特別講演

# RECENT TRENDS IN MYOCARDIAL PROTECTION

M. V. Braimbridge

Surgeons are constantly balancing good operating conditions with a still relaxed but ischemic heart against the demands of myocardial preservation. We have, for the last ten years, used cardioplegia for all cardiac surgery.

## 1. COMPONENTS OF CARDIOPLEGIC PROTECTION.

The essential components of cardioplegic myocardial protection are hypothermia, asystole, and the additional protection available from a properly formulated solution. To achieve these aims it is necessary to consider the cardiopulmonary bypass technique, the cardioplegic solution, the infusion mechanism and the maintenance of hypothermia.

## 2. CRADIOPULMONARY BYPASS TECHNIQUE

Taking first the cardiopulmonary bypass technique, we have to consider flow and temperature. Bypass is begun with the standard flow of 2.4 $l$/min/m$^2$ until the temperature has reached around 30°C when the aorta is occluded, at which point the flow rate is reduced to 1.5 $l$/min/m$^2$ in order to reduce the flow in the non-coronary collaterals into the myocardium. The temperature of the patient is kept at 25° but the heart is re-warmed some 15 minutes before it is anticipated the aortic clamp will be removed, so that the patient's temperature is 37° when it is.

## 3. CARDIOPLEGIC SOLUTION

We then need to consider which cardioplegic solution to use. Should we use crystalloid or blood cardioplegia, which crystalloid solution should we use, either by itself or in blood, and should we use oxygenated or non-oxygenated solution? We have studied this subiect in David Hearse's laboratory using the isolated working rat heart in which the ventricle is perfused via the left atrium at a pressure of 20 cm of water, and ejects via an elasticity chamber at a head of pressure of 100 cm of water when the aortic flow can be measured. The heart can also be perfused in the non-working Langendorff mode and cardioplegic solutions can be infused into the root of the aorta. Coronary sinus flow can be measured

*Dept of Cardiothoracic Surgery, St Thomas Hospital, London.

and analysed.

**a. Potassium**

We looked first at potassium in the Langendorff mode. It was not necessary to increase the potassium concentrtaion beyond 20 mmoles in order to produce asystole. It is of importance to note that increasing concentration of potassium is vasoconstrictive as the coronary flow rate falls off.

**b. Magnesium**

In the protocol for the working mode the working heart has a period of stabilization which is taken as 100% aortic flow. It is then subjected to the cardioplegic infusion, followed by the ischemic interval and then the heart is allowed to recover with the peak recovery being expressed as a percentage of the control and the next few studies will be related to this recovery area. Applying this to magnesium a series of recovery curves show that with the addition of concentrations of magnesium from 02 up to 16 mmoles there is increasing improvement of recovery. If however the concentration is increased further to 20, 25 and 50 mmoles, recovery falls off. A dose-response curve for magnesium can be drawn. At a level of 16 mmoles there is peak recovery of aortic flow. This recovery can be plotted against ATP and creatine phosphate levels in the individual hearts and it can be shown that recovery correlates with preservation of energy rich phosphates with a probability of .001.

**c. Calcium.**

The same can be done for calcium. Fumio Yamamoto worked on this study and showed that the dose response for calcium gave a peak protective concentration of 1.2 mmoles.

**d. Local anesthetics.**

Early cardioplegic solutions from Germany used a high concentration of procaine and we investigated the dose-response curve for procaine showing it to be around 0.2 mmoles. The same type of dose-response curve can be found for lignocaine (lidocaine).

**e. St Thomas' Solution No. 1**

Following these experiments therefore, we designed the St Thomas' solution number 1, which consisted of a litre of 4°C of Ringer's solution to which had been added a 20 m*l* ampoule containing 16 mmoles of potassium chloride making the concentration of potassium to 20 mmoles, 16 mmoles of magnesium chloride and 1 mmole of procaine. So our answer up to this year has been that we should use a crystalloid solution, that the crytsalloid solution should be the St Thomas' solution number 1 in which the ampoule is manufactured by MacCarthy's in London, and that we should not oxygenate the solution. This solution has a pH of 6 which was chosen because Fleckenstein's early work showed that the ischemic myocardium survived best with a high concentration of potassium and magnesium and a low pH.

**f. St Thomas' Solution No. 2 (Plegisol)**

An investigation of buffering agents has caused us to design a new solution, the St Thomas' solution number 2, which is made commercially by Abbott Laboratories under the name of Plegisol$^{R}$. Our new technique therefore is to use one litre of Plegisol to which has been added 10 mmoles of sodium bicarbonate. The final concentrations are 114 mmoles of sodium chloride, 60 mmoles of potassium chloride, 16 mmoles of magnesium chloride,

1.2 mmoles of calcium and 10 mmoles of sodium bicarbonate. The pH is 7.4 and the osmolarity 324 m/osmoles.

Comparing this buffered solution with our original St Thomas' solution number 1 in the isolated rat heart after 3 hours of ischemia has shown that the recovery was less than 20% with No. 1, whereas using Plegisol the recovery was more than 70%.

**g. Oxygen**

We also looked at the effect of oxygen on these solutions, St Thomas' number 1, the MacCarthy's solution, had a recovery of less than 20% without oxygen whereas when it wsa oxygenated after 3 hours of aortic occlusion, recovery improved to 60% but this still did not reach the recovery in this series produced by unoxygenated Plegisol which was over 80%. In order to find out whether oxygen improved Plegisol we had to increase the ischemic interval to 4 hours. At 4 hours Plegisol produced a 60% recovery when it was not oxygenated but, when it was oxygenated, recovery improved to nearly 90%. So by 1986 we plan still to use crystalloid solution, we plan to use Plegisol rather than the St Thomas' solution number 1, and we plan to use an oxygenated solution.

**h. Comparison with other crystalloid solutions**

It is important to compare any recommended solution that one uses with other popular solutions. We have therefore compared creatine kinase release of the St Thomas' solution No. 2 which causes significantly less damage than Tyer's solution, than lactated Ringer's containing potassium, or dextrosesaline containing potassium, all solutions that were in use at one time at Duke University at Durham. Various physiological parametesr-aortic flow, volume, minute work, dp/dt, cardiac output and coronary flow-all show a significant improvement ($p=0.01$) of Plegisol over the other commonly used American solutions.

**i. Calcium antagonists**

Dr Yamamoto has also looked at calcium antagonists such as Nifedipine. Once again a dose response curve can be noted at normal temperatures for nifedipine which at 0.1 mmole significantly improved the aortic flow and significantly reduced creatine kinase release. However the affect of temperature was significant. Looking at three calcium antagonists, Verapamil, Nifedipine and Diltiazem at their optimal concentrations at normal temperatures, one can see significant improvement in terms of recovery of aortic flow with each of them, particularly with Nifedipine. However, at 20°C one can see that adding nifedipine to the solution produced no effect whatsoever. We have not therefore included calcium antagonists in our solution.

**j. Creatine phosphate**

I would like to present to you creatine phosphate as a potential additive to cardioplegic solutions. Its particular value is in the management of arrhythmias. Between concentrations of 10 and 25 mmoles there was no necessity for electrical defibrillation, all hearts starting spontaneously, and at 15 momles there was a significant shortening of the time it took for the hearts to return to sinus rhythm. Not only is creatine phosphate valuable for dysrhythmias but in terms of percentage recovery of function-aortic flow, minute work, stroke volume, cardiac output and coronary flow-there was a significant improvement when 10 mmoles of creatine phosphate had been added to the cardioplegic solution in the hatched bars compared with the control in the clear bars. This solution has been in use clinically

in Russia and has been shown to significantly reduce dysrhythmias after cardiac surgery and to improve myocardial preservation.

**k. Free radicals**

We have also looked at oxygen free radicals. If allopurinol, a xanthine oxidase inhibitor, is used to pretreat rat hearts there is a significant improvement of myocardial function in terms of cardiac output, stroke volume and stroke work, compared with the controls ($p=0.01$). Protection of the reperfused heart from the effects of oxygen free radicals is therefore a potential future advantage in myocardial protection.

**l. Filter**

We have also looked at the necessity for using a filter. Commercial solutions used for intraveneous use are permitted by the British and US Pharmacopoeias a certain number of particles. If the St Thomas' solution is made up in a standard commercial intravenous solution and is not filtered, after twenty minutes coronary flow has decreased markedly to 30%. If however the solution is put through a 0.8 micron filter then this affect is abolished. That the affect is due to spasm produced by the particles is shown by the action of various vasodilators such as Nifedipine, which can partly abolish this affect. This is also true of procaine which has probably been an important component of the St Thomas' solution number 1 that contained 1 mmole of procaine. The type of filter that is available commercially for filtering intravenous solutions is the Pall filter.

## 4. METHOD OF INFUSION

Having decided to use cardioplegia, it is necessary to define the method of infusion.

**a. Initial infusion**

Initially 1 litre of 4°C solution is given over 2–3 minutes which produces approximately 40 mmHg pressures in the root of the aorta, although this is necessarily higher in coronary artery disease. The bag is squeezed by hand. To monitor the initial distribution of cardioplegia we look for immediate uniform asystole, a temperature of 15°C and the flow of cardioplegia from the right atrium on total bypass to become clear. Subsequent infusions are of 500 m*l* of the St Thomas' soltuion every thirty minutes. Monitoring the adequacy of the cardioplegia means no return of electromechanical activity, either of the atria or the ventricles, and that the temperature should remain below 15°C.

**b. Left heart venting**

Of all the different techniques of venting the left ventricle via the aorta, left atrium, pulmonary artery, left ventricle, or no venting at all, we normally vent via the aorta forcoronary artery disease and through the pulmonary artery for valve disease. We perform all our proximal anastomoses in coronary artery surgery with a single application of the aortic clamp. When the aortic clamp is removed the heart is reperfused with fully oxygenated blood to every part. The advantage of this has been that we have virtually eliminated heart block as a post operative problem by re-warming the heart to 37° before removing the aortic clamp (in coronary artery disease fully perfusing each artery). When heart block does occur, sequential pacing with atrial and ventricular leads can be lifesaving.

## 5. MAINTENANCE OF HYPOTHERMIA

Having cooled the heart it is necessary to maintain the level of hypothermia. Rosenfeldt has shown that heat gain in the myocardium comes from the surrounding mediastinum, liver and lung, from room air, from non-coronary collaterals and from venous blood. We separate the heart from mediastinum, liver and lung with a corrugated latex rubber sheet, room air with a cool operating room and pericardial 4° Hartmann's solution, the non-coronary collateral circulation by reducing the core temperature to 25°C and reducing flow to 1.5 $l/min/m_2$ of systemic flow rather than 2.4 $l/min$, and with caval snares on total bypass to keep venous blood out of the right atrium.

## 6. MAXIMUM AORTIC OCCLUSION TIME

With this technique we need to know the maximal aortic occlusion time. We have looked at our cases of prolonged aortic occlusion of more than 120 min and have noted the length of aortic occlusion. Patients who had no complications of low cardiac output or mortality had on average an occlusion time of 130 min, both in multiple valve replacements and in coronary artery grafts with valve replacement, whereas those patients who either died or who had post operative complications on average had aortic occlusion times of around 170 minutes suggesting that the safe aortic occlusion time is around 150 min. When we looked at those cases who had had the aortic clamp on for more than 150 min we noted that the cut off was higher, around 170 or even 200 minutes. 23 multiple valves and 24 valves and coronary artery grafts who had the aortic clamp on for almost three hours had however no complications.

## 7. ASSESSMENT OF MYOCARDIAL PROTECTION

Clinical assessment of myocardial function following cardiac surgery is not easy. People use incidence of mortality or low cardiac output, physiological measurements such as left ventricular function curves, the incidence of infarction on the electrocardiogram, cardiospecific enzymes such as CKMB, scintigraphy and biopsy of the left ventricle.

### a. Myocardial biopsy

We take biopsies with a drill or Trucut needle making a 1.5 mm core of full thickness ventricular muscle. The biopsies are taken at the beginning and the end of bypass. We separate the endo- and the epicardium of both left and right ventricles. Biopsies are cooled in a cryostat and a frozen section is made and looked at under a polarizing microscope. In polarized light disoriented molecules show dark whereas oriented molecules show light. If we look at a frozen section of myocardium in air very little polarized light passes through. If ATP and calcium are added, the molecules become oriented and more light passes through. The difference between these two can be measured.

If the myocardium is damaged already more light passes through and adding ATP and calcium produces a smaller difference. At post mortem adding ATP and calcium to the muscle produces no difference. We have compared this mesaure of myocardial function on the biopsies with physiological measurements at the time of cardiac catheterisation and angiography with pressures being measured instantaneously. Left ventricular volumes are

measured and 8 different monitors of left ventricular function were used to separate the groups into good and bad ventricles. At the same time a bioptome biopsy is taken transeptally from the left ventricle. The biopsy separated those patients with good left ventricles from those patients with bad left ventricles on the basis of the birefringence tests with a probability of 0.001. This biopsy assessment therefore correlates well with physiological function.

The way in which we use this biopsy is shown by the birefringence change in response to ATP and calcium taken before bypass and after bypass in a patient who has had no problems there was no difference. A patient who goes into failure post-operatively has a considerable decrease in birefringence range. We have come to know that a change in birefringence (that is the optical path difference) of the myocardial fibres in response to ATP and calcium showing a decline in value of more than .40 during bypass indicates serious myocardial dysfunction.

**b. Clinical results and biopsy assessment**

Before 1975 we used to use coronary artery pefusion for all surgery but since 1975 we have used cardioplegia. The results of biopsies taken in these three groups of patients, those with continuous coronary perfusion before 1975, those in 1975 and the beginning of 1976 where we used a single infusion of cardioplegia, and those subsequently in which we have used multiple infusions. With coronary perfusion before 1975, only 20% of the biopsies showed protection of the endo-and epi-myocardium. 60% showed deterioration of the endomyocardial half of the biopsy alone and there was very little deterioration of the epimyocardial heart. When we began to use cardioplegia with a single infusion, the good preservation of both endo-and epimyocardium increased to 60% and we abolished endomyocardial deterioration alone completely. However there was a considerably greater amount of deterioration of the outer part of the myocardium. When we repeated multiple infusions and added surface cooling, 85% of patients had good preservation of both parts of the left ventricular myocardium and the incidence of external deterioration was considerably reduced. Multiple infusions of cardioplegia therefore, on our biopsies, was the best technique.

We then looked at results with these three techniques in our clinical practice. In single corrective procedures (single valve replacement and coronary artery surgery alone) using continuous coronary perfusion or intermittent aortic occlusion, 73% of patients had good myocardial protection with no deterioration, but 27% had deterioration on the biopsy. When we used single infusions in 72 patients this number increased to 85% and the incidence of deterioration fell to 15%. With multiple infusions there was no deterioration in 94% and deterioration decreased to 60% in 179 patients. The clinical results run parallel. In 193 single corrective procedures (single valve replacement or coronary artery bypass grafts) with continuous coronary perfusion at 32°C, 81% had an uncomplicated post operative course, 8% had a low cardiac output and 11% died. With single dose cardioplegia, 89% had no complications, 10% had a low cardiac output and mortality was 1%. Multiple infusions made very little difference over this shorter period of ischemia, reducing the low cardiac output to 6% only which is not significant.

When we look at double valve procedures with coronary perfusion the pattern was rather different. 75% of a small number of patients had no deterioration but 25% had

deteriorated on the biopsies with ocntinuous perfusion. Single infusion cardioplegia now however showed inadequate protection of the myocardium over this longer time wth only 47% good preservation on the biopsy and 53% had deteriorated. Multiplie infusions of this longer time returned the situation very much to what it had been at coronary perfusion.

The comparable clinical results showed that with continuous coronary perfusion 64% had no complications, 20% had a low cardiac output and 16% died. With single infusion in these longer periods the incidence of low cardiac output rose to 27% and mortality to 18% and these were significantly improved with multiple infusions, with 76% no complications, 13% low cardiac output and 11% mortality.

Taking all valve replacements with continuous coronary perfusions the incidence of deterioration was 26%, with single infusion 23%, and with multiple infusions 13%. This was reflected in the clinical findings of an 11% low cardiac output and 12% mortality with continuous coronary perfusion, 15% low cardiac output and 6% mortality with single infusion cardioplegia and 7.5% and 4.5% complications in 265 multiple infusions.

### c. Special problem of right heart protection

We then looked at the special problems of the right heart with 64 patients in which we had done both left and right ventricular biopsies. We shoved that in this group 4.6% of the left ventricles deteriorated but 9.4% of the right ventricles deteriorated. We therefore now protect the right heart by establishing total bypass with right heart cooling with 4°C Hartmann's solstion via an infant feeding catheter beside the SVC cannula.

In the clinical assessment of myocardial function, biopsy assessment of myocardial preservation correlates with the post operative course is independent of correction of the caridac defect, it discriminates between the inner and the outer layers of the myocardium and between different areas of the myocardium such as the right ventrilce, it allows continual monitoring of myocardial preservation techniques, and the result is available to the surgeon within one half and three hours which enables him to go straight back to the perfusionist and the anesthetist if evidence of deterioration has been shown.

## 8. EDEMA

Using a scanning densitometer we can look at frozen sections of muscle under polarized light with 2 beams. The reference beam monitors the background and the beam through the specimen is retarded by a degree depending on its optical path difference and therefore its density. If it is retarded half a wave length it appears black. A frozen section of myocardium can be passed through a scanning densitometer which shows the cellular areas as the peaks and the troughs the intracellular material. This can be integrated, this intergrated value per cm trace compared with the standard dry weight/wet weight analysis of water correlating with a probability of 0.001. A noraml rat heart at the beginning of a Langendorff perfusion becomes edematous. At the end of the perfusion with Ringers solution the peark drop considerably, showing cellular edema, and the troughs almost meet the base line, showing marked intercellular edema and the intergrated number has fallen. Edema rarely occurs in patients. For instance in a patient who had an aortic valve replacement with 2 litres of crystalloid cardioplegia, the peaks remain high and the troughs are shallow with the integrated number around 44 units/cm. At the end of bypass the

integrated number is 42, in other words there has been no cellular nor intercellular edema. On the other hand, a patient following aortic valve replacement and coronary artery grafts who had no edema before surgery at 38 units/cm, after surgery showed cellular edema and the value had fallen to 19 units. This patient developed severe low cardiac output post operatively.

We believe therefore that microscopic interferometry and densitometry in studying the myocardium has advantages over traditional wet/dry weight analyses of edema in that the water content can be accurately measured in sections of small tissue samples, the distribution of water in the tissue between cellular and intercellular edema is shown, the technique is rapid, the result is available within hours, and the method is non destructive in that the rest of the biopsy can be used for other types of study.

## 9. SUMMARY

In summary we believe that the technique of myocardial protection that we have developed is simple, is certainly cheap and I hope I have been able to show you is effective. There are however still some residual problems. These are temporary heart block, which we in our hands have largely eliminated by re-warming the patient to 37°C before removing the aortic clamp, supraventricular arrhythmias which can be largely abolished by cooling the right heart. Modification of reperfusion, perfusing the aorta with different solutions immeidatey before removing the aortic clamp, has received a lot of publicity recently but we use normal blood at 37°C only. Patients who require ischemia for more than 150 min are still a problem and the problems of cardioplegia in infants has not yet been answered.