

Left Ventricular Function After Ischemic Cardioplegia

Role of Spontaneous Cardiac Hypothermia and the Bronchial Artery— Coronary Artery Collateral Circulation

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Previous experiments in this laboratory have demonstrated that ischemic cardioplegia results in depression of subsequent ventricular performance, the severity of which is a function of the duration of aortic occlusion. Contractility progressively improves with time, however, and if the period of occlusion is not longer than 30 minutes the contractile state of the myocardium frequently returns to near normal levels.¹ These findings, in addition to the clinical observation that many patients appear to tolerate relatively prolonged periods of normothermic ischemic cardioplegia, suggest that adaptive mechanisms protect the myocardium during a period of aortic occlusion. The roles of spontaneous cardiac hypothermia and the bronchial artery—coronary artery collateral circulation in protecting the myocardium during periods of normothermic ischemic cardioplegia were determined in the experiments described in the following report.

Materials and Methods

Mongrel dogs weighing 19 to 24 kg (42 to 53 lb) were anesthetized with

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intravenously administered pentobarbital sodium (35 mg/kg). A cuffed endotracheal tube was inserted and ventilation was maintained by a positive pressure respirator supplying oxygen. A bilateral transsternal thoracotomy was performed, a catheter was placed in the aorta through the right subclavian artery for the measurement of mean aortic pressure, and heparin sodium (3 mg/kg) was administered intravenously.

Blood temperature was monitored by a thermistor in the inferior vena cava and maintained at 37 C by a heat exchanger in the extracorporeal circuit. The sinoatrial node was crushed, and the heart rate maintained constant during the functional assessments by electrical stimulation of the right atrium at 170 beats per minute. The heart was suspended in a pericardial cradle, and cardiopulmonary bypass was instituted by cannulation of the right atrium and femoral artery. Arterial inflow was measured by a calibrated electromagnetic flow probe placed in the line returning blood to the animal and was maintained at a flow rate sufficient to maintain mean aortic pressure at 100 mm Hg when assessments of ventricular function were being performed; at other times a flow rate of 80 to 100 cc per kilogram per minute was provided. The main pulmonary artery was ligated, and the mitral valve occluded with a fenestrated plug which drained coronary blood returning directly to the left ventricular cavity. Isovolumetric left ventricular contractions were obtained by inserting a latex balloon attached to a metal cannula into the cavity of the left ventricle through a stab incision at its apex. The balloon

was deflated except during assessments of ventricular function, when ventricular volume was established by inflating the balloon with a measured volume of saline. The preparation is diagrammatically illustrated in Fig 1.

Left ventricular function was assessed by systolic length-tension, force-velocity, and diastolic pressure-volume (diastolic compliance) determinations before, and 30 and 60 minutes after a period of occlusion of the ascending aorta. Left ventricular end-diastolic pressure, the full left ventricular pressure pulse, and the rate of development of left ventricular pressure were simultaneously recorded as the volume of the intraventricular balloon was increased to 25 ml in a stepwise fashion. Systolic length-tension curves were constructed by plotting the peak systolic isometric force developed versus the increase in internal ventricular radius. Force-velocity curves were inscribed by determining the instantaneous relations between force and contractile element velocity at 10-msec intervals during the course of single isovolumetric beats. The methods utilized for the calculation of force and contractile element velocity and ventricular radius were identical to those described previously.² If ventricular fibrillation resulted following aortic unclamping, normal rhythm was restored by countershock. Twenty-one dogs comprised three groups.

Group 1.—In six animals the effects of 30 minutes of aortic occlusion on subsequent ventricular function were determined. In four additional dogs intramyocardial thermistors were positioned deep in the anterolateral and posterior left ventricular myocardium. While blood temperature was maintained at 37 C, myocardial temperature was continuously recorded beginning ten minutes before and during the 30-minute period of aortic occlusion.

Group 2.—The effects of 30 minutes of aortic occlusion on subsequent ventricular function were determined in five dogs in which all branches of the thoracic aorta were divided except the coronaries and the brachiocephalic vessels, in order to exclude all extracoronary myocardial blood flow.

Group 3.—In five dogs in which ventricular function studies were carried out, the myocardium was maintained at 37 C by covering the heart with blood and approximating the thoracic

incision during the period of aortic occlusion.

Functional assessments were performed before and after aortic occlusion in one dog in which extracoronary myocardial blood flow was eliminated and myocardial temperature was maintained at 37°C during the period of aortic occlusion.

The length-tension curves and diastolic pressure-volume curves inscribed in each animal 30 and 60 minutes after restoration of normal coronary blood flow were compared to the curves inscribed in the same animal before the aorta was occluded. Impaired ability to generate force and decreases in compliance were expressed as the percent change, computed as the average change between the control force or compliance values and those determined 30 and 60 minutes after aortic unclamping.

Results

Group 1: Thirty Minutes' Normothermic Ischemic Cardioplegia.

—Thirty minutes after unclamping, persistent ventricular fibrillation obviated functional assessment in one dog; in the others average peak systolic isometric force decreased 34% when compared to the force generated before the aorta was cross-clamped. Sixty minutes after unclamping, average peak systolic isometric force was decreased 15% when compared to control values, but in three animals peak force levels returned completely or almost completely to control values. Diastolic compliance decreased an average of 13%, determined 30 minutes after unclamping, and a 30% average decrease was evident 60 minutes after restoration of normal coronary blood flow. In this group, as well as in the following groups, the simultaneously determined force-velocity curves demonstrated a functional deficit of comparable magnitude to that evidenced by the length-tension curves. Decreases in maximum measured velocity, and in its extrapolation to maximum velocity, were evident and would be indicative of a diffuse rather than regional insult to contractile function.³

Typical length-tension curves, force-velocity curves, and diastolic

pressure-volume curves inscribed in an animal from this group are reproduced in Fig 2 to 4.

In the four dogs in which intramyocardial temperature was measured, the posterior left ventricular myocardial temperature averaged 36.8°C (range 36°C to 37°C) and the anterolateral left ventricular myocardial temperature averaged 31°C (range 29.5°C to 32°C). No changes occurred during the control period of observation. Following aortic occlusion, however, myocardial temperature decreased immediately and progressively; anterolateral left ventricle averaged 29°C (range 27.7°C to 30°C), posterior left ventricle averaged 34°C (range 33.8°C to 34.5°C) at 30 minutes (Fig 5).

Group 2: Thirty Minutes' Normothermic Ischemic Cardioplegia Without Bronchial Artery Flow.

—Assessments could not be performed in one dog because of persistent ventricular fibrillation. In the other dogs, average peak systolic force decreased an average of 59% 30 minutes after unclamping, and a 38% decrease persisted one hour after unclamping. Compliance decreased an average of 21% 30 minutes after unclamping and further decreased to 37% 60 minutes after unclamping. Typical length-tension curves inscribed in an animal from this group are reproduced in Fig 6.

Group 3: Thirty Minutes' Normothermic Ischemic Cardioplegia With Myocardial Temperature Maintained at 37°C.

—Assessments could not be performed in one of the dogs in this group because of recurrent ventricular fibrillation. In the other five dogs, a 57% average decrease in peak systolic isometric force was evident 30 minutes after unclamping and a 34% decrease was present 30 minutes later. Decreases in compliance averaged 25% at 30 minutes and 32% 60 minutes after unclamping. Typical length-tension curves inscribed in an animal from this group are reproduced in Fig 7.

Ineffectual ventricular contractions were present after aortic unclamping in the dog in which myocardial temperature was maintained at 37°C, and the bronchial

arteries were ligated. Ventricular fibrillation resulted at very low levels of intraventricular pressure, making functional assessment impossible both 30 and 60 minutes after unclamping, but it appeared that complete depression of ventricular function was evident.

The data from all animals are summarized in the Table.

Comment

Anastomoses between the bronchial and coronary arterial circulations have been known to exist for many years, but their functional significance has not been established.⁴⁻⁶ Littlefield and Ingram⁷ and Littlefield et al⁸ have measured the volume of blood delivered to the isolated coronary arterial bed through these channels under circumstances in which the systemic circulation was maintained by cardiopulmonary bypass, and there was no opportunity for arterial flow into the coronary artery ostia. Their studies demonstrated that the small amount of flow present in normal dogs was greatly augmented following chronic pulmonary arterial ligation, but the direction of blood flow in the intact dog was not determined. Although these findings have been frequently discussed in recent years, doubt regarding the direction of flow through these channels in animals with intact circulations has created uncertainty regarding the functional significance and clinical applications of these experiments. When the ascending aorta is occluded during cardiopulmonary bypass, however, coronary hemodynamics are identical to those established by Littlefield and his associates during their experiments, and under these circumstances the bronchial circulation provides arterialized blood to the heart. In the present experiments the functional significance of the coronary flow supplied by the bronchial arteries when the ascending aorta is occluded was determined. Comparable periods of ischemic cardioplegia induced by occlusion of the aorta produced significantly less impairment of myocardial contrac-

tility in dogs with normal bronchial collateral circulations than in dogs in which the bronchial arteries were ligated. The protection provided to the myocardium by the bronchial circulation during aortic occlusion in some patients may even be considerably more than was demonstrated in the normal dog because the physiologic abnormalities of cardiopulmonary function which are frequently present in patients may augment this collateral circulation, as has been demonstrated to occur in the dog following chronic pulmonary artery ligation.

When arterial circulation to an extremity is impaired, a decrease in the temperature of the extremity results as a consequence of exposure to ambient temperature. It seemed probable, therefore, that some degree of cardiac hypothermia would spontaneously occur following interruption of coronary blood flow, and the results of the present study confirm this view. It was also not unexpected that the anterolateral left ventricle became cooler than the posterior left ventricular myocardium, which was in contact with the mediastinum. When the entire heart was surrounded with 37 C blood, thus maintaining myocardial temperature, aortic occlusion produced a much greater deleterious effect on myocardial contractility than did a similar period of aortic occlusion in animals in which spontaneous cardiac hypothermia was allowed to occur. The already decreased myocardial oxygen demands of the noncontracting heart are further reduced by spontaneous cardiac hypothermia, and thus the injury produced by ischemic cardioplegia is ameliorated.

Although the impaired ability to generate force, which was evident soon after restoration of normal coronary artery blood flow progressively improved with time, it is of considerable importance that diastolic ventricular compliance became progressively more impaired as time elapsed. In the present studies ventricular end-diastolic pressure was not used as an index of fiber length, but myocardial fiber length was di-

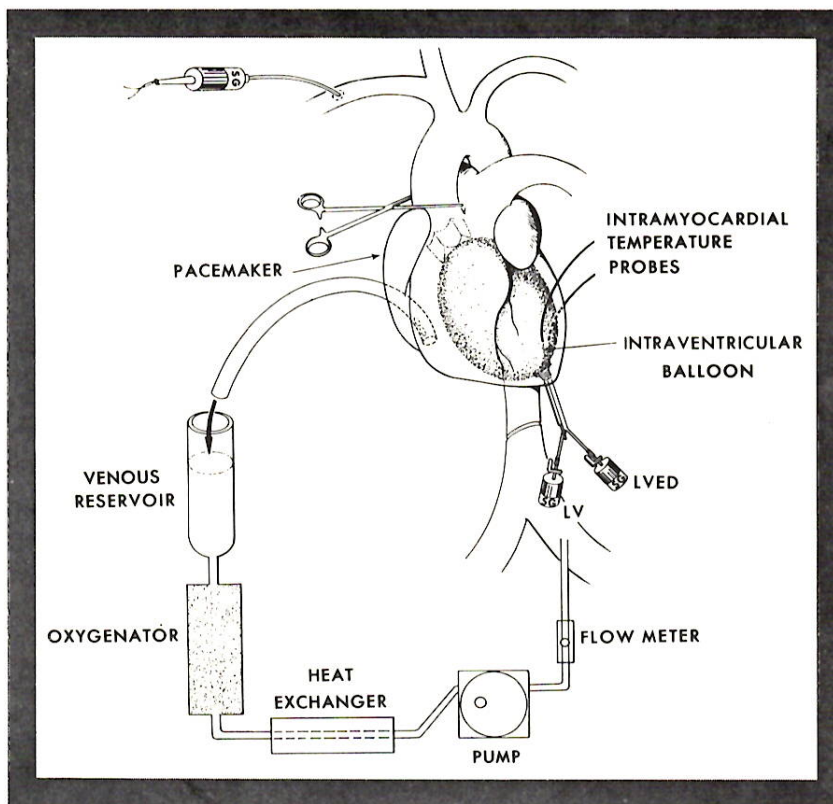


Fig 1.—Schematic representation of preparation used to assess left ventricular contractility and diastolic compliance, or to provide total cardiopulmonary bypass. Intraventricular balloon provided isovolumetric left ventricular contractions. Mean aortic pressure and heart rate were maintained constant during functional assessments. Ischemic cardioplegia was induced by occlusion of ascending aorta.

Decreases in Peak Systolic Force and Diastolic Compliance After Ischemic Cardioplegia

Animal No.	Percent Decrease*			
	Force		Compliance	
	30 min After	60 min After	30 min After	60 min After
1	50	30	0	0
2	22	0	0	0
3	44	25	25	80
4	36	7	15	40
5	Fibrillation	28	Fibrillation	0
6	20	0	25	60
Mean	34	15	13	30
1	66	50	15	20
2	57	31	20	48
3	37	22	29	36
4	Fibrillation	Fibrillation	Fibrillation	Fibrillation
5	74	50	21	45
Mean	59	43	21	37
1	46	24	38	42
2	71	52	40	47
3	52	21	17	37
4	61	47	9	13
5	54	28	19	22
6	Fibrillation	Fibrillation	Fibrillation	Fibrillation
Mean	57	34	25	32

* Decreases in force in group 2 and group 3 animals at both 30 and 60 min were significantly greater than decreases in group 1 dogs ($P < 0.05$). In all groups decreases in force at 60 min were significantly less than at 30 min ($P < 0.01$), and decreases in compliance at 60 min were significantly greater than decreases evident at 30 min ($P < 0.05$).

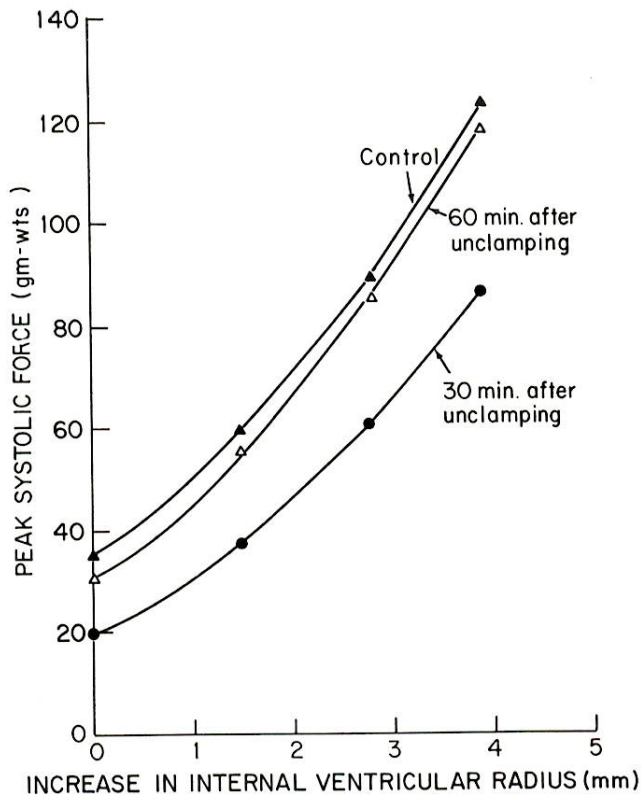


Fig 2.—Length-tension curves inscribed in animal before and after 30-minute period of normothermic ischemic cardioplegia. Thirty minutes after unclamping, moderate depression of contractility is evident. At any given ventricular radius or myocardial fiber length, less peak isometric wall tension was developed after aortic occlusion when compared to tension developed at same fiber length before occlusion. Sixty minutes after unclamping, contractility has nearly returned to control levels.

Fig 4.—Left ventricular diastolic pressure volume curves inscribed in animal before and after 30-minute period of normothermic ischemic cardioplegia. Compliance is decreased 30 minutes after unclamping and further decrease is evident 60 minutes after unclamping.

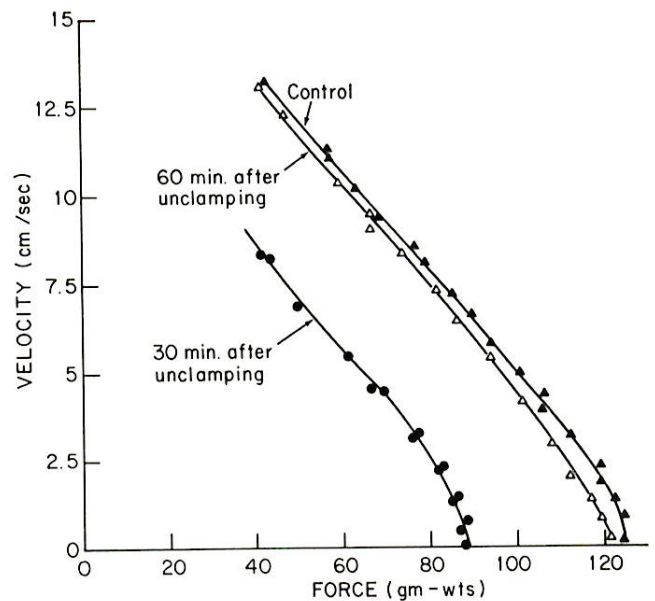
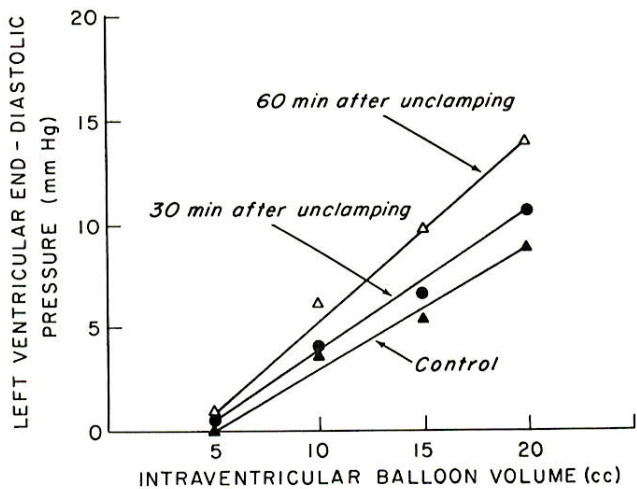
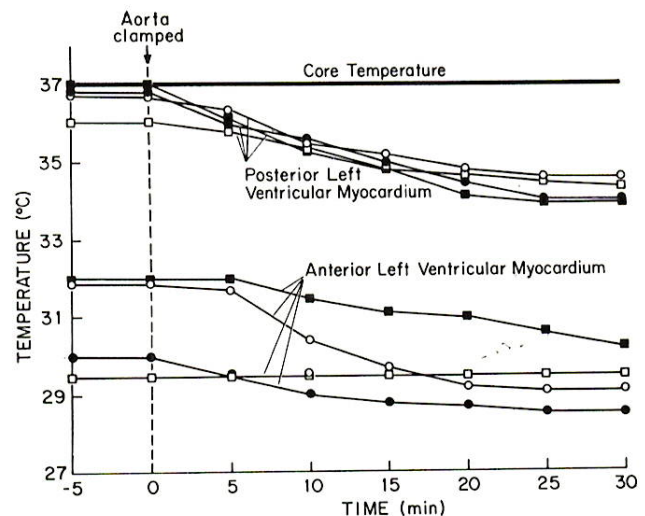


Fig 3.—Force-velocity curves inscribed simultaneously with length-tension curves in same animal. Functional deficit of comparable magnitude to that evidenced by length-tension curves is apparent.

Fig 5.—Temperatures of posterior and anterolateral left ventricular myocardium recorded at five-minute intervals before and during occlusion of ascending aorta in four dogs.



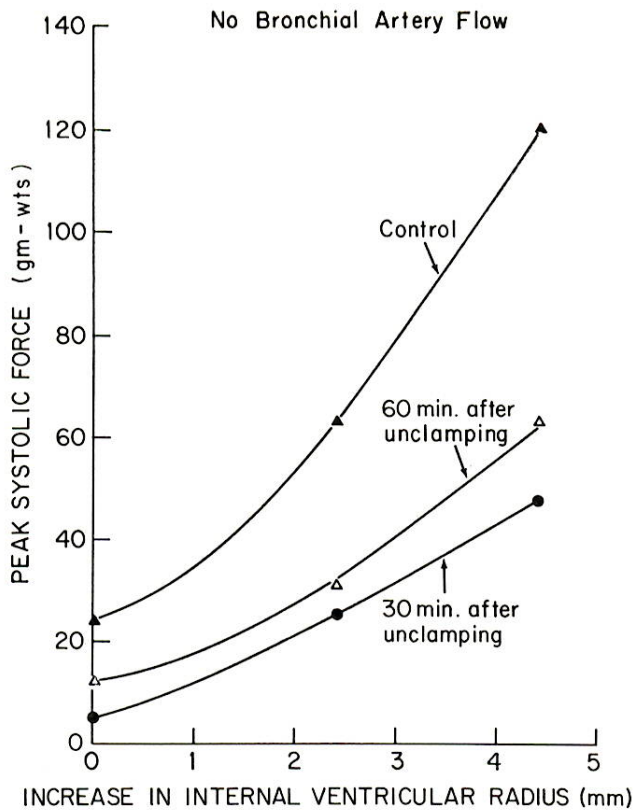


Fig 6.—Length-tension curves before and after ischemic cardioplegia in animal in which bronchial arteries were ligated. Ischemic cardioplegia results in significant and persistent depression of myocardial contractility.

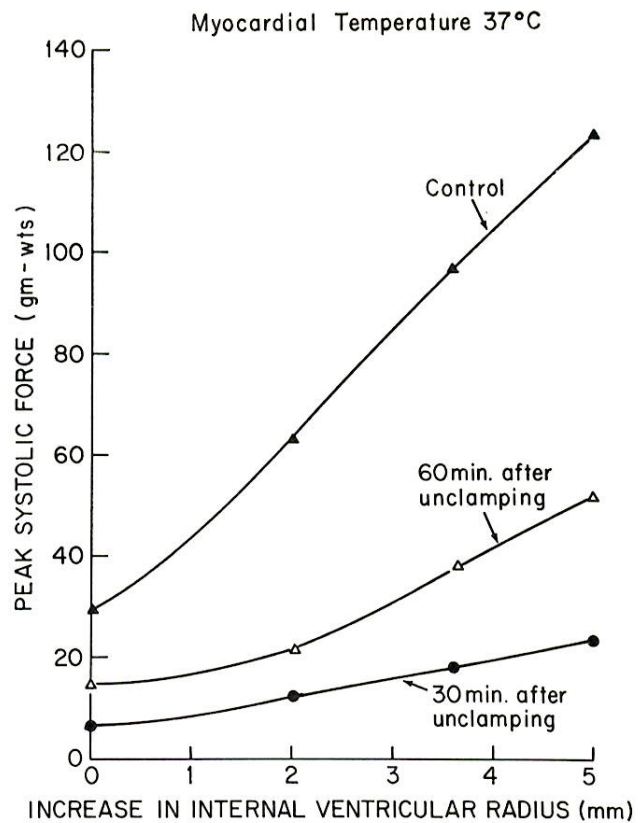


Fig 7.—Length-tension curves before and after ischemic cardioplegia in animal in which myocardial temperature was maintained at 37 C. Severely impaired myocardial contractility is evident 30 minutes after unclamping and although some improvement in function occurs, moderately severe depression persists 60 minutes after unclamping.

rectly determined by the volume of the intraventricular balloon. Although valid assessments of the contractile state of heart muscle were obtained by this method, it should be appreciated that in order to achieve a given level of cardiac performance a higher filling pressure is necessary when compliance is decreased. These considerations may be implicated in circulatory failure which occurs later in the postoperative period in patients in whom cardiac function appeared more adequate in the immediate postoperative period.

Previous studies in this laboratory¹ demonstrated that one hour of aortic occlusion accompanied by coronary artery perfusion with blood at 30 C produced no alterations in subsequent myocardial contractility or compliance. Spontaneous cardiac hypothermia reduces myocardial oxygen demand, and the bronchial collaterals provide some

coronary flow during occlusion of the ascending aorta. These adaptive mechanisms are inadequate, however, and significant depression of ventricular function and decreased diastolic compliance result unless aortic occlusion is accompanied by coronary artery perfusion.

Summary

The effects of ischemic cardioplegia on subsequent ventricular performance were determined in dogs. Employing cardiopulmonary bypass, and with the left ventricle contracting on a balloon, left ventricular function was assessed by force-velocity, systolic length-tension, and diastolic pressure-volume (diastolic compliance) determinations before, and 30 and 60 minutes after a period of aortic occlusion. Blood temperature was maintained at 37 C, and myocardial temperature was measured by intramyocardial thermistors. Thirty minutes of aortic oc-

clusion resulted in moderate depression of contractility and decreased compliance determined 30 minutes after unclamping. Sixty minutes after unclamping, diastolic compliance decreased further but contractility returned to near control levels. Following aortic occlusion, myocardial temperature decreased immediately and progressively: anterolateral left ventricle, to 29 C, and posterior left ventricle, to 34 C, at 30 minutes. When myocardial temperature was maintained at 37 C or if the bronchial arteries were ligated, 30 minutes aortic occlusion caused severe and persistent depression of function. Compliance was also decreased. Spontaneous cardiac hypothermia reduces myocardial oxygen demand, and the bronchial collaterals provide some coronary flow during occlusion of the ascending aorta. These adaptive mechanisms are inadequate, however, and significant depression of ventricular function

and decreased diastolic compliance result unless aortic occlusion is accompanied by coronary artery perfusion.

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Discussion

E. CONVERSE PEIRCE II, MD, Atlanta: I comment on the compliance measurements and the possibility that they might be misinterpreted.

If an animal is given isoproterenol sulfate or any other β -adrenergic agent, there will be an increase in compliance so that unless the hearts are β -blocked, it could be that some neurogenic or hormonal change which occurs after the experimental intervention, rather than a direct action on the heart, accounts for the observed increase in compliance.

JAMES R. MALM, MD, New York: Dr. Cooley, I was hoping you were going to get up because this is suggesting you have been operating on hearts with hypothermia.

DENTON A. COOLEY, MD, Houston: At Baylor, Dr. Beall performed similar studies in dogs and demonstrated the deleterious effects of myocardial ischemia during cardiopulmonary bypass. One may question whether the canine myocardium is less tolerant of ischemia or anoxia than the human.

The body temperature of dogs is

higher than that of humans; and this, plus the known existence of a potentially pathogenic intestinal flora in the dog, may introduce factors which influence the results of the experiment.

A clinical comparison between myocardial ischemia is opposed to myocardial perfusion or hypothermia was done in our hospital by Dr. Robert Bloodwell, who studied the serum enzymes when following patients after aortic valve replacement by the several techniques.

The most critical enzyme was serum phosphokinase. In those patients who had ischemic arrest, a modest but definite increase level of this enzyme was noted in the ischemic group as compared to those who had coronary perfusion. After 48 hours the enzyme levels were almost equal in all cases.

Did the essayists use separate coronary artery perfusion in the dogs? I assume they did root perfusion of the aorta and did not cannulate the individual coronary vessels.

If one elects to use coronary perfusion in clinical cases of aortic valve replacement, he must employ the potentially hazardous technique of individual coronary perfusion and risk injury to artery and capillary network.

An increasing number of surgeons are using ischemic arrest in preference to coronary perfusion in all cases of aortic valve replacement to obviate these hazards.

DWIGHT C. MCGOON, MD, Rochester, Minn: My interpretation of these results is that the myocardium is best preserved by perfusing it and I think that clinical experience would tend also to confirm this view. We haven't found coronary perfusion to be hazardous. I believe a lower operative mortality rate is achieved at centers using coronary perfusion than when ischemia is allowed to persist during the procedure. I think it's also true that most of us would be required to use longer ischemia than might be true in Dr. Cooley's hands; therefore, the difference in viewpoints might be explained from that standpoint.

I don't see why cannulation of the coronary arteries and perfusing them separately is less physiological than putting the blood in a centimeter or two proximal to that point and perfusing through the aortic root, unless trauma to the coronary arteries themselves was caused which would lead to later difficulty. We haven't found this to be true in the majority of patients

or animals that we've studied.

ROBERT L. REIS, MD, Bethesda, Md: With regard to the question relating to compliance, it should be emphasized that in our experiments the conditions existing in each group of animals were identical in every way except for the manner in which the myocardium was protected during aortic occlusion. Therefore, the alterations in compliance which were evident from group to group could justifiably be considered to result from the methods which were employed to protect the myocardium during the period of occlusion of the ascending aorta.

Dr. Cooley raises interesting questions.

We did perfuse the aortic root and not the individual coronary arteries. We certainly would agree, Dr. Cooley, that many patients appear to tolerate relatively prolonged periods of ischemic cardioplegia. If the operative procedure relieves a major mechanical load from the heart, perhaps some degree of impairment of myocardial contractility and compliance can be tolerated. That is, the net gain for the patient may be substantial even though some myocardial injury was produced. Our objective, however, should be to restore cardiac function to the maximum amount possible.

The enzyme changes which you have observed in the early postoperative period are extremely interesting. As you point out, there was a greater rise in the enzyme which reflect myocardial necrosis in the group of patients in whom the coronaries were not perfused compared to the group of patients in whom coronary artery perfusion was employed, but after 24 to 48 hours the enzyme levels were similar in both groups. Since a transient rise in the serum enzyme levels shortly followed by a return toward normal levels is the typical pattern usually seen in patients with acute myocardial infarction, the enzyme changes evident in your patients might suggest that ischemic cardioplegia produced a greater insult to the myocardium than was produced when coronary artery perfusion was employed.

Certainly, there are many differences between the experimental studies which we have done in normal dogs and the circumstances present in patients. It is difficult, therefore, to know precisely how to interpret the results. My personal interpretation, however, is that we should perfuse the coronary arteries.