

Myocardial Injury Associated with Asystole Induced with Potassium Citrate *

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SUCCESSFUL total body perfusion has brought recognition of new problems which could not be anticipated fully before the use of this technic for intracardiac surgery. Several of these problems such as excessive coronary flow and the technical difficulty of suture and prosthesis placement in the actively beating, bypassed heart suggest the value of elective cardiac arrest. Use of potassium citrate solution as suggested by Melrose for arrest of the heart was tried in our laboratory, but the results were not entirely satisfactory. The present report is concerned especially with untoward effects encountered when the Melrose technic was used with our method of extracorporeal oxygenation and circulation.

Method

The dogs used in these experiments varied considerably in size and included several small puppies. No animals with anemia or respiratory infection were used but aside from this they were unselected mongrels that had been prepared with a vermifuge. Sodium pentobarbital was the anesthetic agent used and ventilation was through a large tracheal tube by a mechanical ventilator with a suction phase in its cycle.

Peripheral vessels were cannulated so that pressure was measured in the superior and inferior vena cava and the abdominal aorta. The right thorax was opened through the fourth intercostal space and in most instances the sternum was transected to permit a short extension of the incision in the same interspace to the left of the midline. The cannulation of the cavae for the drainage of venous blood into the heart-lung machine was done through the wall of the right atrium. The cannula for return flow from the extracorporeal system was inserted into the right common femoral artery and directed toward the heart.

The system for complete drainage of blood from the left side of the heart included two parts as illustrated in Figure 1. A large stainless steel cannula was passed through the appendage into the left atrium. This was attached to a suction line which carried the blood into the coronary pumps of the heart-lung machine. Another steel cannula was inserted into the left ventricle through a stab at the apex.¹ This was connected to a line which also carried the blood to the coronary pumps but there was no suction in this system and it drained only by gravity.†

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† It is recognized that a septal defect exists in many conditions for which open heart surgery is performed at present. Right atriotomy or ventriculotomy results, therefore, in some degree of venting of the left side chambers. We do not believe that drainage of the left heart through a

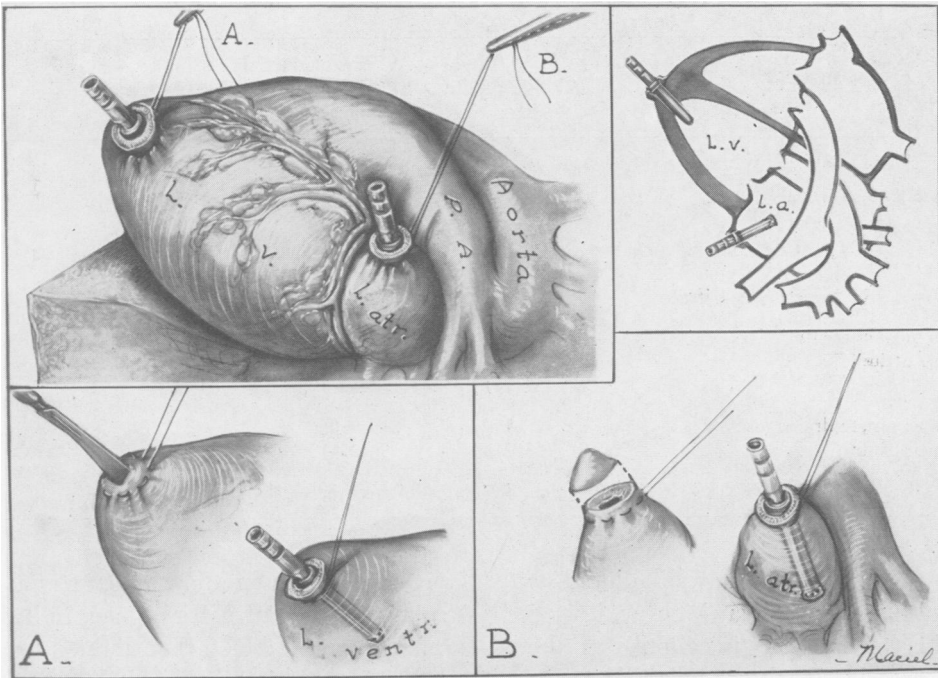


FIG. 1. The apex of the heart is elevated by placing a soft sponge behind it and within the pericardium. A large steel cannula is passed through the appendage into the left atrium. Another cannula is passed through a stab wound into the left ventricle.

The perfusion rate was predetermined according to calculation by L. C. Clark.² As a rule the flow through the oxygenator pump was never less than this arbitrary value and frequently it exceeded the calculated figure. The pressure in the superior and inferior caval systems as well as the arterial pressure were considered also in determining the rate of the perfusion.

Other monitoring instruments supplied information of greater importance perhaps and these were the principal determinants of flow rate during the course of each perfusion. The partial pressure of oxygen in the arterial blood was measured polarographically with a platinum electrode.³ The pH of the "arterialized" blood was recorded

septal defect and right cardiectomy accomplishes the same effect as the cannulas in the left atrium and ventricle. However, further comparison of these two methods is not pertinent to this experimental study.

continuously with a general purpose glass electrode and a fiber-type reference electrode with a Beckman pH meter.⁴ The temperature of the blood was kept normal by a small heating unit which warmed the blood as it entered the extracorporeal circuit.

Experiments in the first part of this study are divided into three groups. The first group consisting of 15 animals, three of which were pups, were subjected to total cardiac bypass for 30 minutes. The cardiac rhythm and the flow in coronary vessels were not altered during the experiment. The system for complete drainage of the left heart was employed and in all other respects the perfusions were conducted as our perfusions are at present in clinical practice. These experiments, therefore, are the control series.

The second group included 17 animals in which the hearts were arrested with potas-

TABLE 1

	Av. Flow Rate cc./Kg./min.	Av. Mean Arterial Pressure mm. Hg	Av. Arterial pH	Deaths
Perfusions in Sinus Rhythm				
15 with complete drainage left atrium	62 (53-81)	66 (40-90)	7.43 (7.35-7.50)	0
Perfusions in Arrest by K Citrate				
17 with incomplete drainage left atrium	61 (52-71)	92 (70-100)	7.46 (7.40-7.52)	8
7 with complete drainage left atrium	89 (65-116)	95 (90-120)	7.43 (7.40-7.47)	1
Range is given in figures in parentheses.				

sium citrate. The salt was diluted with arterial blood in the way Melrose described, and his technic for injection was duplicated exactly. In these experiments, however, there was incomplete drainage of blood from the chambers of the left side of the heart during the 30-minute interval of arrest and total extracardiac perfusion. In several instances blood was released from the left atrium during measurement of pressure in that chamber. The volume that escaped from the left heart was relatively small, however, and no doubt was less than the amount entering via the bronchial arteries and other collateral vessels.

The third group consisted of seven animals in which the hearts were arrested by potassium citrate with an exact duplication of the Melrose technic. This group, however, had complete drainage of blood from the left atrium and ventricle during the 30-minute period of arrest and perfusion of the remainder of the body.

Results and Discussion

The perfusions carried out with the heart in sinus rhythm were uniformly successful. Ventricular fibrillation complicated three of the experiments but it was easily eliminated by electroshock, and all of the animals sur-

vived. The average flow rate, arterial pressure, and arterial pH are given in Table 1. The volume of blood that drained from the left atrium during the interval of total body perfusion was measured several times each during seven of the experiments. In most instances it varied between 30 and 90 cc. per minute. In the experimental conditions of this group this amount of blood was derived from at least two sources, the coronary and the bronchial arterial system.

The perfusions performed during arrest of the heart with potassium citrate and without drainage of the left atrium comprised a group with results that were strikingly different. After injections of the potassium salt and the production of asystole we observed that five hearts developed a true rigor of the left ventricle. This localized change in tone could not be altered by massage or flushing the coronary arteries with blood, and the complication was uniformly fatal.⁵ Altogether, eight animals in the group died, and in every instance they developed ventricular fibrillation after the aorta was opened following the 30-minute period of arrest and interruption of coronary circulation. Table 1 lists additional data on the flow rate, arterial pressure, and arterial pH maintained during these perfusions. As

TABLE 2

Heart in Sinus Rhythm During Perfusion		Heart Arrested During Perfusion									
		Asystole by Anoxia						Asystole by K Citrate (Left Chambers Drained)			
		Sacrificed After 48 Hrs.			Sacrificed Immediately		Sacrificed After 48 Hrs.		Sacrificed After 48 Hrs.		
Exp. No.	CR-14	CR-15	CR-16	231	230	229	228	232	227	226	224
Focal myocardial necrosis	0	+1	±	0	0	0	±	+++	+++	++++	++++ ²
Mineralization of necrotic muscle	0	0	0	0	0	0	0	0	+++	+++	+++
Fatty degeneration of myocardium	0	+	++	0	0	++++	++	+++	+++	+++	0
Focal hemorrhage	0	0	0	+	+	+	0	+	+	0	++

1. Foci of hyaline degeneration in a papillary muscle.
2. Subendocardial infarction.

mentioned earlier, a small amount of blood was drained from the left atrium in eight animals in this group. The single objective in this maneuver was to measure the pressure and to prevent engorgement of the pulmonary veins.

Perfusions done during potassium citrate arrest but with complete drainage of the left atrium gave significantly different results in a group of seven animals. The peculiar tonic contraction of the left ventricle was not observed a single time. Ventricular fibrillation complicated only two of the experiments and the single death in the group was caused by an accidental aortic tear which could not be repaired; additional information on flow rate, arterial pressure, and arterial pH is given in Table 1. The volume of blood collected from the left atrium during perfusion and while the aorta was closed above the coronary orifices was a measurement of flow through the bronchial arteries. There was a wide variation between experiments; in most animals it was from ten to 20 cc. per minute. The lowest measurement recorded was five and the highest 38 cc. per minute.

The striking difference in mortality rate between the first and third groups on one

hand and the second group on the other suggests that drainage of blood from the left atrium has a very beneficial effect upon cardiac function during this type of perfusion. We believe that part of the mechanism for this is the prevention of elevated pressure in the chambers of the left heart—pressure which may result not only in overstretched myocardial fibers but also, when transmitted along pulmonary veins, may cause harmful engorgement of the lungs. Drainage of the left atrium may provide an additional benefit when the Melrose technic is used for asystole. Our measurements have shown that a relatively high concentration of potassium is found in blood from the pulmonary veins and left atrium following the intra-aortic injection of Melrose's solution and we believe that this may be harmful to the myocardium if it is allowed to collect in the left chambers for 30 minutes.⁶

In addition to observations on the immediate reaction of the heart and the rate of survival in the different experimental groups, microscopic examination was made on blocks from the ventricles of three additional groups of dogs. The results of this

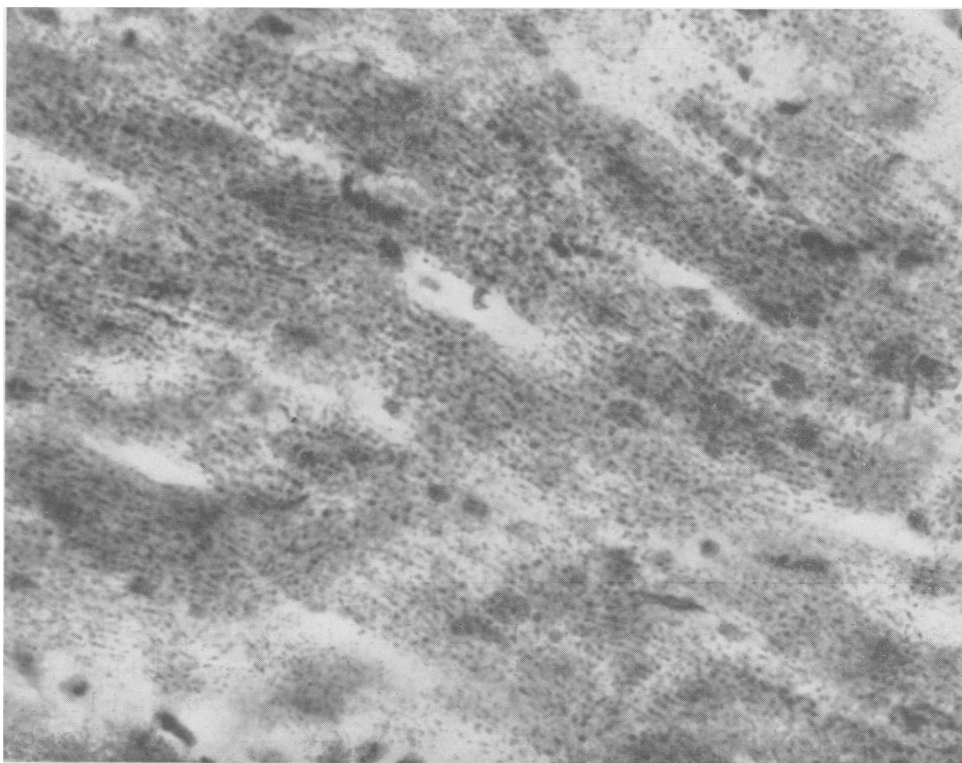


FIG. 2. Dog 229. Fine droplets of sudanophilic material in myocardial fibers. (Sudan IV $\times 650$.)

part of the study have been abbreviated and listed in Table 2.

The first group consisted of three dogs which served as controls for the ones to follow. Their hearts were examined pathologically 48 hours after total bypass. Coronary flow was not altered in any way and no arresting agent was employed during these perfusions. The myocardium of one animal was entirely normal. The second dog had a rare focus of necrobiotic fibers in a papillary muscle of the left ventricle as well as occasional foci of fatty degeneration in the myocardium of both ventricles. The third specimen had rare foci with hyaline appearing muscle fibers but no definite necrobiosis. There were fatty changes in the myocardium, however, which were generalized in distribution with focal areas of accentuation.

The second group subjected to pathological examination of the heart were ones

in which arrest was produced by anoxia resulting from 30 minutes of occlusion of the aorta just above the coronary ostia. Two hearts were removed for examination immediately after the perfusion. The only lesions found in these were focal myocardial hemorrhage. Two other dogs subjected to the same type of perfusion and myocardial anoxia withstood the experiment well and 24 hours later were in good general condition. They were sacrificed 48 hours after the experiment and one heart showed diffuse fatty degeneration, but no necrobiosis (Fig. 2). The other had a rare focus suggestive of necrotic muscle fibers and scattered areas of fatty degeneration. In this latter specimen there was a mantle of fatty degeneration beneath the epicardium, a lesion possibly attributable to a thermal effect of operating lights upon the exposed cardiac surface.

The third group studied histologically in-

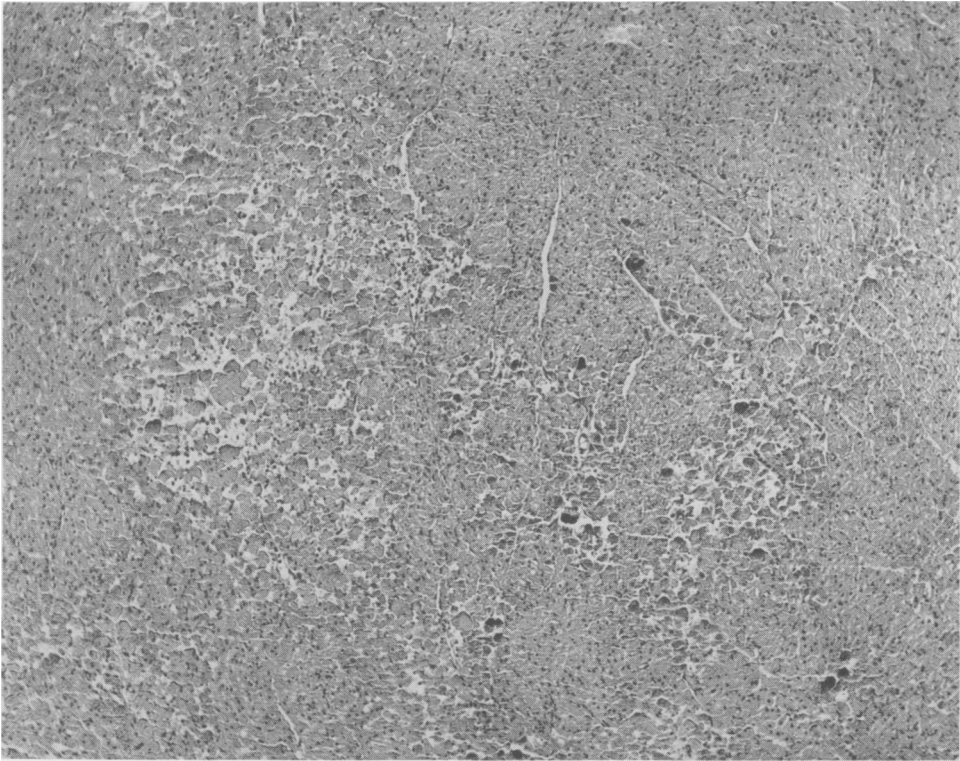


FIG. 3. Dog 226. On the left a large focal area of necrosis is noted without appreciable evidence of inflammation. In the smaller foci to the right the necrotic muscle fibers are mineralized. (Hematoxylin eosin $\times 90$.)

cluded four dogs arrested with potassium citrate and with the left heart drained by the technic described. The animals were allowed to recover from the perfusion and then were sacrificed after 48 hours. Lesions of the myocardium were visible grossly in all of these specimens. These consisted of yellow-grey opaque streaks in the myocardium which were found to be friable. In one dog there was excessive necrosis in association with a cardiotomy wound in the right ventricle. Microscopically all four specimens showed extensive focal areas of myocardial necrosis in which the fibers were shrunken, opaque, and deeply eosinophilic. In three specimens there was mineralization of necrotic muscle fibers in many areas (Fig. 3). The pattern of necrosis was random in both ventricles but often tended to be about branches of the coronary arteries. One animal had a subendo-

cardial infarct. Sudan IV preparations in three specimens demonstrated fine droplet fatty degeneration of a focal type, particularly disposed about the necrotic areas.

The pathologic studies indicate that with total perfusion by our method there is some myocardial damage when asystole is not induced. The fatty degeneration was of a mild degree, however, and frank necrobiosis was limited to rare foci. Asystole produced by potassium citrate was associated with a serious degree of myocardial necrosis and this developed in every instance despite use of a method for drainage of blood from the left heart during total perfusion. Thus the findings on pathologic study did not confirm the impression from experiments in perfusion and left heart drainage in which the main criterion was survival of the animal.

Summary

Arrest of the ventricles by injection of potassium citrate solution resulted in several complications not encountered when total body perfusion is carried out with the heart in sinus rhythm. An unusual rigor of the left ventricle was seen in many of the arrested hearts and irreversible ventricular fibrillation accounted for the high mortality rate in this group. A technic was developed for the complete drainage of blood from the left heart chambers and when this was used with Melrose's method for arrest, ventricular rigor and irreversible fibrillation did not develop in a single experiment.

Hearts from three groups of animals were examined pathologically 48 hours after total perfusion. The first group were three controls, perfused without arrest or alteration in the coronary circulation, and these showed some fatty degeneration. The hearts of four dogs subjected to anoxic arrest by aortic clamping were examined and found to show focal hemorrhages and fatty degeneration but no necrosis. Specimens from four animals arrested with potassium citrate and with complete drainage of the left chambers showed focal areas of necrosis in every instance.

Bibliography

1. Miller, B. T., J. H. Gibbon, Jr., V. F. Greco, C. H. Cohen and F. F. Allbritten, Jr.: Use of a Vent for the Left Ventricle as a Means of Avoiding Air Embolism to the Systemic Circulation During Open Cardiotomy with the Maintenance of the Cardiorespiratory Function of Animals by Pump Oxygenator. *J. Thor. Surg.*, **28**:235, 1954.
2. Clark, L. C.: Optimum Flow Rate in Perfusion. Conference on Problems of Extracorporeal Circulation, September 28, 1957, Chicago, Ill.
3. Clark, L. C., R. Wolf. D. Granger and Z. Taylor: Continuous Recording of Blood Oxygen Tensions by Polarography. *J. Appl. Physiol.*, **6**:189, 1953.
4. Matthews, E. C., L. C. Clark, F. K. Edwards, S. Kaplan and J. A. Helmsworth: Studies During the Immediate Postoperative Period After Total Body Perfusion. 15th Assembly of Central Surgical Association, February 20, 1958.
5. Kaplan, S., L. C. Clark, E. C. Matthews, F. K. Edwards, L. Schwab and J. A. Helmsworth: A Comparison of the Results of Total Body Perfusion in Dogs During Potassium Citrate Cardiac Arrest, Sinus Rhythm, and Induced Ventricular Fibrillation. *Surg.*, **43**:14, 1958.
6. Helmsworth, J. A., R. W. Shabetai and J. Margolian: An Investigation of Cardiac Arrest Produced by Injection of Potassium Citrate into the Coronary Circulation. In Press.