Experimental Comparison of Methods for Protecting the Heart During Aortic Occlusion *

PAUL A. EBERT, M.D., LAZAR J. GREENFIELD, M.D.,
W. GERALD AUSTEN, M.D., ANDREW G. MORROW, M.D.

From the Clinic of Surgery, National Heart Institute, Bethesda 14, Maryland

WITH the increasing application of open operations in the treatment of acquired lesions of the aortic valve, a variety of methods for protecting the heart during prolonged periods of aortic occlusion have been described. These technics have in fact, become nearly as diversified as the methods utilized in the correction of aortic valvular lesions. Elective cardiac arrest, induced by chemical agents such as potassium citrate, acetylcholine and magnesium, was enthusiastically adopted by many surgeons because of the ideal operative field it provided. Both clinical and experimental studies, however, demonstrated that the use of these compounds caused severe depression of myocardial function and even necrotic lesions in the heart.[6,8,11,15,17] Simple aortic occlusion was found to be superior to chemical cardioplegia but it has been shown by several investigators that anoxic arrest provides a safe period of occlusion of only 20 to 30 minutes. Partial or complete replacement of the aortic valve often necessitates a longer period of occlusion and the grossly hypertrophied, fibrotic heart of a patient with acquired aortic valve disease will not tolerate a prolonged period of hypoxia. Experimental and clinical studies by Littlefield and associates,[9] Bahnson and coworkers[1] and the present authors have shown that myocardial oxygenation can be maintained during aortotomy by perfusion of the left or both coronary arteries with oxygenated blood. The inconvenience of this technic, however, has led to a search for a safe method for prolonged cardiac arrest.

Several investigators have shown that external cooling of the heart reduces its metabolic requirements and permits survival after longer periods of anoxic arrest than are possible when the heart is normothermic.[4,6,7,13,16] Urschel and Greenberg[14] extended this technic by combining external cardiac cooling with an initial coronary perfusion of iced Ringer's lactate solution. Bernhard,[2] Long[10] and Gott[5] have utilized coronary perfusion with cold blood, not only to cool the heart but also to supply its reduced oxygen requirement.

In the present study a number of technics for protecting the heart during prolonged aortic occlusion were evaluated by means of left ventricular function curves. Such curves express the amount of work the ventricle can perform at various filling pressures, and provide the most sensitive and reliable index of myocardial impairment.

Materials and Methods

Adult, fasting mongrel dogs weighing 13.5 to 22 Kg. were utilized. After induction of anesthesia with intravenous thiopental, a cuffed endotracheal tube was inserted and ventilation was maintained by a positive pressure respirator supplying room air. Digoxin (0.025 mg./Kg.) was given intravenously.[18] The right chest was opened through the fourth intercostal space and heparin (4 mg./Kg.) was adminis-

* Submitted for publication May 5, 1961.

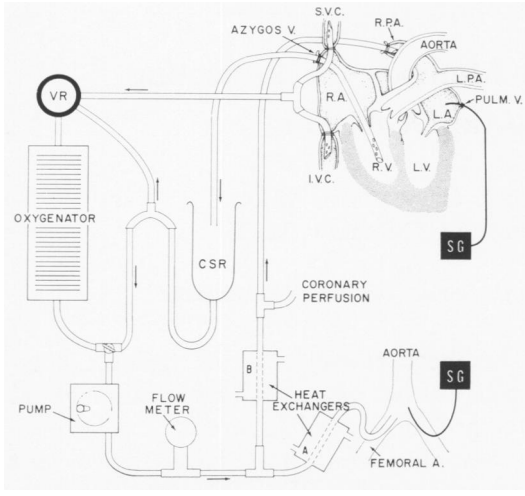

FIG. 1. Schematic representation of the cannulations and extracorporeal circuit utilized to either assess left ventricular function or provide total cardiopulmonary bypass. V.R. = venous drainage reservoir; CSR = coronary return reservoir; SG = Statham pressure transducers. The heat exchanger labelled B controlled the temperature of blood used for coronary perfusion. In establishing ventricular function curves, the venous return bypassed the oxygenator and was pumped through the rotameter into the pulmonary artery. During total bypass vena caval blood was oxygenated and returned to the femoral artery.

tered intravenously. The various cannulations shown schematically in Figure 1 were then carried out. The central aortic and left atrial pressures and the signal from the rotameter were recorded on a multichannel oscillograph. The temperature of the animals was maintained at 34 to 36° C. by a heat exchanger (Fig. 1A). Heart temperature was recorded from a thermistor in the wall of the right ventricle.

Prior to the period of aortic occlusion a control left ventricular function curve was obtained by diverting the venous return from the oxygenator and pumping it, through the rotameter, directly into the pulmonary artery. Left ventricular output (less coronary flow) was then increased in a stepwise fashion while the left atrial and aortic pressures were recorded. Each period of observation lasted two minutes and established one point on the function curve. Each curve was terminated when the mean left atrial pressure reached 26 cm. H_2O or the blood flow exceeded 150 ml./Kg./min.

Left ventricular function was determined by relating left ventricular stroke work to mean left atrial pressure.[12] The former parameter was derived from the equation:

$$LVS = \frac{(Ap - LAp) \times SV}{100}$$

where:

LVS = left ventricular stroke work: gram meters

AP = mean aortic pressure (cm. H_2O)

LAp = mean left atrial pressure (cm. H_2O)

$$SV = \text{stroke volume} = \frac{\text{systemic flow (ml /min.)}}{\text{heart rate}}.$$

Complete cardiopulmonary bypass was then established by diverting the venous blood through the oxygenator and returning it into the femoral artery. Drainage catheters were passed into both the right and left ventricles to decompress the heart during the period of aortic occlusion. Following aortic occlusion, the heart was allowed to recover for a period of ten minutes before defibrillation, if necessary, was attempted. The catheters were removed from the ventricles and a second function curve was inscribed after a total recovery period of 20 min. No drugs were given. When coronary artery perfusion was utilized, the blood was supplied from a T-connector in the arterial return line. The

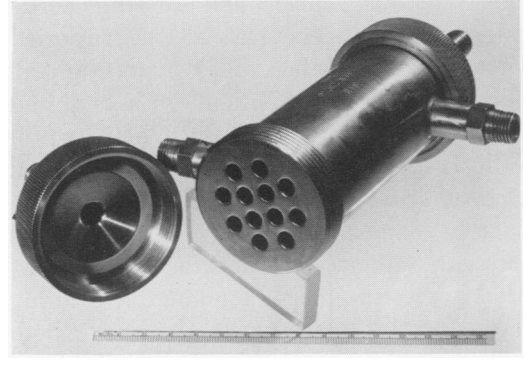

FIG. 2. The small heat exchanger utilized for selective cooling of blood for coronary perfusion. Its volume is 50 cc. and it will cool blood from 37° C. to 15° C. at a flow of 250 cc./min.

temperature of the coronary perfusate was regulated by the second heat exchanger (Fig. 1B, 2).

Left ventricular function was assessed before and after periods of aortic occlusion when the heart was maintained by the following methods:

1. **Control:** Three dogs were subjected to complete cardiopulmonary bypass for a period of 30 minutes without aortic occlusion. Ventricular function curves were inscribed before and 20 minutes after the period of bypass.

2. **Anoxic Arrest—20 Minutes:** In five dogs the ascending aorta was cross-clamped for 20 minutes, while the temperature of the heart and the animal were normal.

3. **Anoxic Arrest—30 Minutes:** In four dogs the ascending aorta was continuously occluded for 30 minutes with normal heart and body temperatures.

4. **Intermittent Normothermic Coronary Perfusion—30 Minutes:** In five animals the proximal aortic segment was perfused with normothermic oxygenated blood during two five-minute periods beginning five and 15 minutes after the aorta was cross-clamped. A short 17-gauge needle, connected to the coronary perfusion line, was inserted into the ascending aorta and supplied a flow of 200 cc./min.

5. **Hypothermic Anoxic Arrest—30 Minutes:** In seven dogs the heart was surrounded with finely chipped ice in saline solution immediately after aortic occlusion. The temperature of the myocardium fell to 10–15° C. within two to three minutes and was maintained at this level by the addition of ice when necessary. At the end of the period of aortic occlusion the heart was rewarmed, as it was in all experiments utilizing local cardiac cooling, by removal of the ice from the pericardium and restoration of coronary flow. The temperature of the heart returned to 34–36° C. within two to five minutes.

6. **Ringer's Lactate Coronary Perfusion and External Cardiac Cooling—30 Minutes:** The method described by Urschel and Greenberg [14] was employed in seven animals. The aorta was cross-clamped, the pericardial sac was immediately filled with crushed ice and saline, and the proximal aorta perfused with iced Ringer's lactate solution for two to three minutes. The temperature of the heart was maintained at 10–12° C. by the application of additional ice.

7. **Intermittent Coronary Perfusion with Cold Blood Combined with External Cardiac Cooling—30 and 45 Minutes:** In six dogs immediately after aortic occlusion the proximal aorta was perfused with oxygenated blood cooled to 15–17° C. After two minutes of perfusion at a rate of 125–150 cc./min., the heart was packed in ice and coronary perfusion continued for an additional three minutes. The proximal aorta was perfused for a second five-minute-period 15 minutes after the onset of aortic occlusion. In four other animals the period of aortic occlusion was extended to 45 minutes and the proximal aorta was perfused with cold blood for an additional five-minute period 30 minutes after cross-clamping of the aorta.

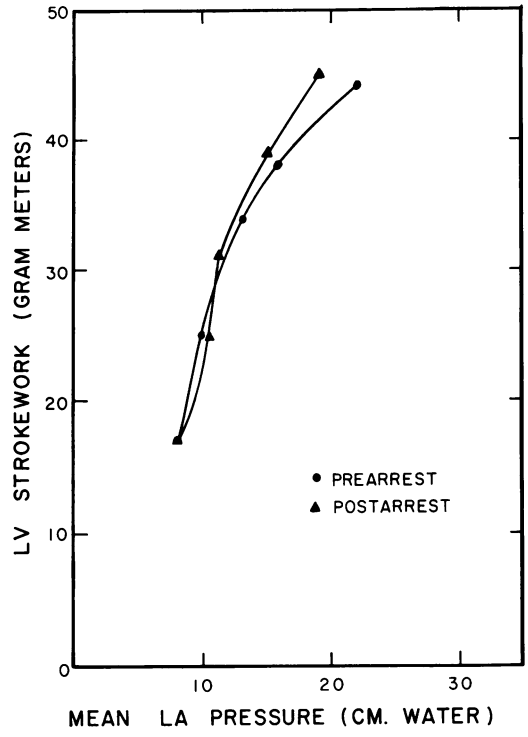

FIG. 3. Left ventricular function curves inscribed before and after 30 minutes of cardiopulmonary bypass without aortic occlusion. The curves are representative of those showing minimal depression of function.

Results

Pairs of ventricular function curves cannot be related by any simple mathematical index and in each experiment the curve obtained after aortic occlusion was classified, in comparison with the preocclusion curve, as showing minimal, moderate or marked depression of function. In some experiments depression was so severe that

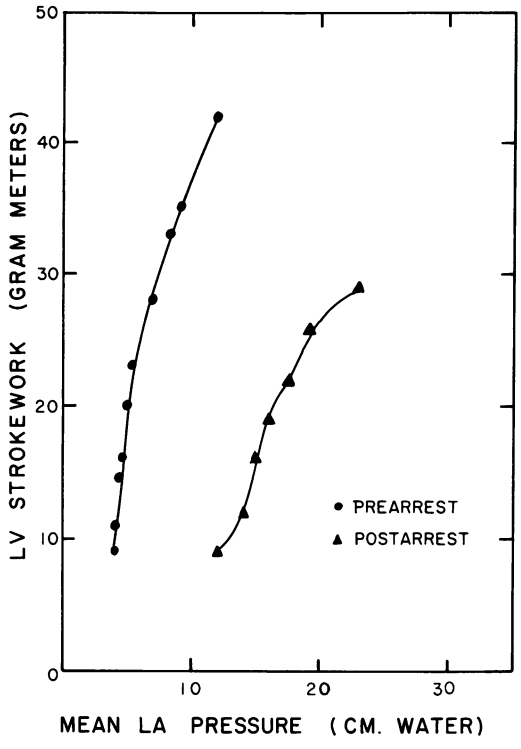

FIG. 4. Left ventricular function curves inscribed before and after 30 minutes of aortic occlusion supplemented by intermittent coronary perfusion with warm blood. The curves are typical of those showing marked depression of function.

no curve could be obtained and these animals are designated as showing complete depression of function. Pairs of curves illustrating the various degrees of depression are shown in Figures 3–7 and the results of all the experiments are summarized in Table 1.

1. Control: In all three dogs subjected to cardiopulmonary bypass alone, without aortic occlusion, the ventricular function curves before and after bypass were virtually identical and revealed no evidence of depression of ventricular function (Fig. 3).

2. Anoxic Arrest—20 Minutes: Four of the five dogs in this group demonstrated moderate or marked depression while one evidenced only minimal depression of left ventricular function.

3. Anoxic Arrest—30 Minutes: Each of these four animals showed complete depression of ventricular function following 30 minutes of normothermic anoxic arrest. All the hearts were easily defibrillated and appeared to have good beats following the recovery period but they were unable to perform any significant amount of work.

4. Intermittent Normothermic Coronary Perfusion—30 Minutes: In this group marked depression occurred in four dogs and moderate depression in one. These hearts slowed markedly during the periods of anoxia but the rate increased and the quality of the contractions noticeably improved during the periods of coronary perfusion. However, ventricular function following aortic occlusion was disappointing compared with the external appearances of the hearts. A typical pair of function curves, demonstrating marked impairment, is shown in Figure 4.

5. Hypothermic Anoxic Arrest—30 Minutes: The amount of myocardial depression after aortic occlusion in these seven dogs ranged from minimal to complete. The heart temperature was always maintained between 10 and 15° C. and there was no correlation between post-arrest function and the temperature of the myocardium during aortic occlusion. All the hearts were defibrillated easily 10 minutes after release of the aortic clamp.

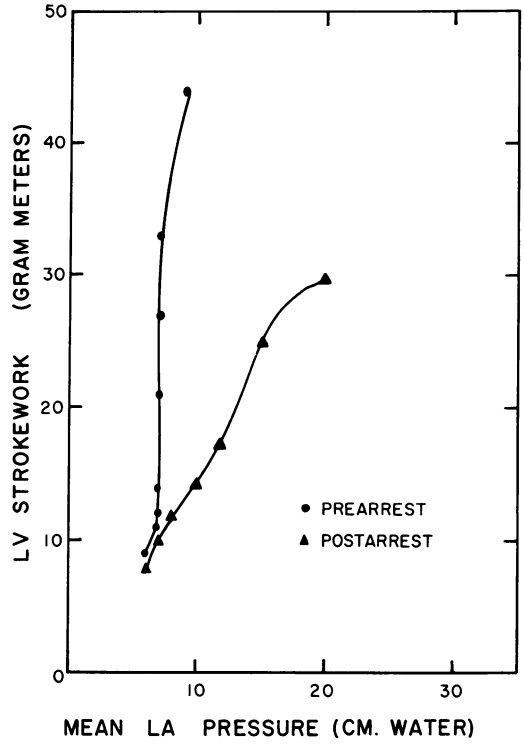

FIG. 5. Left ventricular function curves inscribed before and after 30 minutes of aortic occlusion. Initial cooling was with iced Ringer's lactate coronary perfusion and maintenance with external cooling. The curves are representative of those showing moderate depression of function.

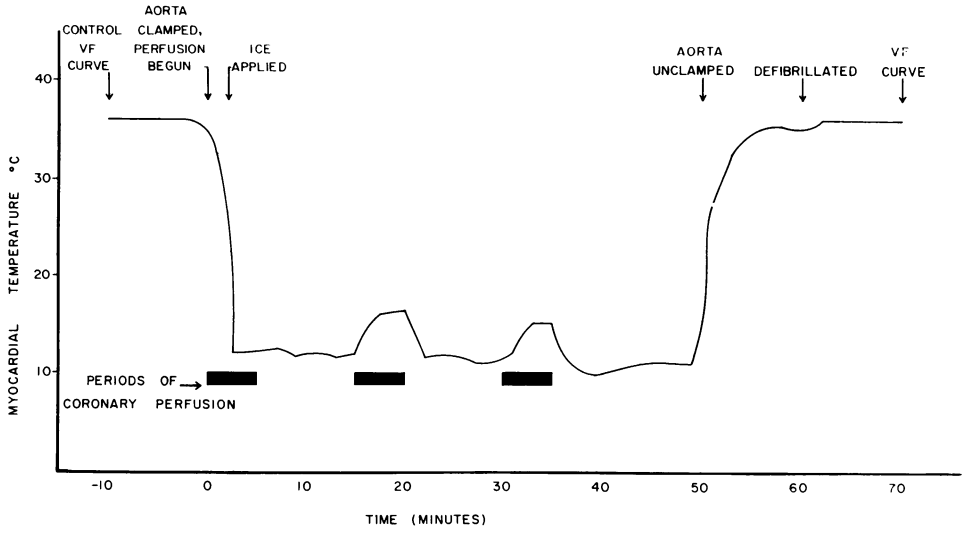

FIG. 6. Myocardial temperature changes during aortic occlusion, intermittent coronary perfusions with cold blood and external cooling.

6. Ringer's Lactate Coronary Perfusion and External Cardiac Cooling—30 Minutes: These seven dogs also demonstrated varying degrees of myocardial depression after occlusion, ranging from minimal to complete. No difficulty was experienced in defibrillating these hearts after they were rewarmed and each appeared to have an effective beat. The function curves obtained in one of these dogs, which are illustrative of moderate myocardial depression, are reproduced in Figure 5.

7. Intermittent Coronary Perfusion with Cold Blood Combined with External Cardiac Cooling—30 and 45 Minutes: Only minimal myocardial depression was observed in five of the six dogs subjected to aortic occlusion for 30 minutes and in three of the four occluded for 45 minutes. The temperature of these hearts fell to 26–28° C. during the initial two minutes of coronary perfusion and their temperatures dropped to 10–13° C. when the ice was packed about them. The myocardial temperature rose to 15–17° C. during each subsequent period of coronary perfusion. In most of these hearts coarse ventricular fibrillation became apparent during the perfusion periods and several, which did not fibrillate, had slow rhythmic contractions. A continuous record of the myocardial temperature in a typical experiment of this type is reproduced in Figure 6. Defibrillation was easily accomplished. A representative pair of function curves, showing only minimal depression of function after 45 minutes of aortic occlusion, is shown in Figure 7.

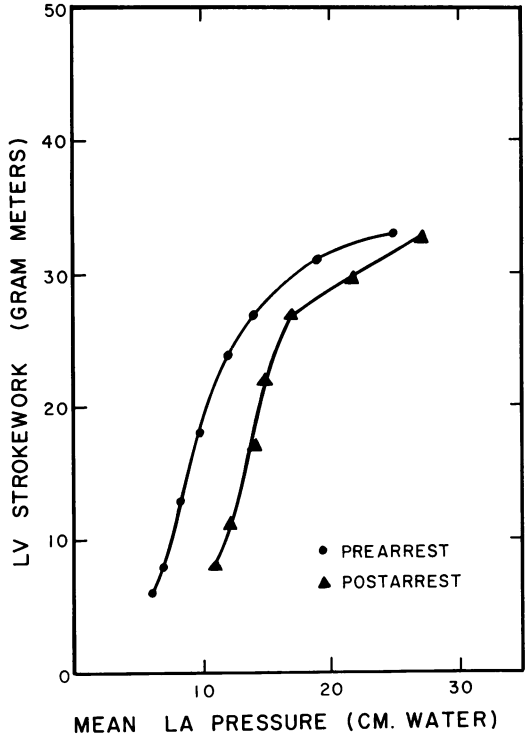

FIG. 7. Left ventricular function curves inscribed before and after 45 minutes of aortic occlusion. The heart was protected by intermittent coronary perfusions of cold blood and external cooling. There is no significant impairment of function.

TABLE 1. *Left Ventricular Function After Aortic Occlusion*

Method	Degree of Ventricular Depression and Numbers of Animals			
	Minimal	Moderate	Marked	Complete
Control (no aortic occlusion)—30 min.	3			
Normothermic anoxic arrest—20 min.	1	2	2	
Normothermic anoxic arrest—30 min.				4
Normothermic arrest, intermittent coronary perfusion with warm blood—30 min.		1	4	
Hypothermic anoxic arrest—30 min.	1	2	2	2
Hypothermic arrest, Ringer's lactate coronary perfusion—30 min.		3	3	1
Hypothermic arrest, intermittent coronary perfusion with cold blood—30 min.	5	1		
Hypothermic arrest, intermittent coronary perfusion with cold blood—45 min.	3	1		

Discussion

Most surgeons will agree that more extensive myocardial damage is usually present in patients with long-standing acquired aortic valvular disease than in those with other acquired or congenital lesions amenable to operation. The muscle is not only hypertrophic, but marked fibrosis and even areas of infarction are often found in histologic sections. Thus, when surgical treatment is undertaken, consideration must be given not only to the most effective method for correcting the valvular abnormality but also to the equally important problem of protecting the myocardium in the most effective way during the period of aortic occlusion. Although each of the technics employed in the present experimental study has been used successfully in clinical practice it seems clear that the one which consistently results in least disturbance of ventricular function will ultimately prove to be the method of choice. Survival or death of an experimental animal after a period of aortic occlusion indicates only whether or not the heart was capable of the minimum work necessary to sustain life, and furnishes no quantitative measure of its ability to perform work in excess of this. For this reason the more critical index provided by function curves was utilized in the experiments described.

As demonstrated previously[15] cardiopulmonary bypass *per se* was found to produce no significant depression of myocardial function. Simple anoxic arrest for a period of 20 minutes, with the heart normothermic, probably represents the longest period that the normal canine heart can tolerate hypoxia and retain a significant functional reserve. After 30 minutes all animals in this study showed complete depression of ventricular function although the hearts defibrillated easily and appeared to have fairly strong beats. It is possible, of course, that effective function could have been restored to some of them by the administration of inotropic drugs. When the normothermic heart was intermittently perfused during a 30-minute occlusion period significant benefit was apparent but marked depression was the usual result. The protection afforded the anoxic heart

by hypothermia was demonstrated in the experiments in which it was employed with simple aortic occlusion or in conjunction with an initial coronary perfusion with iced Ringer's lactate solution. In each group, however, moderately severe depression of function was observed and these data do not indicate that the Ringer's lactate perfusion afforded more protection than simple external cooling.

In the present comparative study the most effective protection of the myocardium during aortic occlusion was provided by intermittent coronary perfusion with cold oxygenated blood supplemented by external cooling of the heart. After either 30 or 45 minutes of arrest all of the hearts defibrillated easily, beat vigorously during the recovery period, and eight of the ten hearts evidenced no significant myocardial depression afterwards (Table 1). Many investigators have shown that the oxygen requirement of the heart is greatly reduced when its work load is lowered by excluding it from the circulation with cardiopulmonary bypass. The oxygen requirement of the excluded heart is still further reduced by hypothermia, but even in the cold arrested heart metabolism continues and a need for oxygen remains. Björk[3] and Urschel[14] have emphasized that maximum benefit from cardiac hypothermia can be obtained only if cooling precedes the period of hypoxia. Wilman[19] and others have concluded that external cooling alone does not result in a uniform temperature change throughout the heart and that such temperature differentials are deleterious. These authors have also pointed out the importance of preventing a rise in the temperature of the heart once hypothermic levels have been achieved. The method of protection described would seem to satisfy the requirements outlined. The initial coronary perfusion with cold oxygenated blood insures rapid and uniform cooling of the heart and prevents any period of hypoxia. The supplemental external cooling maintains the desired myocardial temperature and the reduced oxygen requirement of the arrested heart is supplied by the intermittent coronary perfusions of cold oxygenated blood.

Summary

Myocardial contractility was assessed, by means of left ventricular function curves, in 41 normal dogs before and after periods of aortic occclusion during which the myocardium was protected in various ways. External cooling of the heart during occlusion was found to be of benefit but moderately severe depression of ventricular function resulted in the majority of these animals. Maximum protection was afforded by intermittent coronary perfusion with cold oxygenated blood supplemented by external cardiac cooling. No significant impairment of left ventricular function was found in eight of ten dogs in which this method was utilized during periods of aortic occlusion of 30 and 45 minutes.

References

1. Bahnson, H. T., F. C. Spencer, E. F. G. Busse and F. W. Davis: Cusp Replacement and Coronary Artery Perfusion in Open Operations on the Aortic Valve. Ann. Surg., 152:494, 1960.
2. Bernhard, W., H. Schwarz and N. Mallick: Intermittent Cold Coronary Perfusion as an Adjunct to Open Heart Surgery. Surg. Gynec. & Obst., 111:744, 1960.
3. Björk, V. O.: Perfusion Technic for Surgery on the Aortic Valves. Ann. Surg., 153:173, 1961.
4. Cross, F. S., R. D. Jones and R. M. Berne: Localized Cardiac Hypothermia as an Adjunct to Elective Cardiac Arrest. Surgical Forum, 8:355, 1957.
5. Gott, V. L., R. D. Woodson, D. M. Long, R. D. Sellars and C. W. Lillehei: The Maintenance of Myocardial Viability During Direct-Vision Aortic Valve Surgery. Prosthetic Valves for Cardiac Surgery. Ed. K. A. Merendino, Springfield, Ill., Charles C Thomas, 1961, p. 83.
6. Greenberg, J. J., L. H. Edmunds, Jr. and R. B. Brown: Myocardial Metabolism and

Postarrest Function in the Cold and Chemically Arrested Heart. Surgery, **48**:31, 1960.

7. Kenyon, N. M., R. S. Litwak, H. J. Beck, R. J. Slonim, H. C. Spear and Y. Shibota: Preliminary Observations in Isolated Hypothermic Cardiac Asystole. Surgical Forum, **10**:567, 1959.
8. Kusunoki, T., H. Cheng, H. H. McGuire, Jr. and L. H. Bosher: Myocardial Dysfunction after Cardioplegia: An Experimental Study. J. Thor. & Cardiovasc. Surg., **40**:813, 1960.
9. Littlefield, J. B., E. W. Lowicki and W. H. Muller, Jr.: Experimental Left Coronary Artery Perfusion Through an Aortotomy during Cardiopulmonary Bypass. J. Thor. & Cardiovasc. Surg. **40**:685, 1960.
10. Long, D. M. Jr., L. P. Sterns, R. H. DeRiemer, H. E. Warden and C. W. Lillehei: Subtotal and Total Replacement of the Aortic Valve with Plastic Valve Prosthesis: Experimental Investigation and Successful Clinical Application Utilizing Selective Cardiac Hypothermia. Surgical Forum, **10**:660, 1959.
11. McFarland, J. A., L. B. Thomas, J. W. Gilbert and A. G. Morrow: Myocardial Necrosis Following Elective Cardiac Arrest Induced with Potassium Citrate. J. Thor. & Cardiovasc. Surg., **40**:200, 1960.
12. Sarnoff, S. J. and E. Berglund: Ventricular Function. I. Starling's Law of the Heart Studied by Means of Simultaneous Right and Left Ventricular Function Curves in the Dog. Circulation, **9**:706, 1954.
13. Shumway, N. E. and R. R. Lower: Topical Cardiac Hypothermia for Extended Periods of Anoxic Arrest. Surgical Forum, **10**:563, 1959.
14. Urschel, H. C. and J. J. Greenberg: Differential Hypothermic Cardioplegia. Surgical Forum, **10**:506, 1959.
15. Waldhausen, J. A., N. S. Braunwald, R. D. Bloodwell, W. P. Cornell and A. G. Morrow: Left Ventricular Function Following Elective Cardiac Arrest. J. Thoracic & Cardiovasc. Surg., **39**:799, 1960.
16. Wallace, H. W.: Prosthetic Valves for Cardiac Surgery. Ed. K. A. Merendino, Springfield, Ill., Charles C Thomas, 1961, p. 106.
17. Weirich, W. L., R. W. Jones and M. F. Burke: The Effect of Elective Cardiac Arrest Induced by Potassium Citrate and Acetylcholine on Ventricular Function. Surgical Forum, **10**:528, 1959.
18. William, V. L., T. Cooper, P. ZaFiracopoulos and C. R. Hanlon: Measures to Limit Myocardial Depression Associated with Elective Cardiac Arrest. Surgical Forum, **10**:514, 1959.
19. Willman, V. L., H. S. Howard, T. Cooper and C. R. Hanlon: Ventricular Function After Hypothermic Cardiac Arrest. Arch. Surg., **82**:120, 1961.