencement of cardiopulmonary bypass ($p < 0.03$) and it was also found to be significantly higher in this group than could be explained by experimental error ($p < 0.0002$). It is of interest that

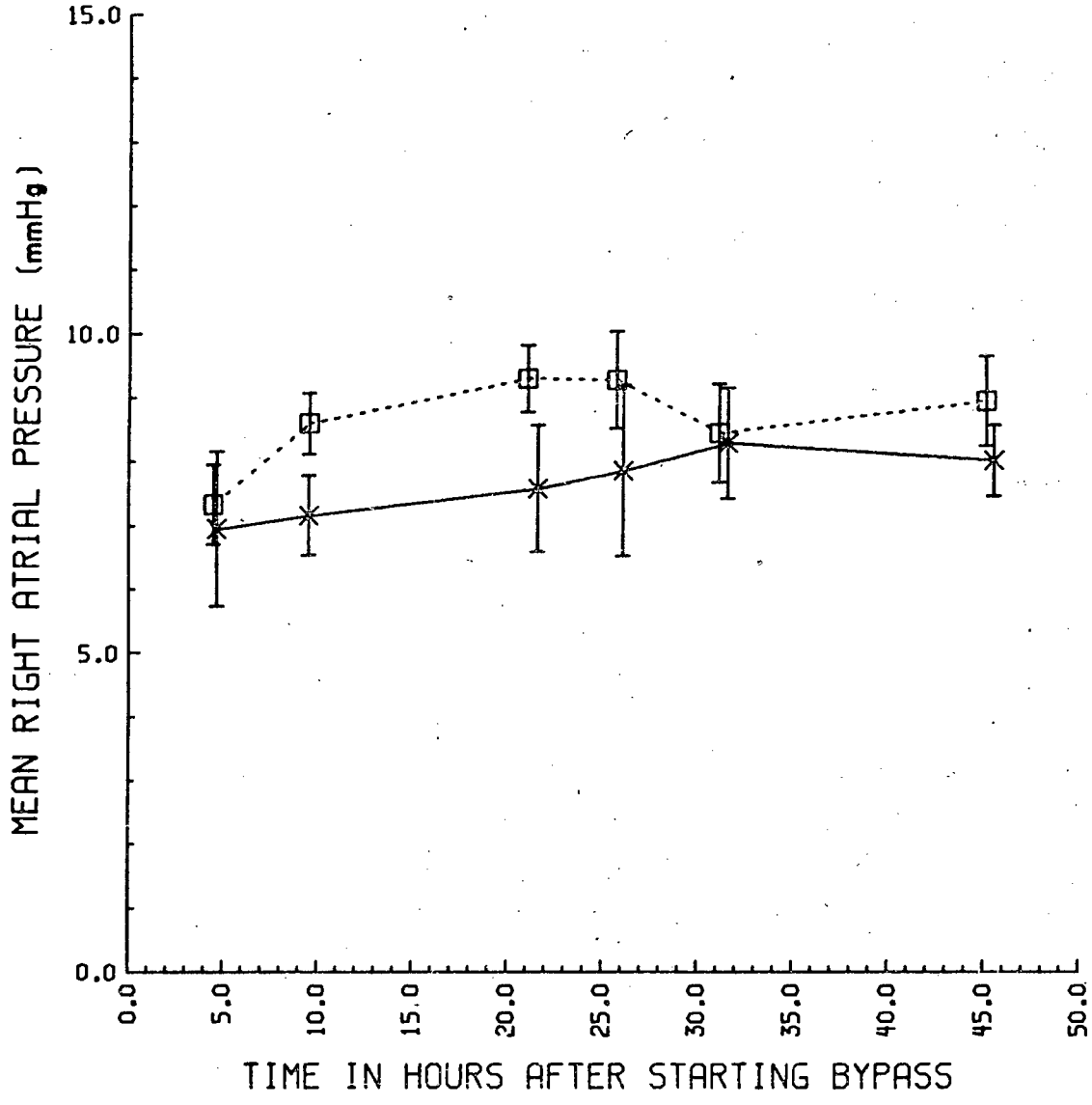

FIGURE 20

The mean right atrial pressure plotted against time after the commencement of cardiopulmonary bypass.

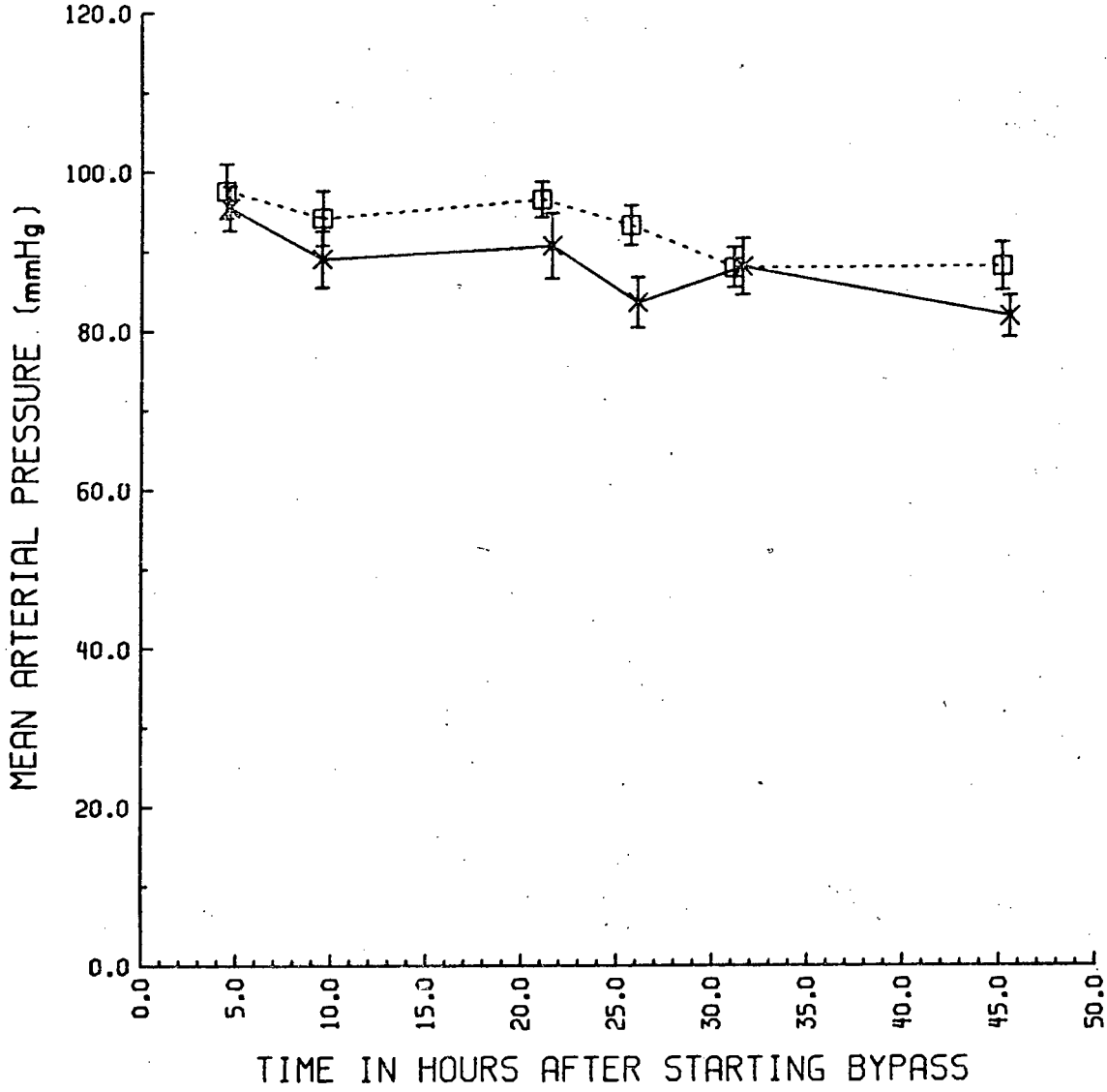

FIGURE 21

The mean arterial pressure plotted against time after the commencement of cardiopulmonary bypass.

five of the six patients, in whom afterload was reduced pharmacologically using Arfonad, in the early post-operative period, were in the profound hypothermic non-perfusion arrest group. According to the protocol of patient management used in these patients, mean arterial pressure was used as an index of afterload, and pharmacological reduction was employed if it was excessively higher when the cardiac index was less than 1.8 litres/min/M^2.

The total peripheral resistance (resistance units) (Figure 22)

There were no significant differences in the averaged overall means, 16.4 resistance units for the coronary perfusion group and 18.5 resistance units for the profound hypothermic non-perfusion arrest group ($p > 0.1$), or in the means at each study period between the groups. Once again, however, there was a significant difference between the groups which could not be explained by experimental error ($p < 0.001$). The patients who had their valves replaced using profound hypothermic non-perfusion arrest had the higher peripheral vascular resistance. It is tempting to ascribe this observed higher peripheral vascular resistance in the profound hypothermic non-perfusion arrest as the cause for the higher mean arterial pressure which was also noted in this group.

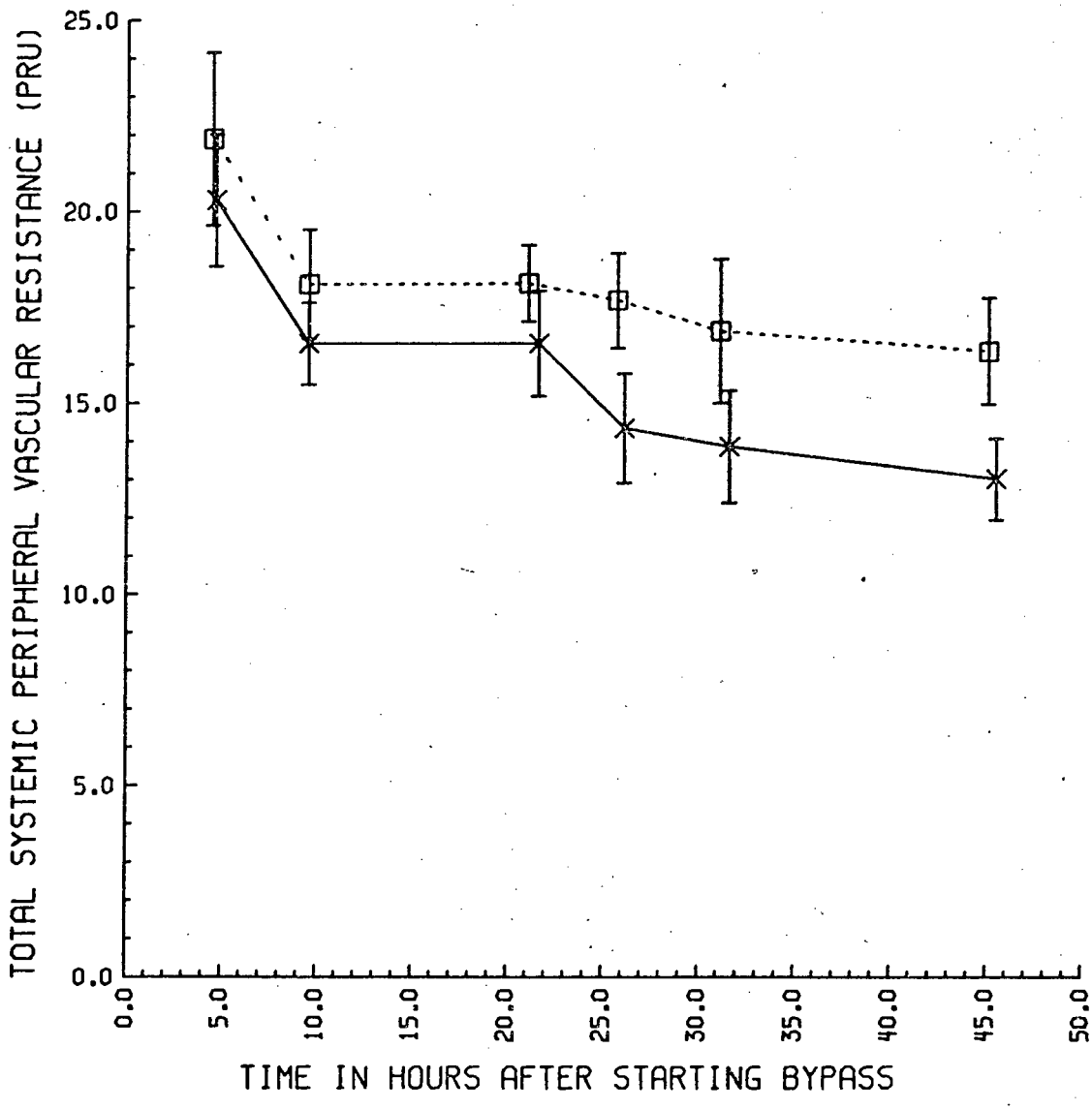

FIGURE 22

The total peripheral resistance plotted against time after the commencement of cardiopulmonary bypass.

The stroke work index (mls/mmHg/M^2) (Figure 23)

There were no differences between the groups in the averaged overall means, 2338.0 mls/mmHg/M^2 for the coronary perfusion group and 2424.0 mls/mmHg/M^2 for the profound hypothermic non-perfusion arrest group ($p > 0.1$), or the means at each study intervals, or which could not be explained by experimental error.

The left ventricular peak DP/DT normalised for developed pressure (sec^{-1}) (Figure 24)

No differences between the groups were found with reference to any of the three methods of analysis. The averaged group means were 27.7 sec^{-1} for the coronary perfusion group and 27.8 sec^{-1} for the profound hypothermic non-perfusion arrest group ($p > 0.1$). Analysis of the three readings for DP/DT obtained from each patient at each study period, from which the DP/DT/P was calculated, showed an overall mean of 1640.0 mmHg/sec, the mean patient-to-patient variation was 1600.0 mmHg/sec, the mean variation between study periods was 411.0 mmHg/sec, and the residual variation was 77.5 mmHg/sec. The coefficient of variation percentage was 4.72 percent.

The coronary blood flow index DPTI/TTI (Figure 25)

There was no difference between the groups in the averaged overall

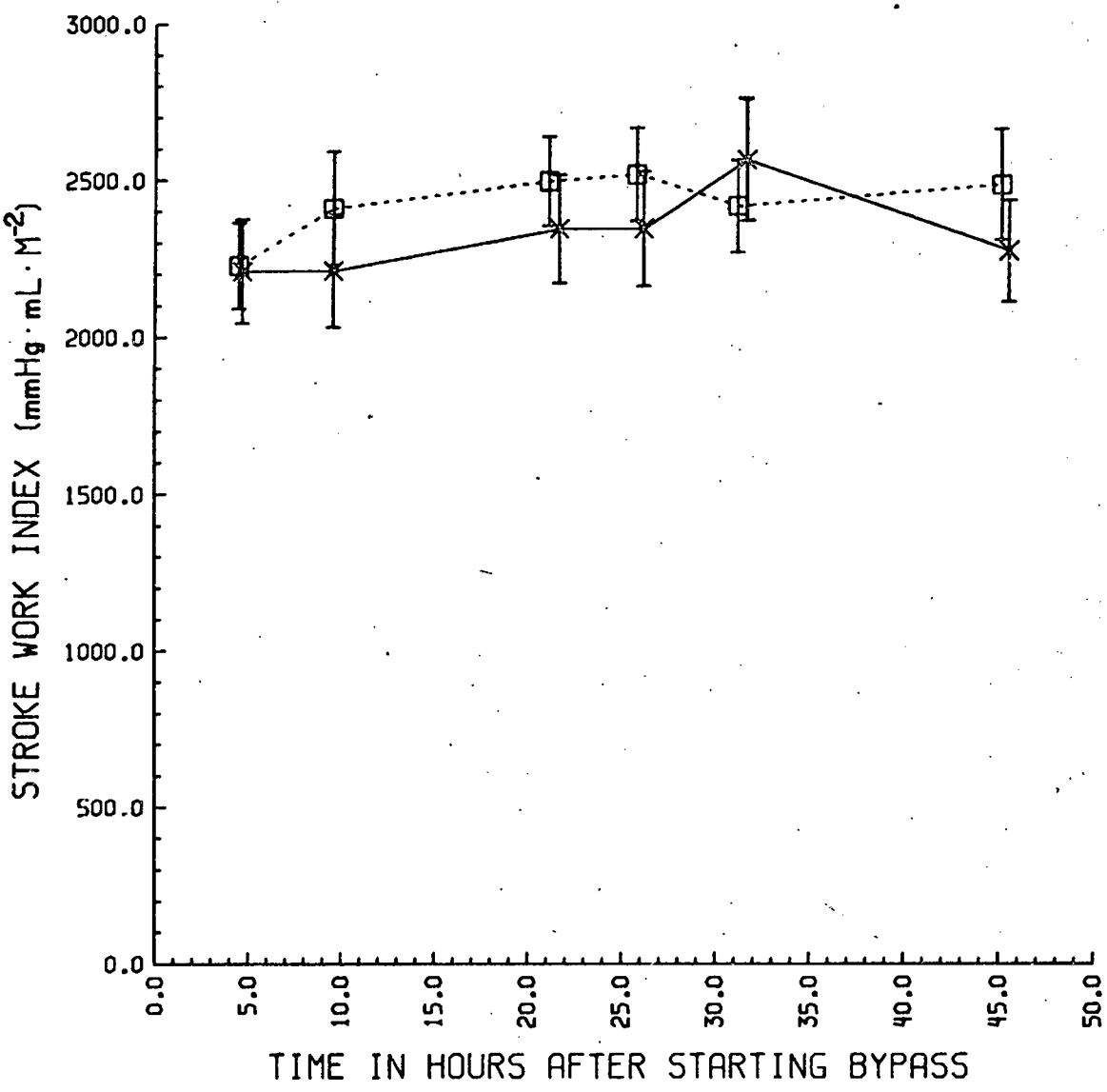

FIGURE 23

The stroke work index plotted against time in hours after the commencement of cardiopulmonary bypass.

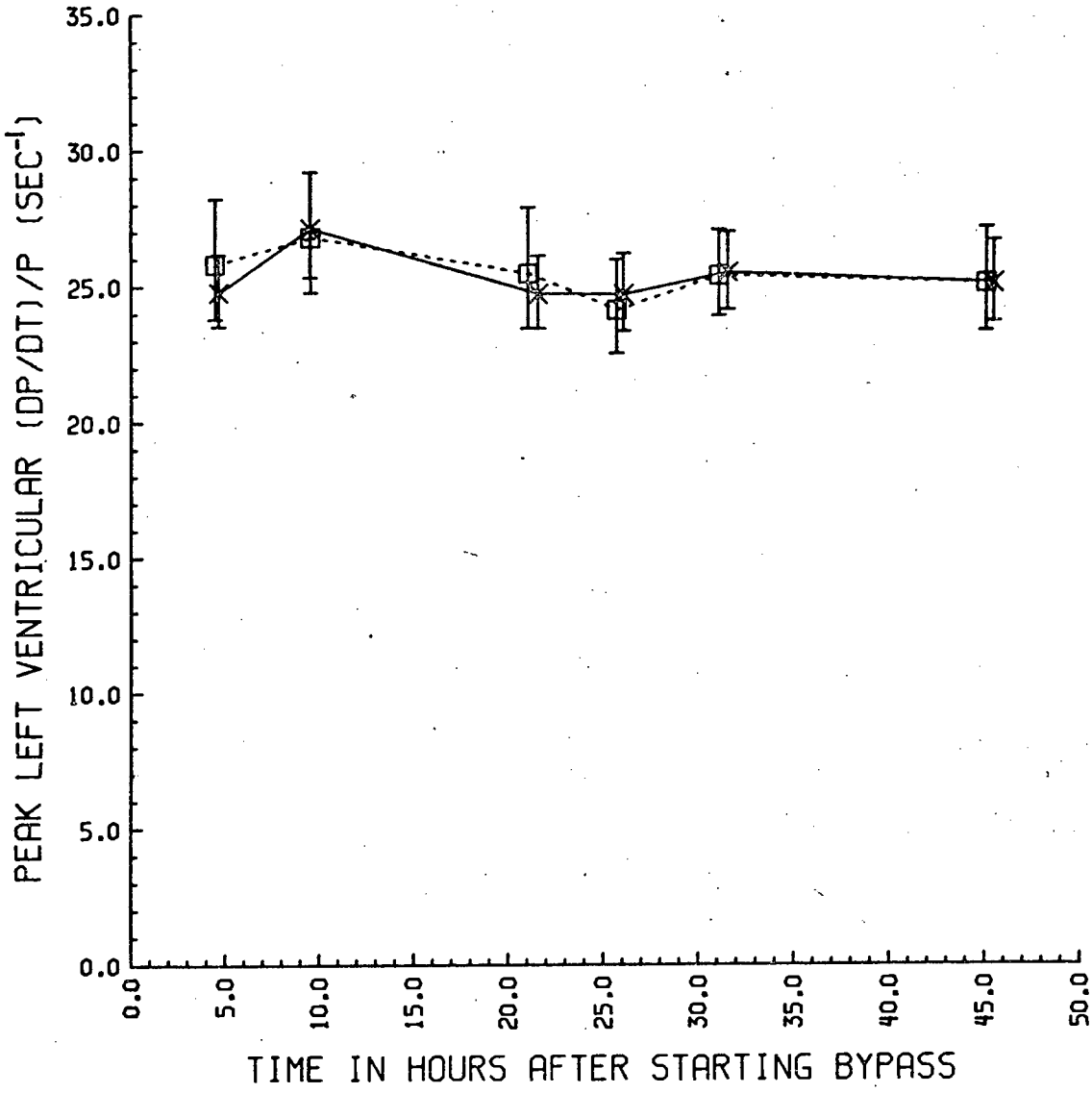

FIGURE 24

The left ventricular peak DP/DT/P plotted against time in hours after the commencement of cardiopulmonary bypass.

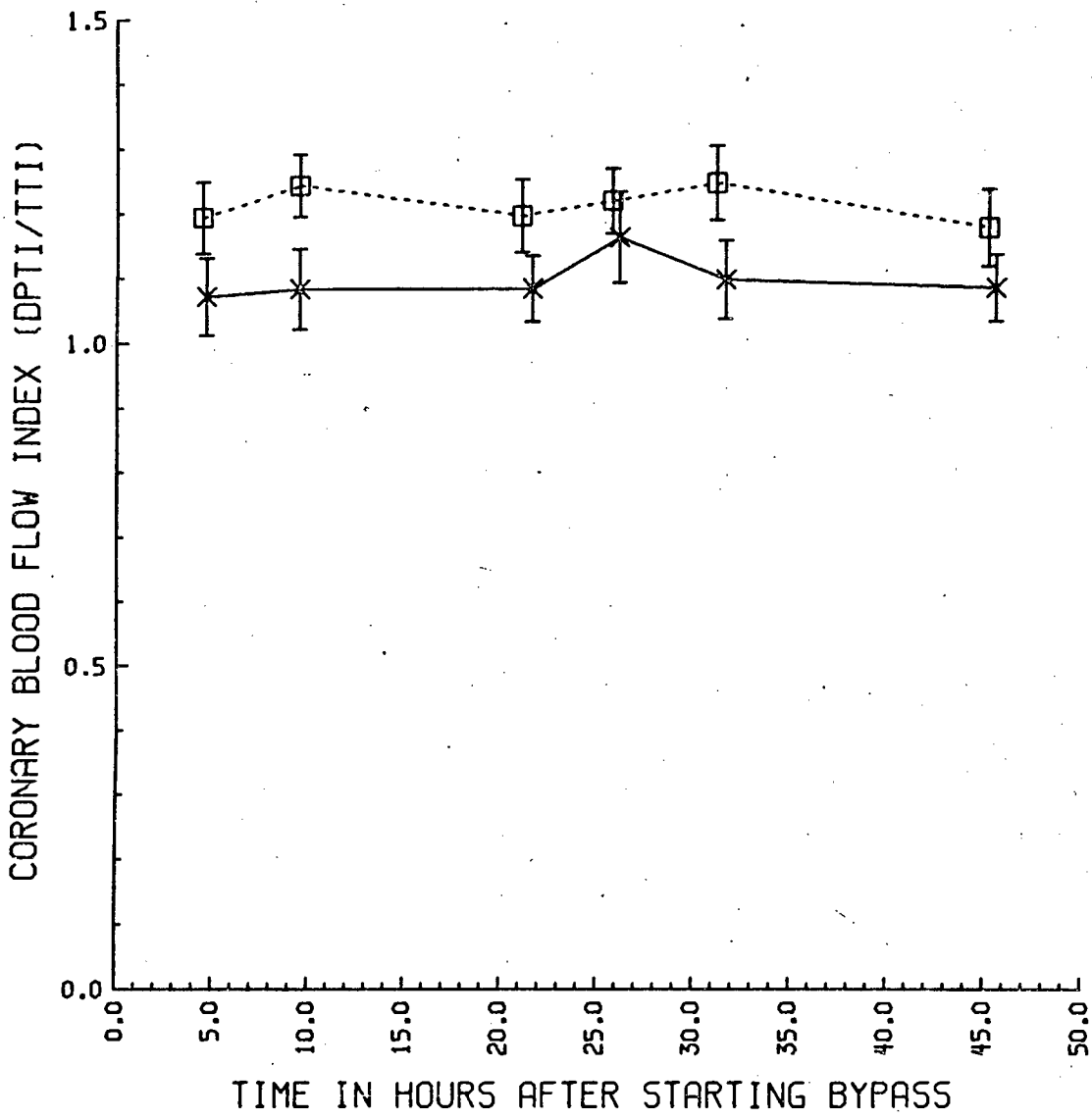

FIGURE 25

The coronary blood flow index DPTI/TTI plotted against time in hours after the commencement of cardiopulmonary bypass.

means, 1.13 for the coronary perfusion group and 1.22 for the profound hypothermic non-perfusion arrest group ($p > 0.1$), nor in the means at any study period. There was, however, a significantly higher coronary blood flow index in the patients who had their valves replaced using profound hypothermic non-perfusion arrest than could be explained by experimental error ($p < 0.0003$). The analysis of the three readings for the tension time index and the diastolic pressure time index, from which the DPTI/TTI was obtained, showed overall means of 2570 and 2970 respectively. The mean patient-to-patient variations were 1400 and 3040. The mean variations between study periods were 477 and 681 and the residual variations were 168 and 192 respectively. The coefficients of variation percentages were 6.51 percent and 5.13 percent.

MYOCARDIAL METABOLISM

Arterial blood gases at each study period were carried out to ensure that no extra-cardiac causes of the observed metabolic phenomena were operating.

No patient in either group was found to be seriously hypoxic, i.e. with a paO_2 less than 60 mmHg at any study period. No patient was found to be significantly hypercapnic, i.e. with a $paCO_2$ greater than 60 mmHg at any study period. Many patients were, however, hypocapnic with $paCO_2$'s ranging from 25 mmHg to 35 mmHg during the first two study periods. This hypocapnia was due to the intermittent positive pressure ventilation used routinely in the Department on all patients who had just undergone surgery using cardiopulmonary bypass. When once intermittent positive pressure ventilation had been discontinued, usually fifteen to twenty hours after the commencement of cardiopulmonary bypass, the patients' $paCO_2$'s returned to the normal range. All the patients were noted to become progressively metabolically alkalotic during the fifty-four hour period. Their base excesses ranged from 0 - 15 mEquivs/litre. No patients in either study group, however, developed any serious metabolic acidosis, i.e. with a base deficit of greater than -3 mEquivs/litre. We were not able to determine whether either the respiratory alkalosis

induced by intermittent positive pressure ventilation early on, or the metabolic alkalosis noted later in any way influenced the lactate and pyruvate estimations or their derivatives.

The measured or computed metabolic parameters are set out in Figures 26 - 34. As with the haemodynamic parameters the variable is on the vertical axis and the time in hours after the commencement of cardiopulmonary bypass is on the horizontal axis. The coronary perfusion group is represented by the crosses $\overset{+}{-}$ 1 standard error of the mean connected by the solid line and the profound hypothermic non-perfusion arrest group is represented by the squares $\overset{+}{-}$ 1 standard error of the mean connected by the dotted line.

Arterial oxygen content (Vols%) (Figure 26)

There were no differences between the group means at each study period. There were likewise no significant differences between the means averaged overall study periods, 16.7 vols% for the coronary perfusion group and 17.6 vols% for theprofound hypothermic non-perfusion arrest group ($p > 0.1$). There was, however, a significant difference between the groups which could not be explained by experimental error ($p < 0.0001$). Tested in this manner patients who had their valves replaced using profound hypothermic non-perfusion arrest had higher arterial oxygen contents.

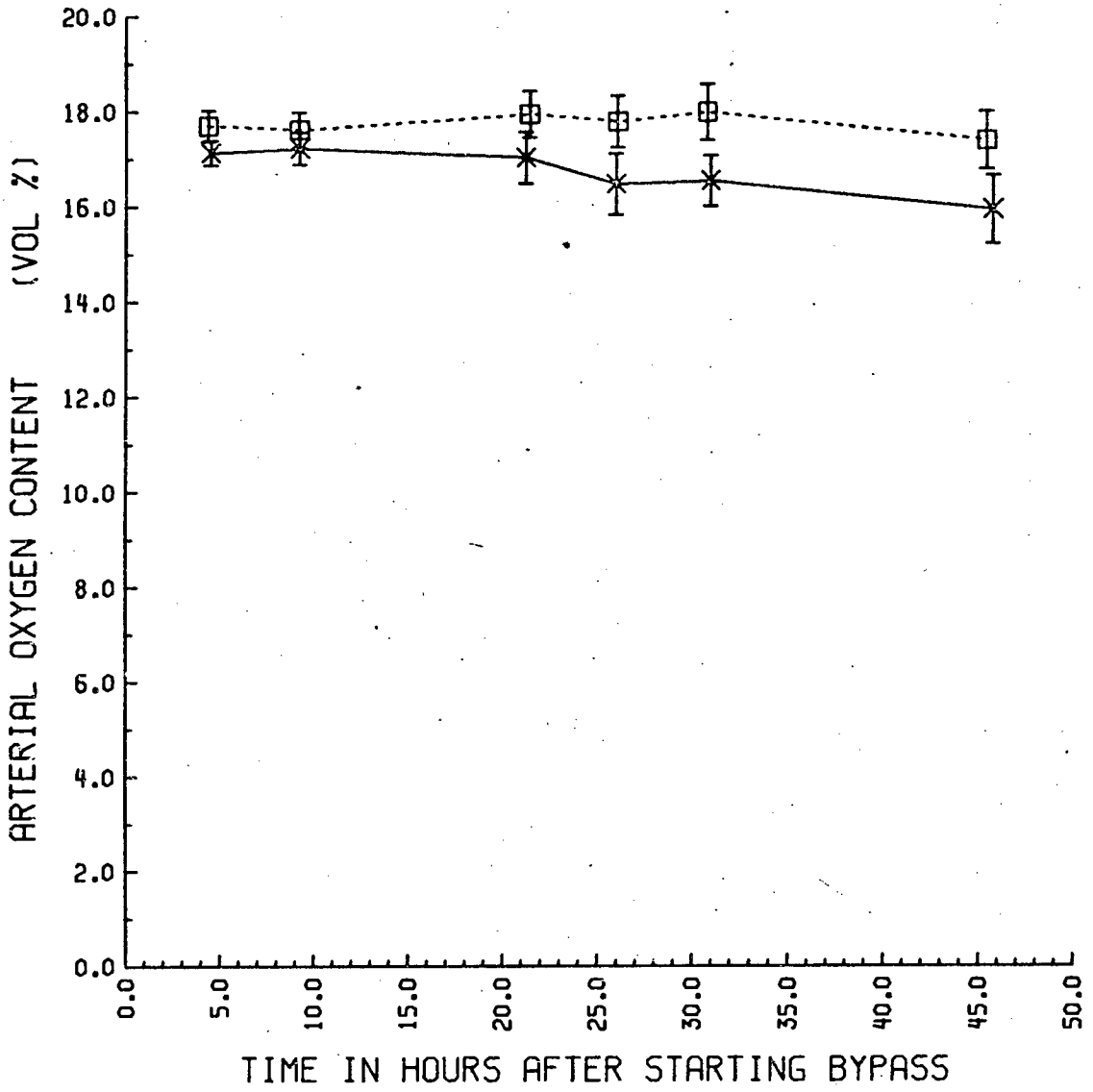

FIGURE 26

The arterial oxygen content plotted against time in hours after the commencement of cardiopulmonary bypass.

The arterial to coronary sinus oxygen extraction (Vols%) (Figure 27)

There were no significant differences in the means at each study period between the groups. The averaged overall means for the coronary perfusion group was 8.40 vols% and 8.68 vols% for the profound hypothermic non-perfusion arrest group ($p > 0.1$) which similarly were not significantly different. There were no differences which could not be explained by experimental error.

The arterial buffer base (M. Equivs/litre) (Figure 28)

No differences were observed between the groups at any study period, or between the averaged overall group means, 6.63 M. Equivs/litre for the coronary perfusion group and 5.97 M. Equivs/litre for the profound hypothermic non-perfusion arrest group ($p > 0.1$). There were also no differences which could not be accounted for by experimental error.

The arterial to coronary sinus buffer base extraction (M. Equivs/litre) (Figure 29)

No differences were encountered by any of the three methods of analysis. The averaged overall means for the coronary perfusion group were -3.44 M. Equivs/litre and -3.74 M. Equivs/litre for the profound hypothermic non-perfusion arrest group ($p > 0.1$).

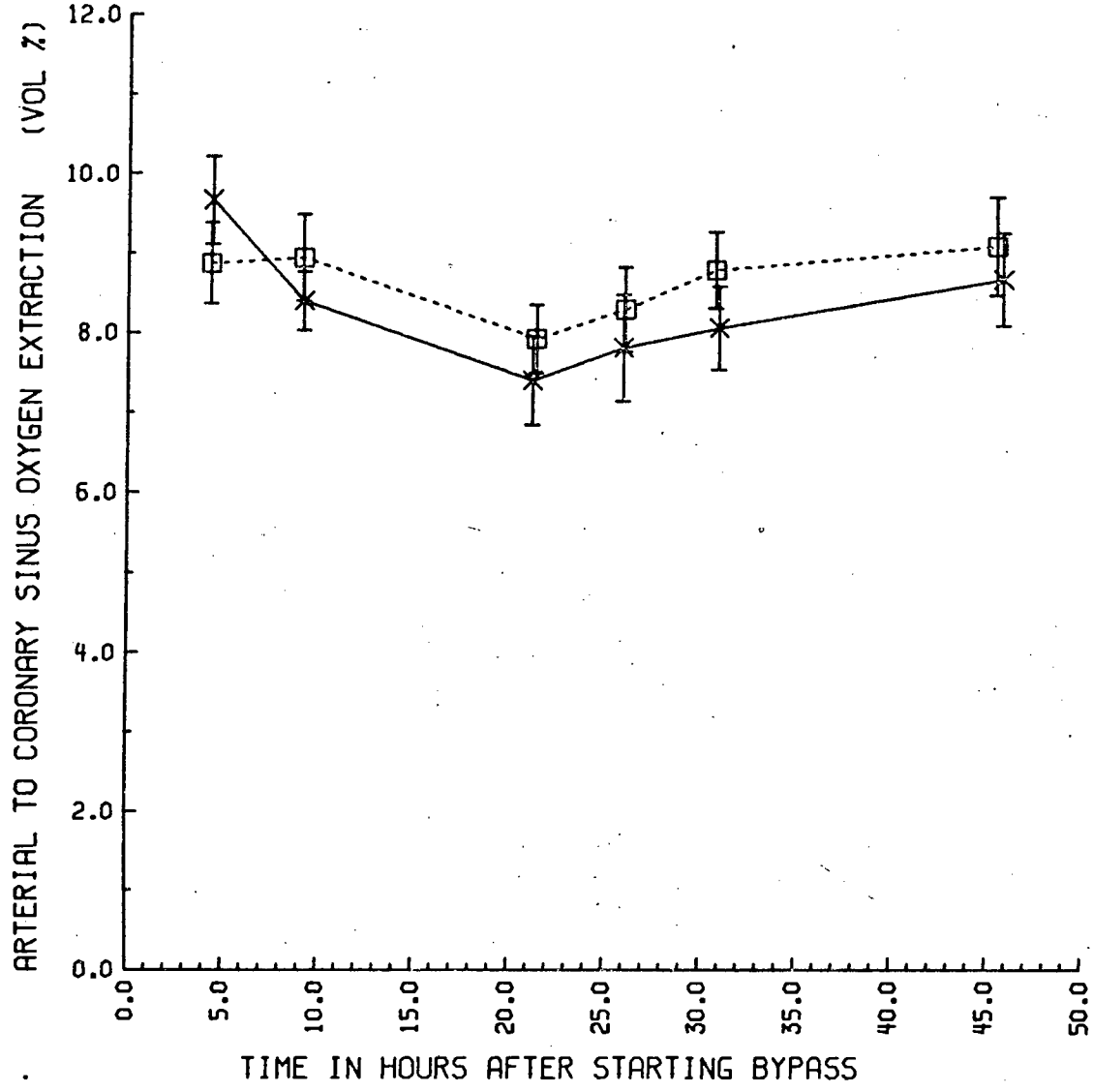

FIGURE 27

The arterial to coronary sinus oxygen extraction plotted against time in hours after the extraction of cardiopulmonary bypass.

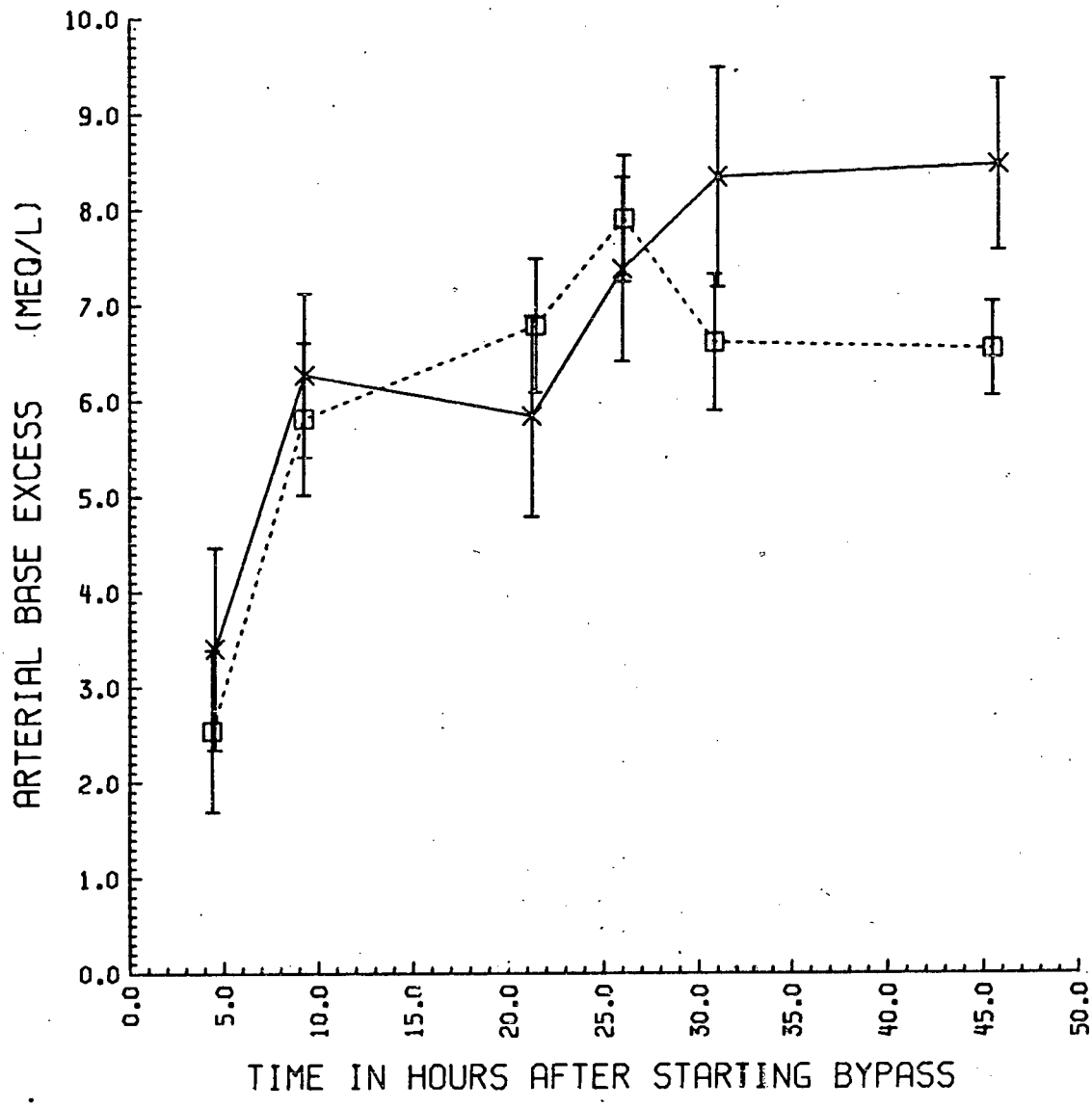

FIGURE 28

The arterial buffer base plotted against time in hours after the commencement of cardiopulmonary bypass.

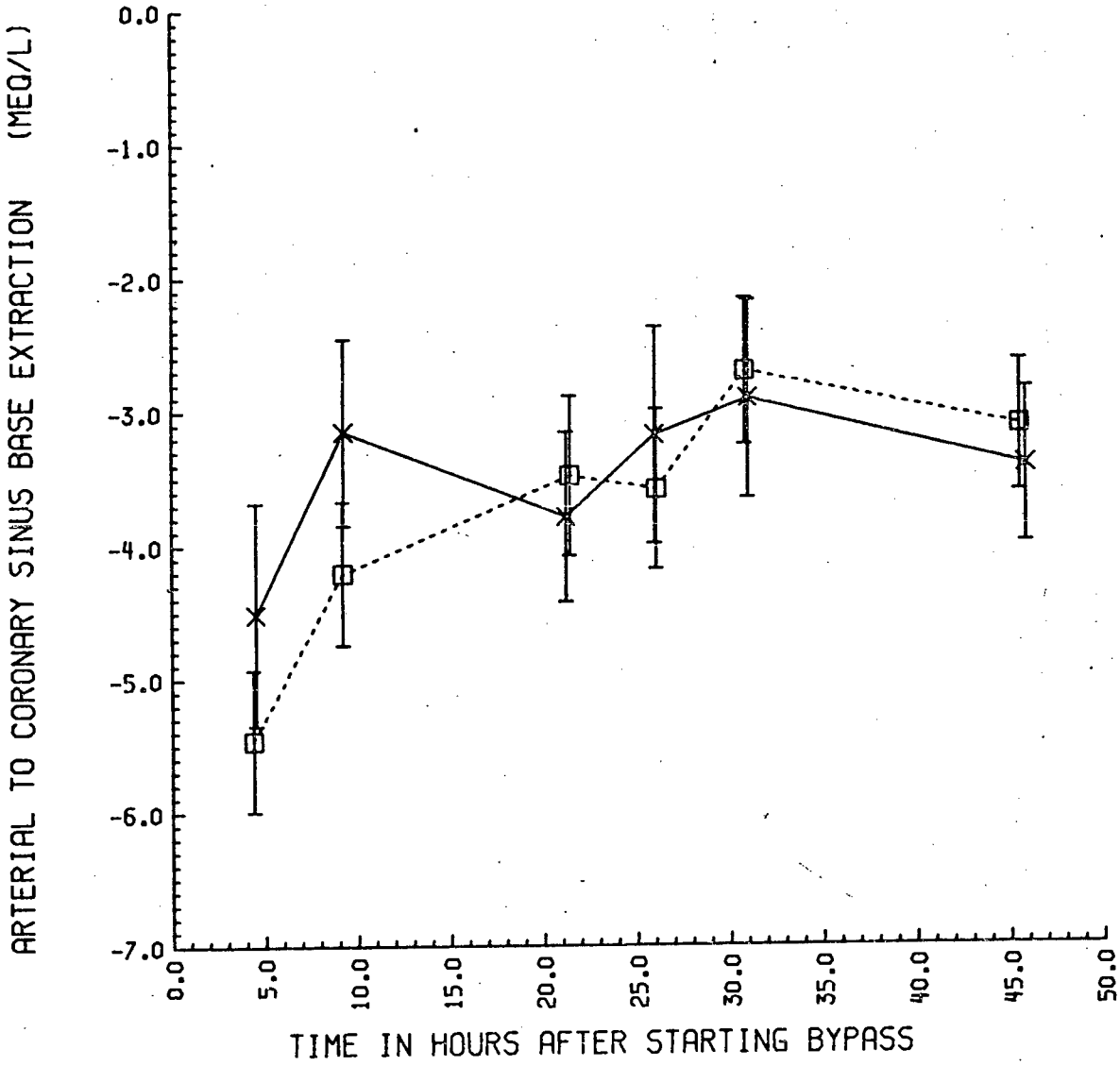

FIGURE 29

The arterial to coronary sinus buffer base extraction plotted against time in hours after the commencement of cardiopulmonary bypass.

The arterial potassium concentration (M. Equivs/litre) (Figure 30)

No differences were observed in the group means at each study period. The overall group means were likewise not significantly different, 4.05 M. Equivs/litre for the coronary perfusion group and 4.17 M. Equivs/litre for the profound hypothermic non-perfusion arrest group ($p > 0.1$). There was a significant difference, however, when tested against experimental error ($p < 0.006$). The profound hypothermic non-perfusion arrest group had higher arterial potassium concentrations.

Arterial to coronary sinus potassium extraction (M. Equivs/litre) (Figure 31)

No difference between the groups, by any of the three methods of analysis was detected. The average overall mean value for the coronary perfusion group was -0.0343 M. Equivs/litre and it was -0.0130 M. Equivs/litre for the profound hypothermic non-perfusion arrest group ($p > 0.1$).

Lactate and pyruvate estimations

Statistical analysis of these duplicate estimations revealed a coefficient of variation percentage for lactate of 2.7% and a departure from standard of 5.82 ± 2.86 % ($n = 78$). A coefficient of variation

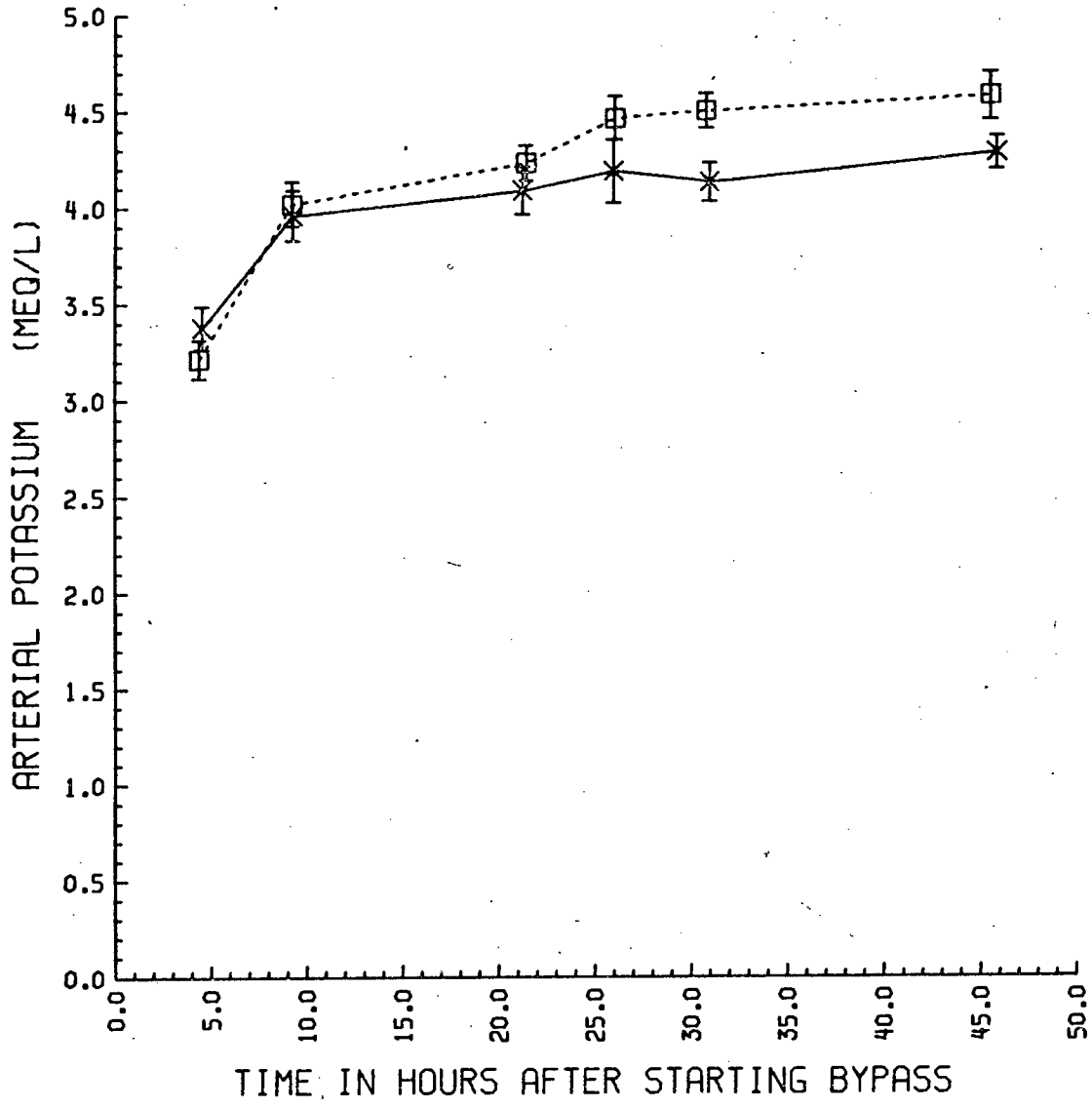

FIGURE 30

The arterial potassium concentration plotted against time in hours after the commencement of cardiopulmonary bypass.

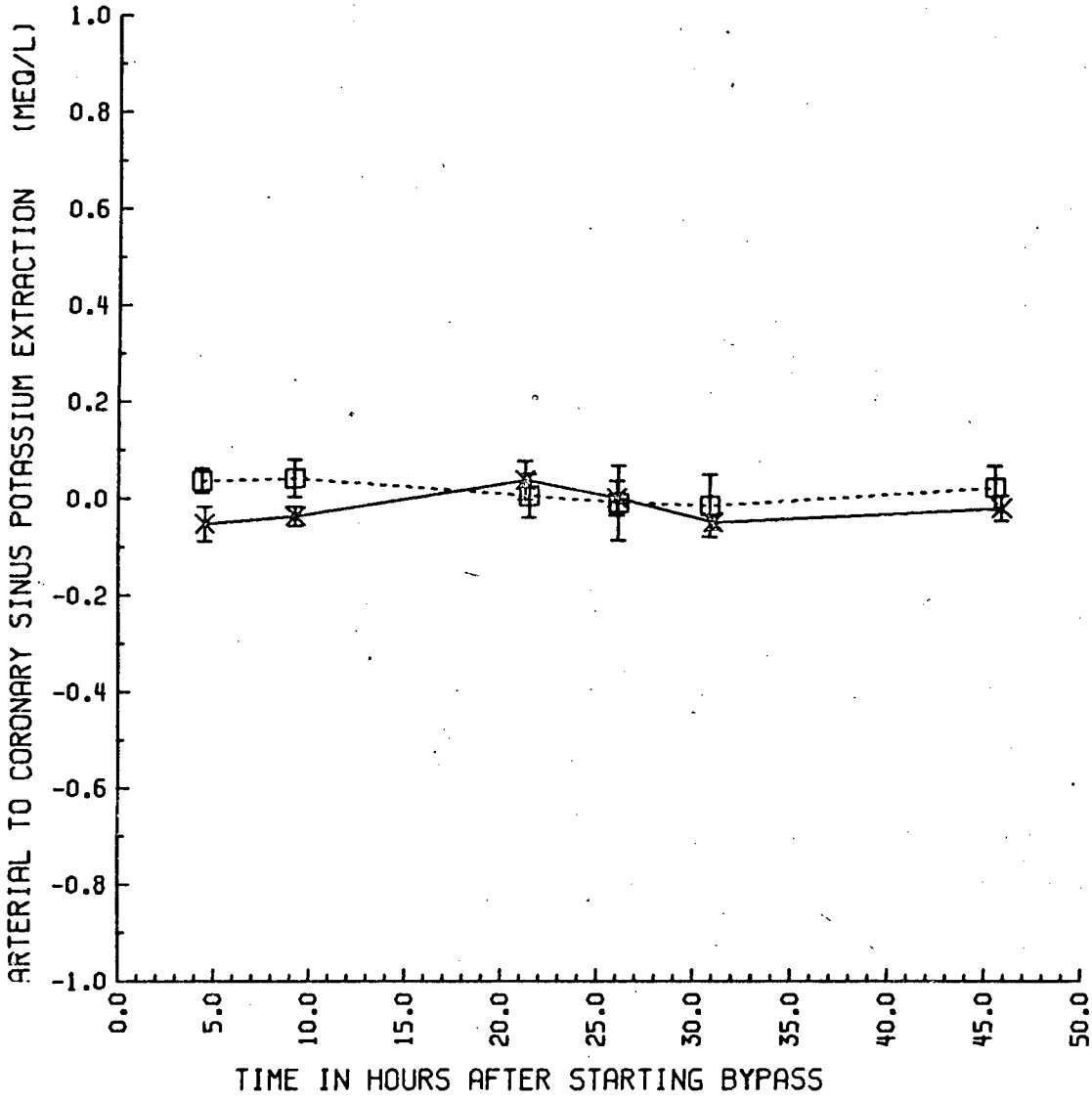

FIGURE 31

The arterial to coronary sinus potassium extraction plotted against time in hours after cardiopulmonary bypass.

percentage of 3.3% was found for pyruvate with a departure from standard of $3.96 \pm 3.149\%$ (n = 56).

The arterial to coronary sinus lactate extraction (M. Equivs/litre) (Figure 32)

The group mean averaged overall study periods was 19.7% for those patients in whom coronary perfusion was used and 20.4% for those patients in whom profound hypothermic non-perfusion arrest was used.; There was no significant difference ($p > 0.1$). There were no significant differences between the means at each study period and there were no differences which could be explained by experimental error. In both groups lactate extraction was low immediately post-operatively and only rose to approach normal levels ten to fifteen hours later.

The arterial to coronary sinus excess lactate (m.mol/litre) (Figure 33)

No differences could be found between the averaged overall means which were 0.183 m.mol/litre for those patients in whom coronary perfusion was used and 0.134 m.mol/litre for those patients in whom profound hypothermic non-perfusion arrest was used ($p > 0.1$). There were no differences between the group means at any study period and there were no differences which could not be explained by experimental error.

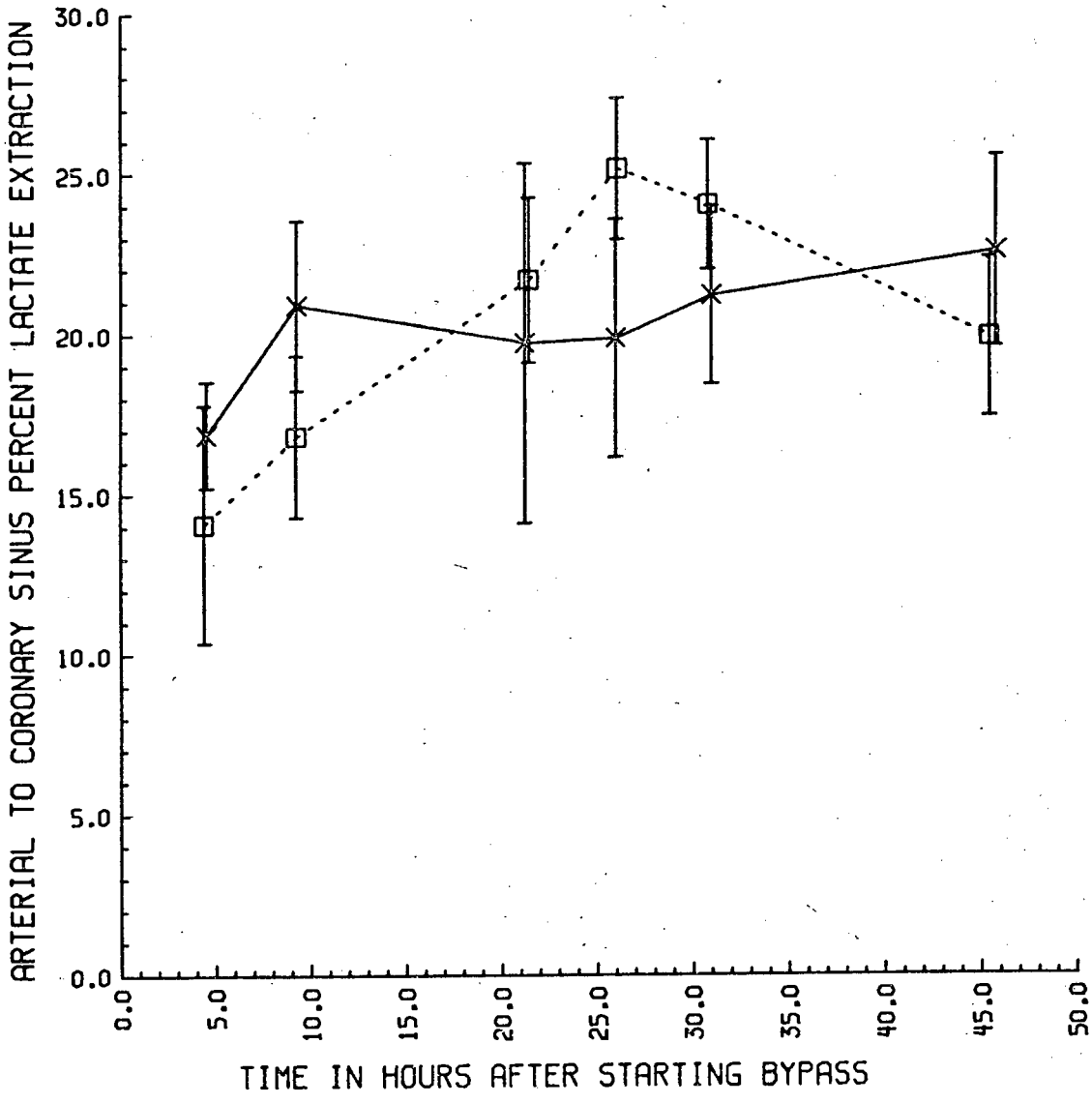

FIGURE 32

The arterial to coronary sinus lactate extraction plotted against time in hours after the commencement of cardiopulmonary bypass.

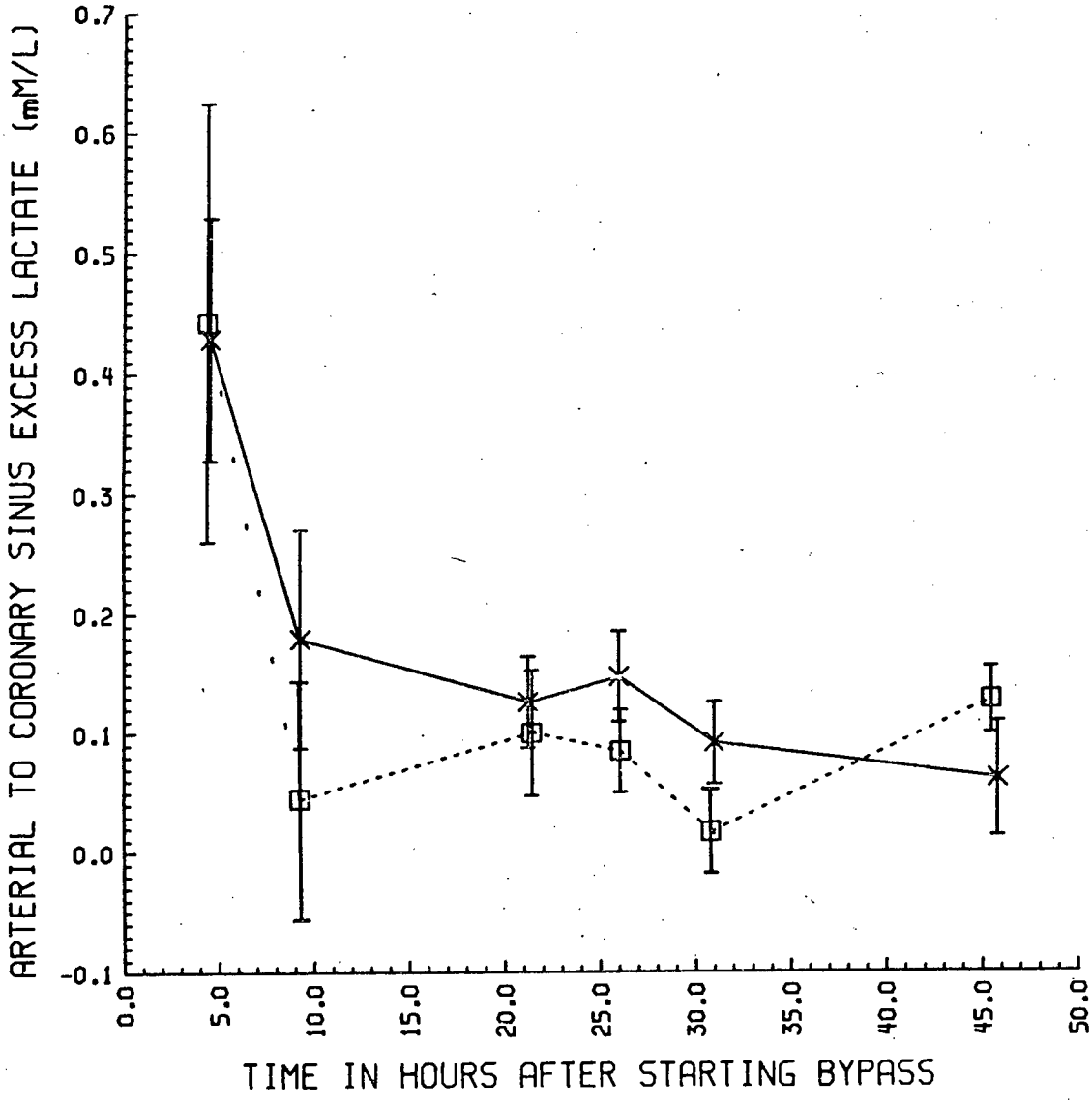

FIGURE 33

The arterial to coronary sinus excess lactate plotted against time in hours after the commencement of cardiopulmonary bypass.

Patients in both groups had small quantities of excess lactate detectable early after cardiopulmonary bypass, but these had all but disappeared by ten hours after starting cardiopulmonary bypass. None of the variables studied for interrelationships with the excess lactate for the study population as a whole, nor for the profound hypothermic non-perfusion arrest group was found to influence it. In the group of patients in whom coronary perfusion was used, the intercept of excess lactate was higher, with lower average flows to the left coronary system and with smaller left ventricular diameters, (the excess lactate intercept was $3.4285 - 0.0055 \pm 0.00183$/average left coronary flow was 0.227 ± 0.0739/left ventricular diameter, $p < 0.01$).

One surgeon's patients exhibited a slower return of excess lactate to zero, -2.83 m.mol/litre/hour ($p < 0.03$) when his patients were tested against the other three surgeons.

The percentage anaerobic metabolism (Figure 34)

No differences were found between the group means at any study period, or which could not be explained by experimental error. The averaged overall group means were 2.17% for the coronary perfusion and 1.96% for the profound hypothermic non-perfusion arrest group ($p > 0.1$).

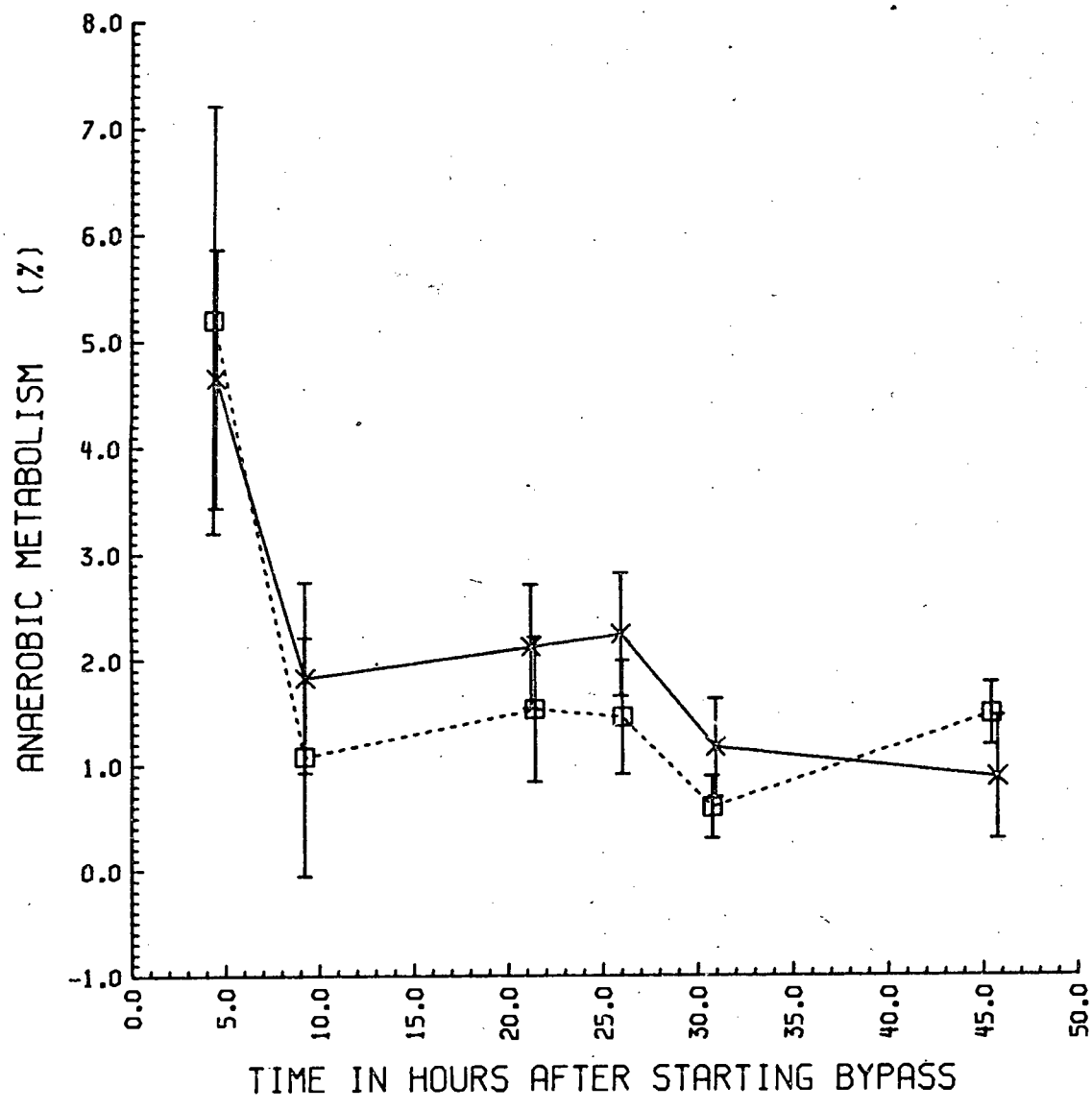

FIGURE 34

The percentage anaerobic metabolism plotted against time in hours of the commencement of cardiopulmonary bypass.

ENZYMES AND ISOENZYMES

The coronary sinus catheter could not be placed correctly in a significant number of the patients, in another group it ceased to function due to blockage or withdrawal into the right atrium at some stage during the study periods. As it was undesirable to lose enzyme and isoenzyme data on any patient in the study, right atrial, peripheral venous or arterial blood was used when coronary sinus blood was not available. This was done because evidence exists that significantly different levels are not found irrespective of the site of sampling (see 'Patients, Materials and Methods'). As previously mentioned, to verify this fact in this study, paired simultaneously obtained, coronary sinus and peripheral blood were analysed in sixteen patients in whom the coronary sinus catheter functioned properly. No differences were found between the paired samples in any patient which could not be explained by experimental error. This information also justified the use of a peripheral sampling site for the sample obtained prior to cardiopulmonary bypass and the last sample obtained on each patient.

Total creatine phosphokinase and total lactic acid dehydrogenase were assessed on each patient at each study period. These values were considered too non-specific, for the purposes of this study and were not statistically compared. Likewise no use was made statistically of

lactic acid dehydrogenase enzymes 3 to 5, although all were assayed. Detailed statistical analysis was confined to the myocardium specific isoenzyme of creatine phosphokinase, namely the creatine phosphokinase - M.B. isoenzyme and the ratio of isoenzymes 1 and 2 of lactic acid dehydrogenase. The latter was possible because significant haemolysis was not found to occur in any patient. This was assessed by plasma haptoglobin estimations on samples that had been allowed to stand for ten hours and by examining a few of the electrophoretic plates at random for migration of haemoglobin.

The isoenzyme data is displayed in Figures 35 and 36. Once more the isoenzyme is on the vertical axis and the time in hours after the commencement of cardiopulmonary bypass is on the horizontal axis. The crosses $\pm$ 1 standard error of the mean joined by the solid line represents the coronary perfusion group and the squares $\pm$ 1 standard error of the mean joined by the dotted line represents the profound hypothermic non-perfusion arrest group.

<u>The creatine phosphokinase - M.B. isoenzyme (International units) (Figure 35)</u>

An elevated level of creatine phosphokinase - M.B. was found in only one patient before the start of cardiopulmonary bypass. This strongly suggested that myocardial cell necrosis had occurred for

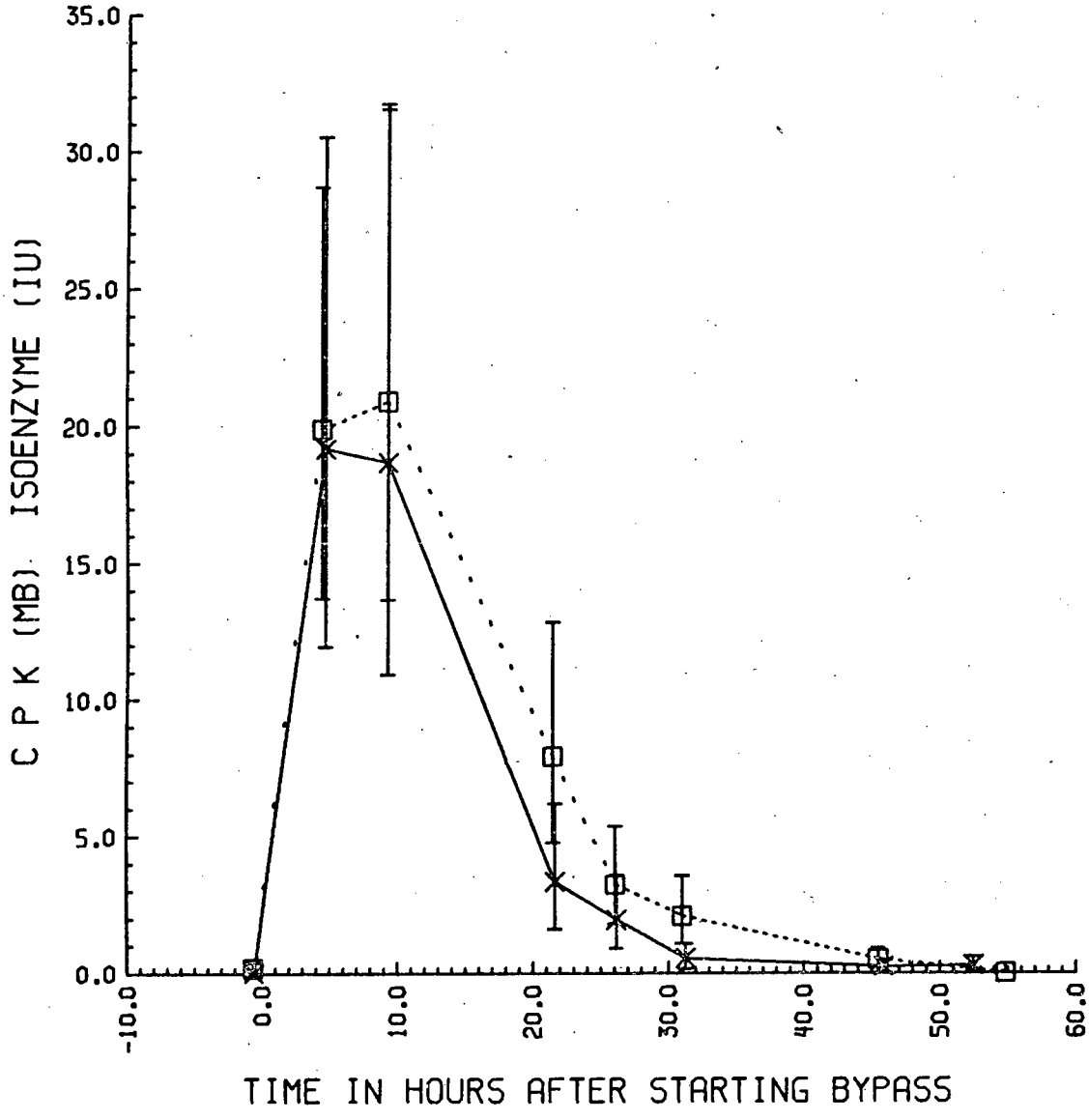

FIGURE 35

Creatine phosphokinase - MB isoenzyme plotted against time in hours after the commencement of cardiopulmonary bypass.

reasons that were not apparent, before cardiopulmonary bypass. In the remainder, creatine phosphokinase - M.B. was only detected, if at all, in the samples taken after cardiopulmonary bypass. It should be remembered that no sampling was carried out during cardiopulmonary bypass or immediately afterwards.

Creatine phosphokinase - M.B. ranged from 1 - 1522 international units for the entire population studied. There were no significant differences for the averaged overall means for each group. These were 3.29 international units for those patients in whom coronary perfusion was used and 4.23 international units for those in whom profound hypothermic non-perfusion arrest was used ($p > 0.1$). Likewise there were no significant differences between the group means at any study period. There were no significant differences which could not be explained by experimental error.

None of the variables studied for interrelationships with the magnitude of creatine phosphokinase - M.B. (see 'Methods') for the study population as a whole or for the profound hypothermic non-perfusion arrest group were found in influence it. In those patients in whom coronary perfusion was used, the magnitude of creatine phosphokinase - M.B. was higher in the patients who had thicker left ventricular walls (regression coefficient for left ventricular wall thickness = 1.68 ± 0.752) ($p < 0.05$). The peak levels of creatine phosphokinase - M.B. occurred

between four and ten hours in both groups and had returned to zero by fifty-four hours in all cases.

The ratio of lactic acid dehydrogenase 1 to lactic acid dehydrogenase 2 (Figure 36)

There were no differences between the averaged overall group means, which were 0.929 for those patients in whom coronary perfusion was used and 0.924 for those patients in whom profound hypothermic non-perfusion arrest was used. The ratio of lactic acid dehydrogenase 1 to lactic acid dehydrogenase 2 exceeded unity in both groups at approximately sixteen hours after the commencement of cardiopulmonary bypass and remained above unity for the duration of the study. There were no differences between the groups at any study period and no differences occurred which could not be explained by experimental error.

A quantitive summary and qualitative statistical analysis of the isoenzyme data is set out in Table XII. Only two patients (4.3%), one from each group, had no creatine phosphokinase - M.B. detected, and did not reverse their lactic acid dehydrogenase 1 to lactic acid dehydrogenase 2 ratio. Thirty-three patients (68.7%), fourteen from the coronary perfusion group and nineteen from the profound hypothermic non-perfusion arrest group had both detectable levels of creatine phosphokinase - M.B. and a reversed lactic acid dehydrogenase 1 to

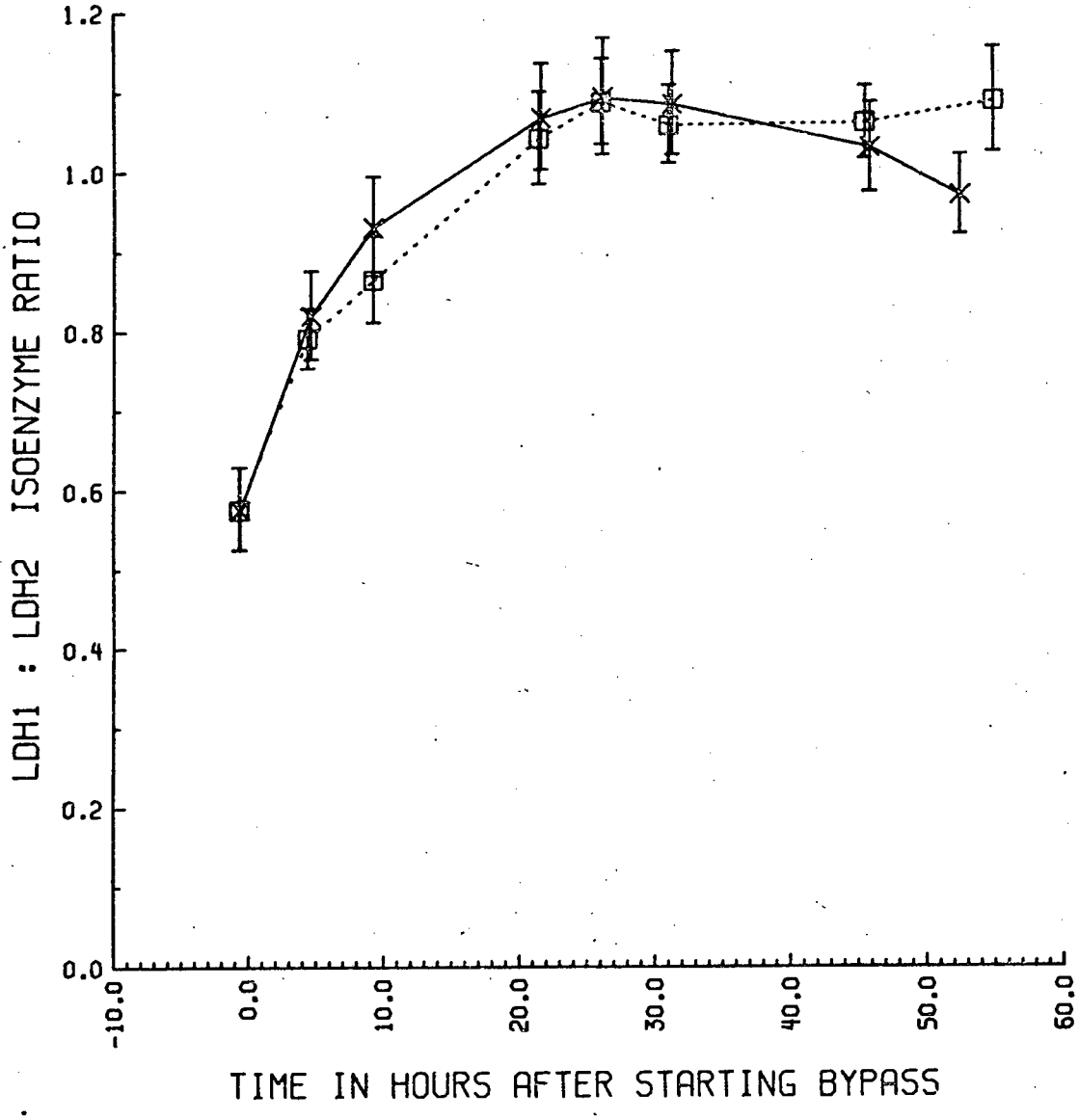

FIGURE 36

The ratio of lactic acid dehydrogenase isoenzyme 1 to isoenzyme 2 plotted against time in hours after the commencement of cardiopulmonary bypass.

TABLE XII

Myocardial Necrosis Assessed by Isoenzymes of CPK and LDH

	No CPK - MB LDH 1 _ LDH 2	CPK - MB and LDH 1 LDH 2	No CPK - MB LDH 1 LDH 2	CPK - MB and LDH 1 _ LDH 2	TOTAL
Coronary Perfusion	1	14	4	3	22
Ischaemic Arrest	1	19	2	4	26
Totals	2 (4.2%)	33 (68.7%)	6 (12.5%)	7 (14.6%)	48
Interpretation	None	Diagnostic	Presumptive	Presumptive	

P for table by X^2 tests is not significant DF = 4

A quantitative and qualitative analysis of the isoenzyme data for the two groups of patients.

lactic acid dehydrogenase 2 ratio. This group had isoenzyme findings diagnostic of myocardial cell necrosis. Seven patients (14.6%), three from the coronary perfusion group and four from the profound hypothermic non-perfusion arrest group, had detectable levels of creatine phosphokinase - M.B. but who did not reverse their lactic acid dehydrogenase 1 to lactic acid hydrogenase 2 ratio. Six patients (12.5%), four from the coronary perfusion group and two from the profound hypothermic non-perfusion arrest group had no detectable creatine phosphokinase - M.B., but did have a reversed lactic acid dehydrogenase 1 to lactic acid dehydrogenase 2 ratio. It is possible that some patients in this group had a very early and transitory rise in creatine phosphokinase - M.B. which was missed by the sampling regime used in this study.

The changes in the latter two groups of patients are presumptive evidence of myocardial cell necrosis. There were no significant differences between the two groups of patients with reference to myocardial cell necrosis, but it is apparent that 68.7% of the total group of patients had isoenzyme features diagnostic of necrosis and a further 27.1% features presumptive of necrosis, irrespective of the method used to preserve the myocardium while replacing the aortic valve.

THE POST-OPERATIVE ELECTROCARDIOGRAM.

The blind evaluation of the seven to ten day post-operative electrocardiogram is set out in Table XIII. Seven patients (13.5%), five from the coronary perfusion group and two from the profound hypothermic non-perfusion arrest group had changes diagnostic of new myocardial infarctions. Seven additional patients (13.5%), two from the coronary perfusion group and five from the profound hypothermic non-perfusion arrest group had features of ischaemia which were not present before. These two groups of patients are mutually exclusive and there were no significant differences between the two groups.

No factors in the population as a whole or in either of the two groups was found to influence the development of these changes. A total of 27% of the entire population showed electrocardiographic evidence of myocardial infarction or ischaemia. All these patients had combined creatine phosphokinase - M.B. and lactic acid dehydrogenase 1 and 2 isoenzyme changes diagnostic of necrosis, but there was no significant difference in the magnitude of these changes by comparison with the 73% of patients who showed no electrocardiographic changes.

The difference between the number of patients who showed

TABLE XIII

	Coronary Perfusion	Profound Hypothermic Non-Perfusion Arrest	Total
New Myocardial Infarctions	5	2	7 (13.5%)
New Ischaemic Changes	2	5	7 (13.5%)
No Changes	20	18	38 (73.0%)
Total	27	25	52

P for table BX X^2 is not significant. DF = 3

Electrocardiographic evidence of myocardial injury at 7 - 10 days post-operatively.

isoenzymatic evidence of myocardial cell necrosis as opposed to those who showed electrocardiographic evidence is striking. This is perhaps not so surprising if it is accepted that we are looking at two different forms of pathology in the myocardium (see 'Pathology').

POST-OPERATIVE COURSE

The clinical post-operative course of every patient was recorded. Table XIV sets out the details of the complications encountered and compares them for the two groups of patients using X^2 for a two-way contingency table.

Fourteen patients (22.2%), six from the coronary perfusion group and eight from the profound hypothermic non-perfusion arrest group had complicated courses. The complications encountered included: haemorrhage, this complication occured in five patients (7.9%), two from the coronary perfusion group and three from the profound hypothermic non-perfusion arrest group. It was recorded only if the patient had to be returned to the operating room to control the haemorrhage. Surgical re-exploration for haemorrhage was carried out in the Department according to a definite protocol which related the patient's weight, the amount of blood lost and the periods of time in which this blood was lost (Table XV). The low output state, this was defined as existing in those patients if after elevating the mean left atrial pressure, used as an index of pre-load, to 12 - 14 mmHg with blood or plasma, the cardiac index was still below 1.8 litres/min/M^2. The patients were then either treated with Adrenaline or Isoprenaline if the mean arterial pressure was low, i.e. less than 60 mmHg, or

TABLE XIV

		Total		Coronary Perfusion		Non-Perfusion Arrest		Significance	
		No.	%	No.	%	No.	%	X^2	DF
Course	Uncomplicated	49	77.8	24	80.0	25	75.8		
	Complicated	14	22.2	6	20.0	8	24.2		
	Total	63	100.0	30	100.0	33	100.0	0.54	2
Cardiac Complications	No Complication	49	77.8	24	80.0	25	75.8		
	Haemorrhage	5	7.9	2	6.7	3	9.1		
	Low Output State	8	12.7	4	13.3	4	12.1		
	Thrombus Formation	1	1.6	0	0	1	3.0		
	Total	63	100.0	30	100.0	33	100.0	0.71	4
Dysrhythmias	No Dysrhythmias	61	96.8	29	96.7	32	97.0		
	Atrial Fibrillation	1	1.6	0	0	1	3.0		
	Atrial Flutter	1	1.6	1	3.3	0	0		
	Total	63	100.0	30	100.0	33	100.0	0.38	3

An analysis and comparison of the complications encountered in the patients' post-operatively.

TABLE XV

Chest Drainage Indicating Re-Operation

Pre-op weight	ml/hr No. of hours in succession			total ml Hour number		
Kg	1	2	3	4th	5th	6th
5.0	70	60	50	120	130	140
6.0	70	60	50	130	155	NA
7.0	70	61	50	152	181	NA
8.0	90	69	52	174	207	NA
9.0	90	78	59	195	233	NA
10.0	108	87	65	217	259	NA
12.0	130	104	78	260	311	NA
14.0	152	122	91	304	363	NA
16.0	174	139	104	347	414	NA
18.0	195	156	117	391	466	NA
30.0	217	174	130	434	518	NA
25.0	271	217	163	542	647	NA
30.0	325	260	195	651	777	NA
35.0	380	304	228	759	906	NA
40.0	434	347	260	868	1036	NA
45.0	488	391	293	976	1165	NA
50.0	500	400	300	1000	1200	NA

Patient management programme for re-operation after intracardiac surgery.

Arfonad or Sodium Nitroprusside if the mean arterial pressure was high, i.e. greater than 100 mmHg. The low output state occurred in a total of eight patients (12.7%), four from each group. One patient, in whom profound hypothermic non-perfusion arrest was used, developed a femoral arterial thrombosis at the site of a femoral artery puncture, used to perform a cardiac catheterisation by the Seldinger technique, two days prior to operation. The thrombus was successfully removed sixteen hours after her aortic valve replacement, with the restoration of a good circulation to the affected leg. It was of interest that her creatine phosphokinase - M.M. isoenzyme was not unduly higher than any of the other patients, suggesting either that she did not suffer any extensive skeletal muscle necrosis as a consequence of the thrombus formation, or that the creatine phosphokinase - M.M. isoenzyme release from the leg was comparatively modest in amount by comparison with that released by the effects of cardiopulmonary bypass and did not separate her from the rest.

Two further patients (3.2%) developed serious dysrhythmias, significantly different from their pre-operative rhythms. One patient in the coronary perfusion group developed atrial fibrillation and one patient in the profound hypothermic non-perfusion arrest group developed atrial flutter. These dysrhythmias are quoted as post-

operative compliations because they are not dysrhythmias usually caused by ischaemia or infarction of the ventricles and in each case they contributed to low output states in the patients concerned. There was a low incidence of this problem, since transient episodes of ventricular extrasystoles were not recorded in patients who otherwise remained in their pre-operative rhythm. One patient who was in total atrio-ventricular dissociation pre-operatively, who already had a pacemaker implanted was also not recorded. The remainder were in, and remained in, sinus rhythm. There were no significant differences between the groups with reference to any of these complications. All the patients who had complications had isoenzyme changes diagnostic of myocardial cell necrosis, but there was no correlation between the levels of isoenzymes released and the occurrence of the complications.

CHAPTER XII

DISCUSSION

All patients scheduled to have aortic valve replacements were pre-operatively randomly allocated to have their valve replacements carried out using either one or other of the methods under study.

All eligible patients were randomised for all surgeons as a precaution to preclude the argument of patient selection since the study was consecutive. This resulted in an unequal number of patients done by each surgeon. The exclusion of six patients from the study population detracts from complete randomisation, although the necessity of allowing for such exclusions in therapeutic surgical trials is evident. The method used for handling these exclusions did not involve removing data from the study, so the data set is without gaps and completely random. All changes from the randomly allocated method consisted of changing from coronary perfusion to profound hypothermic non-perfusion arrest, which occasionally was not carried out according to the prescribed method, thus possibly introducing an unmeasurable bias into the study, but as these patients were rejected this gave rise to no problems.

The randomisation was also done separately for each of the four faculty surgeons since significant surgeon-to-surgeon differences were expected and would have to be removed so that all patients

treated by each method could be examined in combined groups. An uncontrolled factor was that four operations were carried out by a senior resident assisted by the faculty surgeon to whom the case was referred. The paired randomisation was also used to determine whether any trends with time occurred for each of the four surgeons over the five month study period. This precaution was not needed as shown in the results. Finally randomisation by pairs per surgeon was used to ensure approximately equal groups of patients allocated to each method. The effectiveness of the randomisation process was well demonstrated by the equal sixed groups and the remarkable lack of significant differences in the patient population variables. Surgeon-to-surgeon differences were able to be assessed and removed where necessary, and no significant surgeons trends with time were demonstrated to bias the results.

Coronary perfusion and profound hypothermic non-perfusion arrest, as described in 'Methods', were both in use, as a means of preserving the myocardium, in patients undergoing aortic valve replacement, utilising cardiopulmonary bypass in the Department of Surgery, The University of Alabama, prior to this study. The mortality and morbidity figures alone were not considered sufficiently sensitive parameters and were of such low incidence that an unacceptably large study would have had to be carried out to document significant differences

between the methods; on this account the early post-operative haemodynamic, metabolic, isoenzyme and electrocardiogram parameters and determinations used in this study were chosen, and because they were practical to carry out in the immediate post-operative intensive care environment.

Pre-operative haemodynamic data was not available as control measures for most patients, and no attempt was made to compare the pre-operative haemodynamic status with the post-operative situation in those patients in whom pre-operative data was available. The post-operative haemodynamic state was therefore not specifically stressed to demonstrate differences in cardiac performance and reserve brought about by either of the methods, but were used to compare the effects of the two methods on post-operative performance. In similar fashion no pre-operative levels of the various metabolic parameters in the patients were known. These were assumed to be normal, and the serial levels obtained post-operatively were used to compare the two methods with reference to derangements in metabolically produced transmyocardial parameters.

The appearance of creatine phosphokinase - M.B. with the techniques used in this study has been shown to be specific for myocardial cell necrosis (Roe, C.R., Limbird, L.E., Wagner, G.S. 1972). In the absence of haemolysis, as occurred in this study, elevations above the

normal levels of lactic acid dehydrogenase 1 and lactic acid dehydrogenase 2 together with a reversal of the normal lactic acid dehydrogenase 1 to 2 ratio is considered to be strong presumptive evidence of myocardial cell necrosis (Rosalki, S.B. 1967). When both these are present in patients who have sustained acute myocardial infarctions as a consequence of coronary artery occlusions, myocardial necrosis has clearly occurred (Roe, C.R., Limbird, L.E., Wagner, G.S. 1972) and there is now good evidence that the same inference can be drawn in patients who have had cardiac operations carried out utilising cardiopulmonary bypass (Dixon, S.H.Jr., Limbird, L.E., Roe, C.R., Wagner, G.S., Oldham, H.N.Jr., Sabiston, D. C. Jr. 1973). The isoenzymes are presumably released from the necrotic myocardial cells in the patchy areas of necrosis found circumferentially distributed around the ventricles, principally the left, which were described by Henson and Najafi (Henson, D.E., Najafi, H., Callaghan, R., Coogan, P., Julian, O.C., Eisenstein, R. 1969) and others (Taber, R.E., Morales, A.R., Fine, G. 1967), as opposed to the areas of necrosis confined to the anatomical territories of supply of the coronary arteries, found in acute myocardial infarctions.

The post-operative haemodynamic state of patients in whom coronary perfusion was utilised has not been shown with confidence to be different from that found in patients in whom profound hypothermic non-perfusion

arrest was used. Significant differences were found in two out of sixty tests. This was no greater than could be expected by chance alone and cannot be used as an indication that there were any differences. Differences between the groups with respect to cardiac index, heart rate, arterial mean pressure, peripheral vascular resistance, right atrial mean pressure and coronary blood flow index, while not significant due to large patient-to-patient variability, were significantly larger than experimental error. This large patient-to-patient variability was presumably due to inherent individual differences between the patients with respect to age, sex, race and the degree to which their heart and consequently their bodies were affected by their basic aortic valve pathology. No attempt was made to compare patient-to-patient to assess these influences. The patients in groups were merely compared with reference to those quantitative variables. Since the stroke index was practically identical in the two groups, the difference in cardiac index resulted from a difference in heart rate. The difference in heart rate, in arterial pressure and peripheral vascular resistance may result from differing extrinsic autoregulatory effects upon the circulation, resulting from differing cardiac and whole body temperature during cardiopulmonary bypass in the two patient populations.

There is, therefore, insufficient evidence from this study to draw

a conclusive inference that there was no difference in these variables between the two groups.

We failed to demonstrate any relationship between any of the early post-operative haemodynamic parameters and the myocardial temperatures or aortic cross-clamp time in the profound hypothermic non-perfusion arrest group. Since the mean aortic croos-clamp time, plus two standard deviations, was 68 minutes, we know nothing from this study of the effects of longer periods of profound hypothermic non-perfusion arrest. Some of the variability in myocardial temperature around the mean of 22.4^{o}C at aortic cross-clamping and 24.6^{o}C at release of the aortic cross-clamp, may have resulted from variability in depth or location of the thermistor temperature probe tip. We do not know the effect of lower or higher myocardial temperatures during profound hypothermic non-perfusion arrest.

The duration of direct coronary perfusion (about 10 minutes less than aortic cross-clamping time) did not relate to any of the post-operative haemodynamic parameters either, but the average blood flow delivered to the left coronary artery did have a definite relationship, either as a direct factor or as part of a mechanism which resulted in decreased coronary blood flow. Abnormal myocardial metabolism reflected by pyruvate and lactate concentration differences across the myocardium has been reported previously, during the

operation, in both patients who have had their procedures carried out with and without coronary perfusion (Goldschlager, N., Gerbode, F., Osborn, J.J., Cohn, K.E. 1972; Isom, O.W., Kutin, N.D., Fawk, E.A., Spencer, F.C., 1973). Our findings in the early post-operative period probably represented the tail end of these processes, in hearts which were once more normally perfused, and there were no significant differences between the groups with respect to the levels or patterns of lactate metabolism, not even individual variability was responsible for differences which could not be explained by experimental error. The finding in the coronary perfusion group that higher early post-operative excess lactate concentrations were associated with lower intra-operative flow rates to the left coronary artery was not unexpected, but we were not able to offer a clear explanation for the inverse relationship observed in this group between the left coronary flow rate and the left ventricular diameter.

Sixty-nine percent of all the patients studied developed isoenzyme abnormalities diagnostic of myocardial cell necrosis. Neither coronary perfusion nor profound hypothermic non-perfusion arrest was superior in minimising these abnormalities. The lack of interrelationship between the isoenzyme abnormalities and the length of aortic cross-clamping or myocardial temperature in the profound hypothermic non-perfusion arrest group, the duration of direct coronary artery perfusion

in the coronary perfusion group and the duration of cardiopulmonary bypass in both groups is noteworth. It is also of interest that none of the recorded qualitative variables in either patient group correlated with the observed isoenzyme abnormalities. There is no evidence from this study that larger hearts had a greater tendency to develop these abnormalities, nor that aortic stenosis, as opposed to aortic regurgitation, predisposed to them. However, hearts which were found to have greater left ventricular wall thickness, in the coronary perfusion group, did result in significantly higher levels of creatine phosphokinase - M.B. There was no interrelationship between the early post-operative cardiac output and the isoenzyme abnormalities. The haemodynamic function of the rat heart under some circumstances has been shown to be unaltered inspite of enzyme release (De Weikis, J., Feuvray, D. 1973). However, cardiac reserve may be limited by such isoenzymatically documented injury as by electrocardiographically demonstrable myocardial infarctions. This limitation in reserve may be capable of assessment, if accurate and comparable pre-operative and post-operative haemodynamic parameters were available, or it was possible to assess the effect of the patients ability to meet a demand for an increased cardiac output, such as during exercise or if some more sensitive parameters were used. The limitations of cardiac reserve might also have been obvious in this study if the patients

had been more seriously ill pre-operatively. In this case more of them may have fulfilled the criteria used in the study to diagnose the low output state. As it was there was also no correlation between the low output state and the isoenzyme abnormalities, apart from the fact that no patient who developed a low output state did not also have marked isoenzyme abnormalities.

In this study 13% of all the patients developed electrocardiographic evidence of acute myocardial infarction on their seven to ten day post-operative electrocardiograms. Another 13% developed new ischaemic changes. All these patients had characteristic isoenzyme abnormalities. The incidence of these events in our patients was similar to that reported in patients undergoing aorto-coronary bypass grafts for ischaemic heart disease (Dixon, S.H.Jr., Limbird, L.E., Roe, C.R., Wagner, G.S., Oldham, H.N.Jr., Sabiston, D.C.Jr. 1973). The evidence all suggests that factors common to both methods and to the methods used in patients undergoing aorto-coronary bypass grafting and probably other cardiac operations utilising cardiopulmonary bypass as well are responsible for these developments. These may include: exposure of the heart, along with the rest of the body, at the start of cardiopulmonary bypass to the perfusate, from the pump oxygenator, containing its denatured microaggregates of platelets and fibrin and together with air microemboli (Bloom, A.L. 1962;

Ashmore, P.G., Svitek, V., Ambrose, P. 1968); the change from a normal pulsatile to a non-pulsatile flow resulting in changes in the autoregulation of the myocardial blood flow, causing mal-distribution. This can be further aggravated if the usual perfusion pressure at capillary level falls below the critical closing pressure of the capillaries and a sufficient pressure is then not re-established to open them before irreversible damage to the myocardial cells occurs. The strength of these common factors may be so great as to mask any differences in our study between profound hypothermic non-perfusion arrest, with its depletion of intra-cellular glycogen and high energy phosphate reserves, on the one hand, and coronary perfusion, which perpetuates all the previously mentioned causes of injury on the other hand. The 27% reduction in aortic cross-clamping time and the 21% reduction in total cardiopulmonary bypass time, when profound hypothermic non-perfusion arrest was employed, together with the fact that the aortic valve replacement was easier with this method, are all of practical significance. In view of this, and because we failed in this study to show any conclusive differences in the effects of coronary perfusion and profound hypothermic non-perfusion arrest on the parameters studied, profound hypothermic non-perfusion arrest seems to be preferable for isolated aortic valve replacements when the cross-clamping time can be kept less than 68 minutes and the myocardial

temperature between 22°C and 24°C. None of the factors, usually thought to influence the prognosis in patients with aortic valve disease, such as age, severity of symptoms, presence or absence of coronary artery disease, degree of left ventricular hypertophy, stenosis or regurgitation, could be shown in this study to suggest modifying this view.

CHAPTER XIII

SUMMARY

Eighty-one consecutive patients requiring elective aortic valve replacement were randomly allocated, in pairs per surgeon, to have their valves replaced using either coronary perfusion at 32°C or profound myocardial hypothermic non-perfusion arrest. Four patients were inadvertently not randomised, the randomisation was not adhered to in six patients, because the surgeon decided that it was not in the patients' best interests. Seven patients had homograft valves inserted using coronary perfusion, obviating randomisation. The remaining sixty-four patients were studied to determine the safety of these two methods. Thirty-one patients had their valves replaced using coronary perfusion and thirty-three patients had their valves replaced using profound hypothermic non-perfusion arrest.

Results

1) The two populations were statistically compared with reference to their vital statistics such as age, sex, etc., their symptoms, their signs, and diagnosis, their radiological features, their pre-operative electrocardiograms, their pre-operative haemodynamic and angiographic data, their left ventricular wall thickness and diameters measured at operation. No significant

differences were found between the two. The two methods were statistically compared with reference to the myocardial temperatures at the time of aortic cross-clamping and at the time of release of the aortic cross-clamp, with reference to the aortic cross-clamping time and the total cardiopulmonary bypass time. The temperatures were significantly different for the two method ($p < 0.0001$). Aortic cross-clamping and cardiopulmonary bypass times were less by 27% and 21% respectively when profound hypothermic non-perfusion arrest was used. One patient died during his operation. Coronary perfusion had been used to preserve the myocardium during the procedure.

2) Serial haemodynamic parameters, including the cardiac index, heart rate, stroke index, stroke work index, mean arterial pressure, mean left atrial pressure, mean right atrial pressure, total systemic peripheral vascular resistance, peak left ventricular dp/dt/p and the coronary blood flow index, were either measured or computed post-operatively. No differences were found between the two methods used; however, the difference between group means of several haemodynamic variables was significantly larger than experimental error.

Serial metabolic studies including arterial to coronary

sinus excess lactate and arterial to coronary sinus percent lactate extraction were also carried out. The former was elevated immediately post-operatively, but fell to near normal over the next twenty-four hours with both methods. No differences between the methods was found.

3) Serial coronary sinus or right atrial samples were analysed for their creatine phosphokinase and lactic acid dehydrogenase myocardium specific isoenzymes. Combined isoenzyme abnormalities diagnostic of myocardial cell necrosis were found in thirty-three of fourty-eight patients (68.7%) so studied. The incidence was similar for the two methods. If those patients who only had changes in their lactic acid dehydrogenase isoenzymes, which are presumptive evidence of myocardial cell necrosis, are added the incidence of myocardial cell necrosis rose to 81%.

4) An electrocardiograph obtained seven to ten days post-operatively in fifty-two patients was blindly evaluated. Fourteen of these patients (27%) showed changes of new infarction or ischaemia, but no differences in incidence between the two methods were apparent.

5) Finally a large number of facts which were known about the patients were statistically regressed against the presence of

myocardial cell necrosis in order to determine a causal relationship, no clearly defined causes were found.

CONCLUSION

A detailed, randomised, prospective comparison of two methods of myocardial preservation used during aortic valve replacement was carried out. It was confidently expected that one or other of the two methods would be found to be superior. Careful analysis of the data produced by the study, however, failed to show any convincing differences between the two. The patients were evenly divided between the two methods with reference to their pre-operative status. Both methods clearly produced myocardial cell necrosis, but none worse than the other. Both clearly produced minor depressions of myocardial function and metabolic derangements but not of sufficient severity to produce more than a low incidence of the low output state in the post-operative period. Aortic cross-clamp time and cardiopulmonary bypass time was shorter using profound hypothermic non-perfusion arrest and on a subjective level the surgeons all reported that the operations were easier to perform using this method.

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ORIGINAL ARTICLE

Coronary Perfusion Versus Cold Ischemic Arrest During Aortic Valve Surgery

A Randomized Study

By RALPH N. SAPSFORD, M.B., CH. B., F.R.C.S., EUGENE H. BLACKSTONE, M.D., JOHN W. KIRKLIN, M.D., ROBERT B. KARP, M.D., NICHOLAS T. KOUCHOUKOS, M.D., ALBERT D. PACIFICO, M.D., CHARLES R. ROE, M.D., AND EDWIN L. BRADLEY, PH. D.

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SUMMARY

Sixty-four randomized patients undergoing primary, isolated, scheduled, prosthetic aortic valve replacement were studied to determine the safety of coronary perfusion and mild hypothermia (31 patients) and of cold ischemic arrest (33 patients). Cardiac performance, metabolism, and isoenzyme release and the electrocardiogram were studied early postoperatively. No differences greater than expected by chance were found between the two groups; however, the difference between group means of several hemodynamic variables was significantly larger than experimental error. Combined abnormalities of creatine phosphokinase (CPK) and lactic dehydrogenase (LDH) heart-specific isoenzymes, indicative of myocardial necrosis, were found in 33 of 48 patients (68.7%) so studied. The incidence was similar in both study groups. In 14 of 52 (27%) patients with electrocardiographic studies, changes indicative of new infarction or ischemia were demonstrated, but no differences in incidence between the two groups of patients were found. In both groups the transmyocardial excess lactate immediately postoperatively was elevated, falling to near normal over the next 24 hours. Aortic crossclamp and cardiopulmonary bypass times were less by 27% and 21% respectively when cold ischemic arrest was used.

Additional Indexing Words:

Cardiopulmonary bypass
Micromanometers
Isoenzymes
Myocardial preservation

DURING OPEN INTRACARDIAC OPERATIONS the myocardium should be as fully protected against damage as is compatible with adequate surgical exposure. For aortic valve replacement, this has been attempted by a variety of methods, including direct coronary arterial perfusion and ischemic arrest with varying myocardial temperatures. The mortality and morbidity reported with most methods are low but real. The causes of the residual morbidity and mortality are not clear, and there is disagreement as to what method is the best. We wished to study this matter and to determine the comparative safety of the two methods we had been employing clinically, coronary perfusion with mild hypothermia and a beating heart, and cold ischemic arrest.

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Materials and Methods

Study Groups

Sixty-four patients undergoing primary, isolated, scheduled, prosthetic aortic valve replacement were studied in a five month period beginning 2 February 1973. Thirty-one patients (48.4%) were randomized to the coronary perfusion group and 33 (51.6%) to the cold ischemic arrest group. One patient died; he succumbed in the operating room of intractable ventricular fibrillation after being managed by coronary perfusion.

Technique of Randomization

Consecutive patients were randomized by pairs separately for each faculty surgeon using a random digit table.[1] At operation the surgeon decided to abort the randomization in the patient's best interests in six instances. In each case the surgeon's next patient was done by the method previously assigned to the excluded patient.

Surgical Management

For coronary perfusion both coronary arteries were cannulated and perfused at a temperature of 32° C soon after the aorta was crossclamped (in one patient, only the left was perfused). Mean flow to the left coronary artery was 158 ± 6.5 ml/min at a mean pressure in the coronary perfusion line of 111 ± 2.7 mm Hg and to the right 109 ± 7.1 ml/min at 109 ± 2.3 mm Hg. Occasionally coronary perfusion was interrupted briefly to improve exposure. Near the end of the perfusion the temperature of the perfusate was elevated to 39° to rewarm the patient. Spontaneous ventricular fibrillation, when it occurred, was promptly reversed by electroversion.

For cold ischemic arrest, bypass was initiated and maintained for about 4 min at a perfusate temperature of 25°C after which the temperature was lowered for about 2 min to 12°. The aorta was then crossclamped and the perfusate temperature raised to 28° until near the end of the perfusion when it was elevated to 39°C for rewarming the patient.

A bubble oxygenator was used.* The pump oxygenator was primed with 500 ml ACD blood drawn the day prior to surgery, 7.5 ml heparin, 60 ml 1.4% $NaHCO_3$, 1500 ml 5% dextrose in 0.45% saline, and 5 ml 10% $CaCl_2$. A Starr-Edwards cloth-covered, composite seat prosthesis was used for valve replacement in 57 of the 64 patients (89.1%), a Bjork-Shiley in three (4.7%), a Braunwald-Cutter in three (4.7%), and a valvulotomy was performed in one (1.6%).

Postoperatively all patients were managed by our usual patient management programs.[2] Drug administration included isoproterenol and/or epinephrine when cardiac index was less than about 1.8 $L \cdot min^{-1} \cdot m^{-2}$ (ten patients), trimethaphan camsylate (Arfonad) for reducing afterload (six patients)[3] and lidocaine for arrhythmias (three patients).

Instrumentation

Left ventricular (LV) wall thickness was measured with a 22 gauge needle introduced into the LV just until blood flowed back from the LV cavity. LV transverse diameter was measured using a caliper. LV subepicardial temperature was measured using a needle thermistor.†

A high fidelity pressure micromanometer‡ was introduced into the right superior pulmonary vein and advanced into the LV. A 14 gauge catheter,§ with 4 side holes was inserted through the right atrial wall and advanced into the coronary sinus and its position reconfirmed at each study period.[4] Routine pressure monitoring catheters were placed in the left and right atria, and the pulmonary and radial arteries.

Postoperative Studies

Hemodynamic, enzyme, and metabolic data were obtained at study periods which averaged 4, 9, 21, 26, 31, and 46 hours after initiation of cardiopulmonary bypass. In addition, blood for enzyme analyses was obtained 30 min prior to bypass (control sample) and again at 52 hours.

Cardiac index was derived by computer from triplicate measurements of cardiac output (coefficient of variation (CV) = 6.94%) by the indicator dilution technique using indocyanine green as the indicator.[5] Peak $(dp/dt) \cdot p^{-1}$ was derived from triplicate measurements of LV pressure derivative (CV = 4.72%) divided by the difference between LV pressure at peak dp/dt and LV end-diastolic pressure. Other derived variables were obtained in the usual fashion.[6]

Total creatine phosphokinase (CPK)[7] and its isoenzymes, MM, MB, and BB,[8] and total lactate dehydrogenase (LDH)[9] and its five numbered isoenzymes[10] were obtained in blood drawn from the coronary sinus, but on occasion from the right atrium; the final sample was always from a peripheral vein. Heart-specific CPK-MB isoenzyme, as analyzed by the method cited, is consistently absent in normal serum; in nonsurgical patients sustaining documented myocardial infarction it remains detectable for no less than 24 hours after its initial appearance; and in patients undergoing intracardiac operations it has been absent despite left ventricular venting and multiple defibrillation attempts.[11] Thus, the detection of CPK-MB in serum was considered abnormal and indicative of myocardial damage. Haptoglobin levels were determined in three patients early in the study to ascertain the level of hemolysis.

Arterial and coronary sinus lactate and pyruvate concentrations were determined in duplicate enzymatically[12] (CV = 2.7%, departure from standard = 5.82 ± 2.865%, n = 78; pyruvate CV = 3.3%, departure from standard = 3.96 ± 3.149%, n = 56). Arterial − coronary sinus excess lactate[13] and percent lactate extracted were calculated.

Electrocardiogram Studies

A 12 lead electrocardiogram was recorded for each patient 2 to 3 days preoperatively and again 7 to 10 days postoperatively. These were assessed¶ for the presence of myocardial infarction, or of ischemic changes (mutually exclusive diagnoses).[14]

Data Analysis

Each hemodynamic, isoenzyme, and metabolic variable was tested in three separate ways against the hypothesis that the mean value for all patients done by coronary perfusion was the same as that for cold ischemic arrest. 1) The difference between the two group means at each study period was tested by student's t test. 2) The difference between the two group means averaged over all study periods, obtained by least squares analysis, was tested by the F ratio of variation between groups to the variation between patients in the groups. 3) The difference between the two group means was tested against experimental error as in 2) using as experimental error the variability within patients in each group. For 2) and 3) a least squares rather than a standard analysis of variance was employed because of unequal group sizes and incomplete data for some patients. Averaging over periods to obtain a best unbiased estimate of population means was permitted because the group · period interaction term used in the analysis was never significantly different from zero.

Interrelations among certain variables were examined by correlation and regression. The following variables were

*Temptrol Q 100, Bentley Laboratories, Inc., Irvine, California.

†Model 524, Yellow Springs Instrument Co., Inc., Yellow Springs, Ohio.

‡PC-350A with TCB-100 Control, 5 French, Millar Instruments, Inc., Houston, Texas.

§Bardic 1914R, 24" catheter, C. R. Bard, Inc., Murray Hill, New Jersey.

¶We are indebted to Dr. Brian Maurer for the scoring of the electrocardiograms.

studied for correlation of each with all others in the patient population as a whole: cardiac index (time intercept and slope obtained by least squares), CPK-MB and LDH_1/LDH_2 (magnitude and rates of rise and disappearance fit with a gamma function), excess lactate (intercept and rate of return to zero), cardiothoracic ratio, LV diameter and wall thickness, the two myocardial temperatures, and crossclamp and bypass times. Cardiac index, CPK-MB, LDH_1/LDH_2, and excess lactate were regressed against age, sex, race, diagnosis of stenosis or incompetence at the aortic valve, orthopnea, angina, syncope, cardiothoracic ratio, LV diameter and wall thickness, macroscopic coronary artery disease, crossclamp and bypass times; additionally, for the coronary perfusion group, against average flows and pressures in the right and left perfusion cannulae. A forward stepwise regression procedure was used both for the patient population as a whole, using "group" as a regression variable, and separately by groups. Only those variables which had a $P \leq 0.1$ remained in the model.

When departures from the normal distribution were encountered, data transformations were selected to equalize as nearly as possible the variation within each group. All enzyme data were log transformed, and the reciprocal of $(dp/dt) \cdot p^{-1}$ was employed.

Qualitative variables were tested by Chi Square for a 2-way contingency table. As an estimate of reproducibility for hemodynamic and metabolic variables, the ratio of the stan-

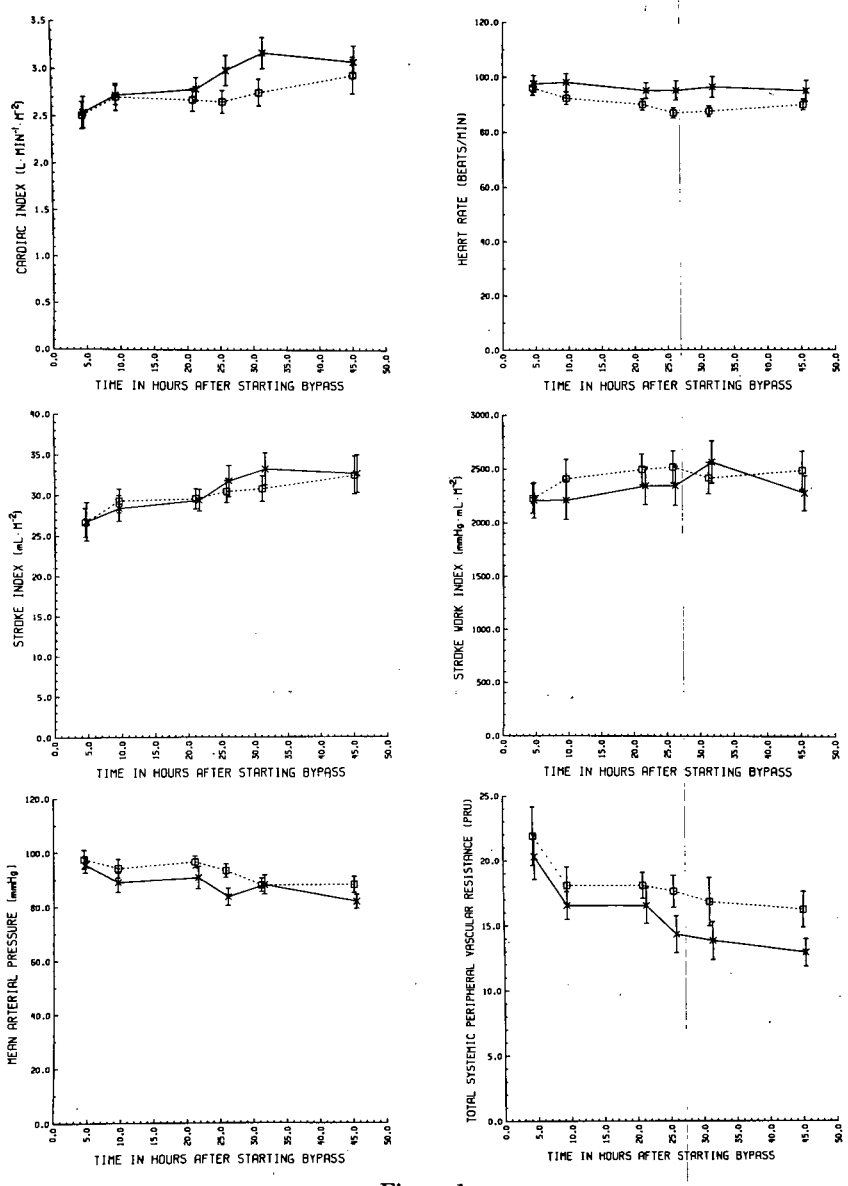

Figure 1a

Hemodynamic variables plotted against time in hours after starting bypass. The group means ± one standard error are plotted at the average time of observation for each study period. The X's connected by the solid line are for the coronary perfusion group and the open squares connected by the dotted line for the cold ischemic arrest group.

dard deviation of repeated measurements at each study period to the over-all mean was calculated using a nested analysis of variance and expressing it as a coefficient of variation. Trends over the five month study were examined by regressing each variable against the order in which patients were treated, and surgeon to surgeon differences by regressing against each surgeon. Each variable was also regressed against the interaction term, surgeon · group, to test for differences between group means which were significantly different from surgeon to surgeon.

The term "not significant" refers to the $P \geqq 0.05$ significance level.

Results

Hemodynamics

The two group means at each study period for cardiac index, heart rate, stroke index, stroke work index, arterial mean pressure, systemic resistance, right and left atrial mean pressures, $(dp/dt) \cdot p^{-1}$, and coronary blood flow index were not significantly different at any period with two exceptions (fig. 1). Heart rate at 31 hours was lower in the cold ischemic arrest group than in the coronary perfusion group ($P < 0.04$). Arterial mean pressure in the cold ischemic arrest group at 26 hours was higher than in the coronary perfusion group ($P < 0.03$). It is of interest that five of the six patients in whom afterload was reduced pharmacologically early postoperatively were in the cold ischemic arrest group.

There were no significant differences between the two group means averaged over all study periods (table 1). However, differences between the two group means significantly greater than experimental error were found. Cardiac output and heart rate were higher, and arterial mean pressure, systemic resistance, right atrial pressure and coronary blood flow index lower in the coronary perfusion than in the cold ischemic arrest group.

None of the variables studied for interrelations with cardiac index (see Methods) for the study population as a whole and for each study group separately was found to influence it except three. For the study population as a whole the intercept of cardiac index (roughly equivalent to the first postoperative measurement) was negatively correlated with cardiothoracic ratio ($r = -0.336$), and older patients had lower cardiac indices (intercept regression coefficient for age $= -0.025 \pm 0.0061$, $P < 0.001$; slope regression coefficient for age $= 1.00045 \pm 0.000199$, $P < 0.05$). When the two study groups were examined

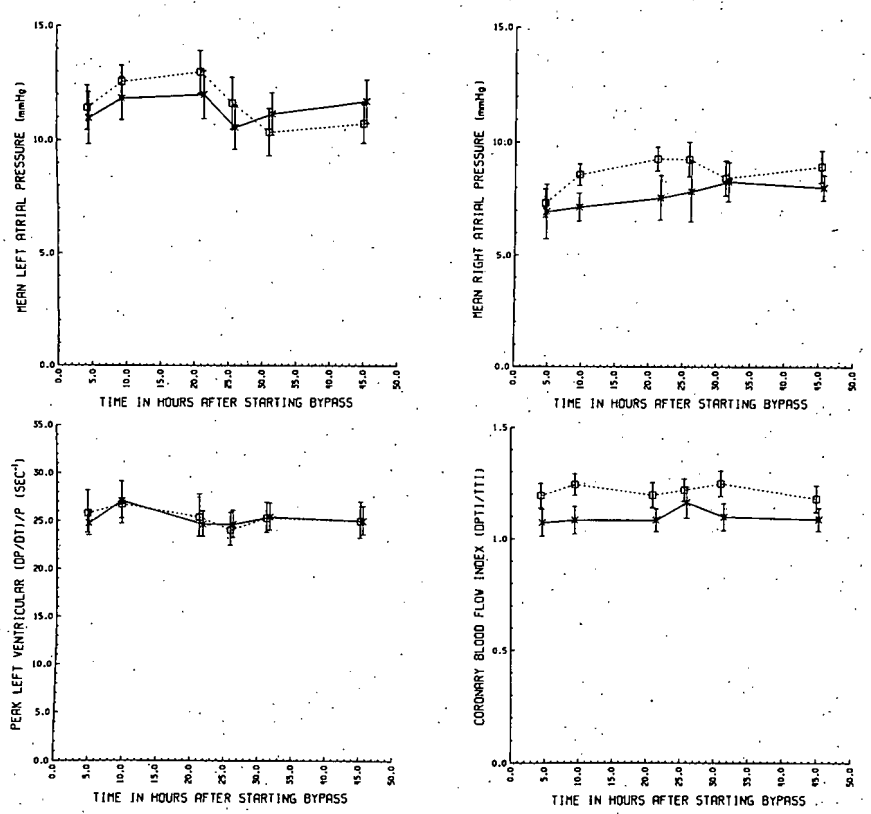

Figure 1b

Table 1

Postoperative Hemodynamic Data Averaged Over All Periods

	Group means		Significance level	
	Coronary perfusion	Cold ischemic arrest	Using patient variability	Using experimental variability
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.87	2.69	$P \geqq 0.1$	$P < 0.006$
Heart rate (beats $\cdot min^{-1}$)	96.6	90.9	$P < 0.1$	$P < 0.0001$
Stroke index ($ml \cdot m^{-2}$)	30.5	29.9	$P \geqq 0.1$	$P \geqq 0.1$
Stroke work index ($ml \cdot mm\ Hg \cdot m^{-2}$)	2338.0	2424.0	$P \geqq 0.1$	$P \geqq 0.1$
Arterial mean pressure (mm Hg)	88.5	93.5	$P \geqq 0.1$	$P < 0.0002$
Systemic resistance (pru)	16.4	18.5	$P \geqq 0.1$	$P < 0.001$
Left atrial mean pressure (mm Hg)	11.3	11.7	$P \geqq 0.1$	$P \geqq 0.1$
Right atrial mean pressure (mm Hg)	7.3	8.5	$P \geqq 0.1$	$P < 0.002$
$(dp/dt) \cdot p^{-1}$ (sec^{-1})	27.7	27.8	$P \geqq 0.1$	$P \geqq 0.1$
Coronary blood flow index	1.13	1.22	$P < 0.1$	$P < 0.0003$

separately, these same two influencing variables were found. In the cold ischemic arrest group no other influencing variable was found. In the coronary perfusion group one additional influencing variable was found: the intercept of cardiac index was higher when average flow to the left coronary artery had been higher (regression coefficient for left coronary flow = 0.0125 ± 0.00470, $P < 0.05$).

Isoenzymes

Matched coronary sinus and right atrial levels of the isoenzymes were not significantly different. In the early patients tested, hemolysis sufficient to interfere with enzyme analysis was not present. CPK-MB ranged from 0 to 1522 International Units (IU). No significant differences between the group means of the two patient groups at each study period were found in CPK-MB and LDH_1/LDH_2 isoenzymes (fig. 2). The group mean averaged over all study periods for CPK-MB was 3.29 IU for the coronary perfusion group and 4.23 IU for the cold ischemic arrest group. The group mean averaged over all study periods for LDH_1/LDH_2 was 0.929 for the coronary perfusion group and 0.924 for the cold ischemic arrest group. No

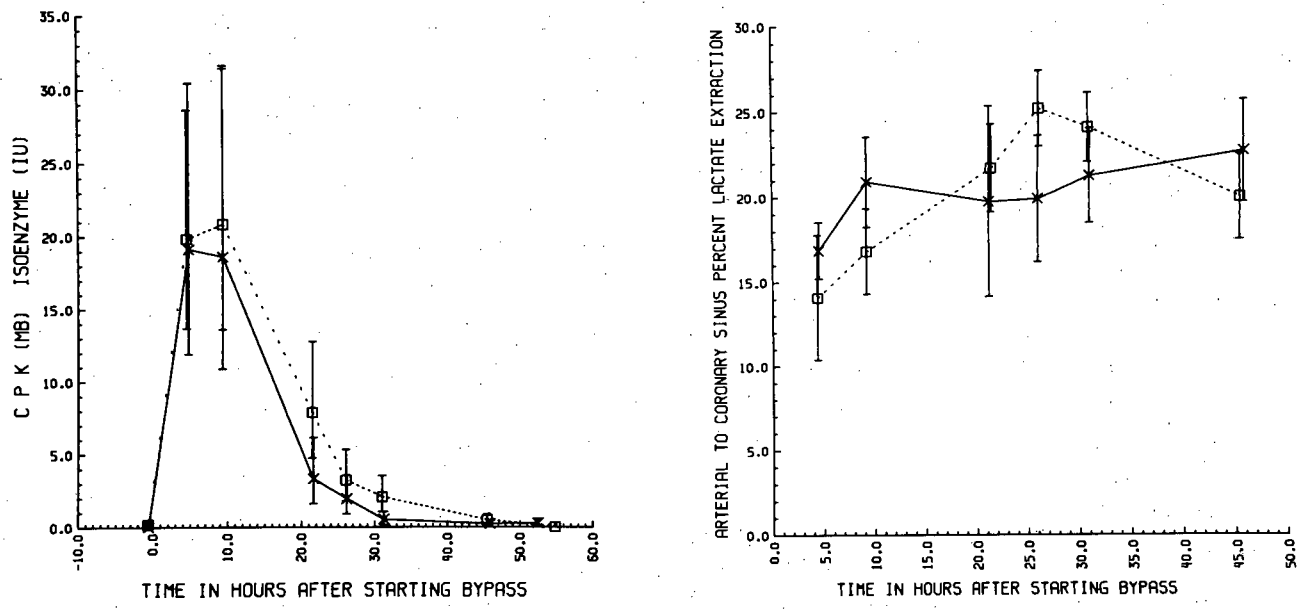

Figure 2

CPK-MB and LDH_1/LDH_2 heart-specific isoenzymes plotted similarly to figure 1 against time in hours after starting bypass. Reversal of the usual LDH_1 and LDH_2 isoenzymes is indicated when their ratio becomes greater than one, which is seen about 16 hours after bypass was started. The asymmetric standard errors (vertical bars) result from the data transformations (see Methods).

Table 2

Myocardial Necrosis Assessed by Isoenzymes of CPK and LDH

	No CPK-MB $LDH_1 \leq LDH_2$	CPK-MB and $LDH_1 > LDH_2$	No CPK-MB $LDH_1 > LDH_2$	CPK-MB and $LDH_1 \leq LDH_2$	Total
Coronary perfusion	1	14	4	3	22
Ischemic arrest	1	19	2	4	26
Totals	2 (4.2%)	33 (68.7%)	6 (12.5%)	7 (14.6%)	48
Interpretation	None	Diagnostic	?	?	

P for table by χ^2 test is not significant.

significant difference between these two group means was found for either isoenzyme, nor was a difference found significantly greater than experimental error.

None of the variables studied for interrelations with the magnitude of CPK-MB (see Methods) for the study population as a whole nor for the cold ischemic arrest group was found to influence it. In the coronary perfusion group CPK-MB magnitude was higher when left ventricular wall thickness was greater (regression coefficient for LV wall thickness = 1.68 ± 0.752, $P < 0.05$).

A qualitative summary of the isoenzyme data in terms of evidence of myocardial necrosis revealed no significant difference between the two groups (table 2). The table does indicate, however, that 69% of the patients who had enzyme studies had combined enzyme abnormalities indicative of myocardial necrosis, and another 27% had single enzyme changes.

Electrocardiogram

Electrocardiographic evidence of myocardial injury was not significantly different between the two groups (table 3). Thirteen percent of the patients with these studies developed electrocardiographic evidence of myocardial infarction early postoperatively and an additional 13%, of new ischemic changes. The incidence of these changes was not significantly different for patients with stenosis as opposed to insufficiency at the aortic valve. All patients with these changes had combined CPK-MB and LDH_1/LDH_2 isoenzyme abnormalities. However, the isoenzyme magnitudes were not significantly greater in these patients versus those without detectable electrocardiographic changes.

Table 3

Electrocardiographic Evidence of Myocardial Injury (7-10 Days Postoperatively)

	Coronary perfusion	Ischemic arrest	Total
New ischemic changes	2	5	7 (13.5%)
New myocardial infarctions	5	2	7 (13.5%)
No changes	20	18	38 (73.0%)
Total	27	25	52

P for table by χ^2 is not significant.

Myocardial Metabolism

No significant differences were found between the two group means at each study period for arterial − coronary sinus excess lactate or lactate extraction (fig. 3). The group mean averaged over all study periods for excess lactate was 0.183 $mM \cdot L^{-1}$ for the coronary perfusion group and 0.134 $mM \cdot L^{-1}$ for the cold ischemic arrest group. The group mean averaged over all study periods for lactate extraction was 19.7% for the coronary perfusion group and 20.4% for the cold ischemic arrest group. No significant difference between these two group means was found for either metabolic variable, nor was a difference found significantly greater than experimental error.

None of the variables studied for interrelations with the excess lactate (see Methods) for the study population as a whole nor for the cold ischemic arrest group was found to influence it. In the coronary perfusion group the intercept of excess lactate was higher when average flow to the left coronary artery had been lower and when left ventricular diameter was smaller (excess lactate intercept = $3.4285 - 0.0055 \pm 0.00183 \cdot$ left coronary flow $- 0.227 \pm 0.0739 \cdot$ LV diameter, $P < 0.01$).

Surgical Events

Aortic crossclamping and cardiopulmonary bypass times were significantly less by 27 and 21 percent respectively in the cold ischemic arrest group (table 4). Myocardial temperatures were significantly different as expected. The myocardial temperature at aortic crossclamping for each group was not statistically different for patients with stenosis as opposed to insufficiency at the aortic valve. In the coronary perfusion group average flow to the left coronary artery was significantly less for those patients with thicker left ventricular walls (regression

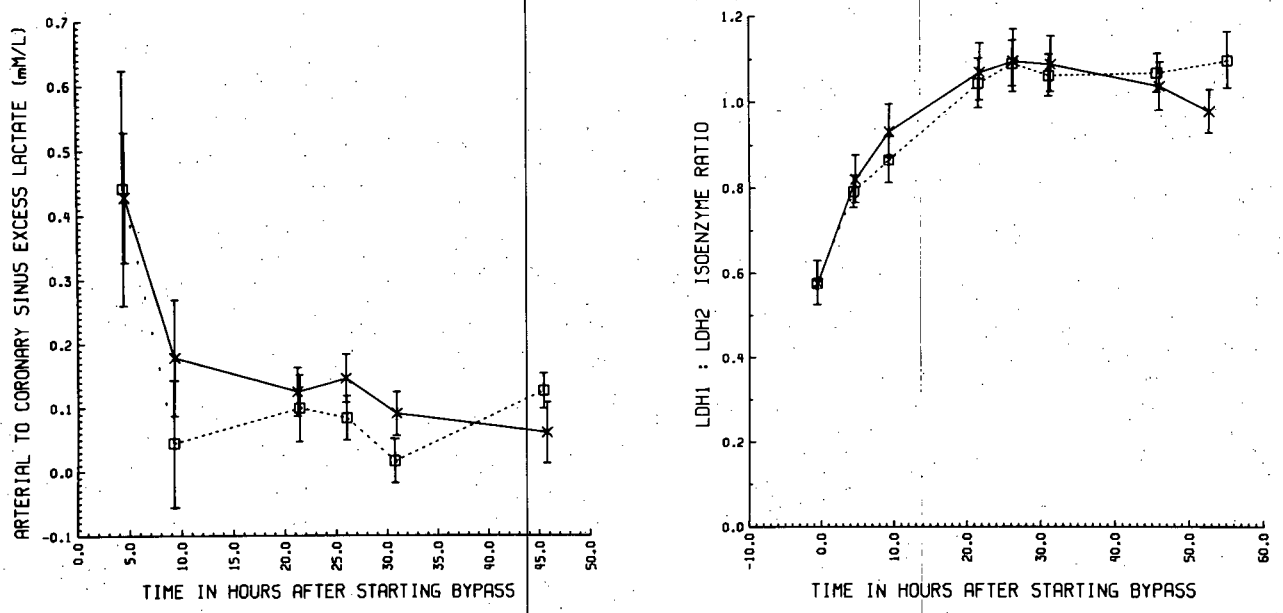

Figure 3

Arterial − coronary sinus excess lactate and percent lactate extraction plotted similarly to figure 1 against time in hours after starting bypass. The X's represent the means for the coronary perfusion group, the open squares, means for the cold ischemic arrest group.

coefficient for left coronary flow = −281 ± 10.4, $P < 0.025$).

Patient Population Variables

No significant differences between the two groups were found for certain vital statistics, diagnostic category, and cardiac symptoms (table 5), nor for certain preoperative quantitative variables (table 6). No significant difference between the groups was found with respect to the preoperative electrocardiogram. One patient in the coronary perfusion group had the electrocardiographic findings of an old myocardial infarction preoperatively.

Apropos of the Randomization Technique

No significant trend of any variable over the five month study period was found. Six significant individual surgeon differences were found and are presented as a departure from the mean of the other three surgeons: a higher cardiac index intercept (0.44 $L \cdot min^{-1} \cdot m^{-2} \cdot hr^{-1}$, $P < 0.005$); a slower return of excess lactate to zero (−2.83 $mM \cdot L^{-1} \cdot hr^{-1}$, $P < 0.03$); a lower myocardial temperature at aortic crossclamping time (−4.32°C, $P < 0.0006$); a higher temperature at the time of crossclamp release (4.55°C, $P < 0.0001$); a shorter aortic crossclamping time (−7.04 min, $P < 0.04$); and a longer bypass time (9.27 min, $P < 0.05$). No significant interaction of a surgeon with the two groups was found.

Discussion

Methods

The randomization was done separately for each faculty surgeon since significant surgeon to surgeon

Table 4

Surgical Variables

	Coronary perfusion			Cold ischemic arrest			Significance level
	Range	Mean ± SE	N	Range	Mean ± SE	N	
Aortic crossclamp time (min)	42–100	68.3 ± 2.54	31	31–74	49.7 ± 1.58	33	$P < 0.0001$
Cardiopulmonary bypass time (min)	58–119	82.4 ± 2.71	30	45–100	65.1 ± 2.13	33	$P < 0.0001$
Myocardial temperature at aortic crossclamping (°C)	28.1–34.4	31.4 ± 0.33	25	15.7–28.1	22.4 ± 0.64	26	$P < 0.0001$
Myocardial temperature at crossclamp release (°C)	24.7–35.6	29.6 ± 0.46	24	16.1–28.8	24.6 ± 0.71	26	$P < 0.0001$

Table 5

Qualitative Population Variables

		Coronary perfusion		Cold ischemic arrest		Significance level
		Number	Percent	Number	Percent	
Sex	Male	26	83.9%	24	72.7%	$P \geqq 0.1$
	Female	5	16.1%	9	27.3%	
Race	White	28	90.3%	29	87.9%	$P \geqq 0.1$
	Black	3	9.7%	4	12.1%	
Diagnosis	Stenosis	21	67.7%	25	75.8%	$P \geqq 0.1$
	Insufficiency	10	32.3%	8	24.2%	
Orthopnea	Positive history	6	19.4%	12	36.4%	$P \geqq 0.1$
	Negative history	25	80.6%	21	63.6%	
Angina	Positive history	17	54.8%	14	42.4%	$P \geqq 0.1$
	Negative history	14	45.2%	19	57.6%	
Syncope	Positive history	12	38.7%	10	30.3%	$P \geqq 0.1$
	Negative history	19	61.3%	23	69.7%	

differences were expected and would have to be removed so that all patients treated by each method could be examined in combined groups. The results demonstrate that this was a necessary precaution. An uncontrolled factor was that some operations were done by a senior resident with the personal supervision of the faculty surgeon to whom the case was assigned. The paired randomization which assured an approximately equal number of patients in each group throughout the study was a protection against trends over the five month study. This precaution was not needed as shown in the results. The third precaution, randomization of all eligible patients for all surgeons, was taken to preclude the argument of patient selection since the study was consecutive. However, this resulted in an unequal number of patients done by each surgeon. The lack of significant differences in patient population variables between the two groups indicates the effectiveness of the randomization procedure. The exclusion of six patients from the study population detracts from complete randomization. The necessity of allowing for such exclusions in therapeutic surgical trials is evident. The method used for handling these exclusions did not involve removing data from the study, so the data set is gapless and completely random. All abortions of randomization consisted of a switch from coronary perfusion to another form of myocardial preservation, thus possibly introducing an unmeasurable bias into the study.

The early postoperative hemodynamic, isoenzyme, electrocardiographic, and metabolic states were chosen for the comparison since mortality and morbidity alone are insensitive parameters and are of such low incidence that an unacceptably large study would have had to have been done to document significant differences. The hemodynamic state was not specifically stressed to demonstrate differences in cardiac reserve, nor were preoperative hemodynamic data available as control measurements for most patients.

The appearance of CPK-MB, with the techniques

Table 6

Quantitative Population Variables

	Coronary perfusion			Cold ischemic arrest			Significance level
	Range	Mean ± SE	N	Range	Mean ± SE	N	
Age (years)	24–77	50.5 ± 2.46	31	22–72	51.0 ± 2.17	33	$P \geqq 0.1$
LV diameter (cm)	7.5–13.0	9.6 ± 0.25	29	7.0–12.5	9.5 ± 0.27	32	$P \geqq 0.1$
LV wall thickness (cm)	2.2–4.8	3.1 ± 0.11	30	2.1–4.0	3.2 ± 0.08	31	$P \geqq 0.1$
Cardiac thoracic ratio	0.40–0.66	0.50 ± 0.014	25	0.35–0.71	0.51 ± 0.015	30	$P \geqq 0.1$
Cardiac index*	1.4–3.6	2.36 ± 0.190	12	1.74–4.11	2.74 ± 0.231	10	$P \geqq 0.1$
Left atrial mean pressure*	4–45	13.5 ± 3.04	14	2.0–28.0	13.3 ± 2.93	9	$P \geqq 0.1$
LV end-diastolic pressure*	5–37	21.9 ± 3.69	10	5–37	21.0 ± 3.08	11	$P \geqq 0.1$

LV = left ventricular.

*Obtained at cardiac catheterization preoperatively.

used in this study, has been shown to be specific for myocardial necrosis.[8] In the absence of hemolysis, as was so in this study, the finding of $LDH_1 > LDH_2$ is also considered indicative of myocardial necrosis.[15] When both these are present in patients with acute myocardial infarction from coronary artery disease, myocardial necrosis has clearly developed.[8]

Data

The hemodynamic state of patients in whom coronary perfusion was utilized has not been shown with confidence to be different from that of patients in whom cold ischemic arrest was employed. The occurrence of significant differences in 2 of 60 tests from study period to study period was no greater than expected by chance alone. However, differences between the groups with respect to cardiac index, heart rate, arterial mean pressure, systemic resistance, right atrial mean pressure, and coronary blood flow index, while not significant due to large patient to patient variability, were significantly larger than experimental error. Therefore the evidence from this study is insufficient to draw a conclusive inference that there is no difference in these variables between the two groups. Since stroke volume was practically identical in the two groups, the difference in cardiac index resulted from a difference in heart rate. The latter, and differences in arterial pressure and resistance, may result from differing extrinsic autoregulatory effects upon the circulation resulting from differing cardiac and whole body temperatures during cardiopulmonary bypass in the two patient populations.

We failed to demonstrate a relation between cardiac output early postoperatively and the myocardial temperatures or aortic crossclamp time in the cold ischemic arrest group. Since the mean aortic crossclamp time plus two standard deviations was 68 min, we know nothing from this study of the effects of longer periods of cold ischemia. Some of the variability in myocardial temperature around the mean of 22.4°C at aortic crossclamping and 24.6° at release may have resulted from variability in depth or location of the thermistor tip. We do not know the effect of lower or higher myocardial temperatures during cold ischemic arrest. The duration of direct coronary perfusion (about 10 min less than aortic crossclamp time) did not relate to the cardiac output early postoperatively, although the average flow to the left coronary artery did, either as a direct factor or as part of a mechanism which resulted in decreased coronary flow.

The lack of interrelation between cardiac output early postoperatively and isoenzyme changes indicating myocardial necrosis is noteworthy. The hemodynamic function of the rat heart under some circumstances has been shown to be unaltered in spite of enzyme release.[16] However, cardiac reserve may be limited by such events and by electrocardiographically demonstrable myocardial infarctions, and patients more seriously ill and with less cardiac reserve initially than most of the ones in this study might have been more affected by them.

Important findings in this study are that 13% of the patients developed electrocardiographic evidence of myocardial infarction early postoperatively, and another 13% of new ischemic changes; that 69% of the patients developed isoenzyme abnormalities indicative of myocardial necrosis; and that in this setting neither coronary perfusion nor cold ischemic arrest was superior to the other in minimizing these occurrences. Again, the lack of interrelation between isoenzyme changes and length of aortic crossclamping or myocardial temperature in the cold ischemic arrest group, duration of direct coronary artery perfusion in the other group, and duration of cardiopulmonary bypass in both groups, is noteworthy. We have no evidence that larger hearts in either group had a greater tendency to develop these changes, nor that aortic stenosis versus incompetence predisposed to them. However, thicker hearts in the coronary perfusion group did have higher CPK-MB. The incidence of these events in our patients is similar to that reported in patients undergoing coronary bypass grafting for ischemic heart disease.[17] This all suggests that factors common to both study groups and to patients undergoing coronary bypass grafting (and probably other procedures as well) are responsible for these serious developments. These may include exposure of the heart at the start of cardiopulmonary bypass to the perfusate from the pump oxygenator with its denatured protein,[18] microaggregates of platelets and fibrin,[19, 20] and microemboli of air. The strength of these common factors may be so great as to mask in our study the additive effects of myocardial ischemia with its depletion of intracellular glycogen[21, 22] and high energy phosphate reserves.[23, 24]

Abnormal cardiac metabolism reflected by lactate concentration differences across the heart has been reported previously for both coronary perfusion and ischemic arrest intraoperatively.[25] The finding in the coronary perfusion group that higher early postoperative excess lactate concentrations were associated with lower intraoperative perfusion to the left coronary artery was not unexpected, but we are not able to offer a clear explanation for the inverse relationship observed in this group between left coronary flow rate and left ventricular diameter.

The 27% reduction in aortic crossclamping time

and 21% reduction in total cardiopulmonary bypass time when cold ischemic arrest was employed is of practical significance. In view of this and the failure of this study to show any conclusive difference in the effects of coronary perfusion and cold ischemic arrest on the parameters studied, cold ischemic arrest seems preferable for isolated aortic valve replacement when the crossclamping time can be kept less than 68 minutes and the myocardial temperature between 22° and 24°C.

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