A DEMONSTRATION OF THE ROLE OF POTASSIUM AND CITRATE IONS UNDER THE CONDITIONS OF ELECTIVE CARDIAC ARREST FOR OPEN-HEART OPERATION

WILLEM J. KOLFF, M.D.,
Division of Research

PATRICK P. MORACA, M.D.,* DONALD E. HALE, M.D.,
Department of Anesthesiology

and

WILLIAM L. PROUDFIT, M.D.
Department of Cardiovascular Disease

SINCE the preliminary report[1] in April 1956, 75 more patients have undergone open-heart operations with elective cardiac arrest according to the Melrose technic[2] at the Cleveland Clinic Hospital. Cardiac arrest with potassium citrate permits the surgeon to operate in a quiet, relatively bloodless, open heart.

In this paper no new facts are presented, rather an attempt is made to demonstrate old and well-known truths concerning the effects of certain cations on the myocardium under the conditions of their present clinical application.

Ringer[3] was the first to study the effect of electrolytes on the heart muscle; Hering[4] arrested ventricular fibrillation in the perfused rabbit's heart with potassium and saw that the normal beat gradually redeveloped as soon as the perfusate had washed out the excess potassium. Wiggers[5] used potassium arrest as a standard laboratory experiment or demonstration for more than 40 years; undoubtedly others have similarly used it for many years. In 1927, concern about the increased death rate from accidental electrocution prompted simultaneous but independent investigations by Hooker[6] and by Wiggers.[7] They stopped ventricular fibrillation in intact animals by an electric shock or by intracardiac or intra-arterial infusion of potassium chloride. Calcium chloride was thereafter injected to re-establish the heart beat. Those studies formed the basis for cardiac resuscitation as it is now generally accepted. Montgomery, Prevedel, and Swan[8] used potassium chloride to stop ventricular fibrillation in hypothermia.

The conversion of ventricular fibrillation by injection of potassium salts is justified by the desperation of the situation. However, the premeditated arrest of the normally beating human heart was not practiced until it was suggested for clinical use in open-heart surgery by Melrose, Dreyer, Bentall, and Baker.[2]

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**Fellow in the Department of Anesthesiology.*

Melrose and associates perfused excised hearts with oxygenated Locke's solution by the method of aortic cannulation. Potassium citrate was added to the perfusate; 5 mg. per milliliter always caused complete cardiac arrest. Diastolic cardiac arrest always occurred within 20 seconds after infusion of the potassium solutions. During the period of arrest, coronary flow was stopped for 15 minutes without subsequent evidence of cardiac damage. Spontaneous beating usually resumed within three minutes after perfusion with pure Locke's solution. The heart rate was normal within less than one minute, and the force was almost fully recovered within an additional three minutes. Restarting of the arrested heart did not require stimulation but only perfusion of the coronary arteries with oxygenated fluid. Melrose and associates applied this principle in intact animals, establishing a technic that we have followed and described in detail.[9]

For the demonstration discussed in this report we used three dogs, each weighing approximately 10 kg. The dog's circulation was maintained with a heart-lung machine in the usual manner. Blood was withdrawn from both venae cavae, was oxygenated in an artificial lung and was pumped back into the aorta either through the subclavian artery or through one of the carotid arteries. The perfusion rate was at least 60 and sometimes 100 ml. per kilogram per minute, and during most of the experiments the blood pressure could be maintained at 50 at the least, and often at 80 or 100 mm. Hg, even when the dog's own heart was excluded from the circulation. A cardiac catheter was inserted through one of the carotid arteries into the root of the aorta. After occlusion of the venae cavae and clamping of the root of the aorta, equivalent amounts of electrolyte solutions were injected through the cardiac catheter into the root of the aorta. To compare the action of individual ions, solutions of 4.5 mEq. of the following salts were prepared, each in 20 ml. of water*: potassium chloride, potassium citrate, sodium lactate, and sodium citrate.

An electrocardiograph (lead 2) continuously registered the changes in the cardiac rhythm, which were verified by direct observations of the ventricles and auricles through the open chest during the experiments. After the effect of an electrolyte had been obtained, the clamp was removed from the root of the aorta; blood from the heart-lung machine then entered the coronary arteries and flushed the electrolyte out of the myocardium.

Potassium citrate, 4.5 mEq., was injected six times in the three animals either to defibrillate the heart or, toward the end of the experiment, to prove that the heart still could be stopped and started. Potassium citrate stopped the heart whether a sinus mechanism or fibrillation existed before the injection. Normal sinus rhythm was restored after release of the clamp from the aorta; fibrillation recurred once, necessitating a second injection.

Sodium citrate, 4.5 mEq., was used to test the effect of the citrate ion. In the first experiment (Fig. 1, *1B*), the cardiac rate decreased, the T waves

**Melrose diluted the potassium citrate in 20 ml. of blood, but for simplicity our solutions were diluted in 20 ml. of water.*

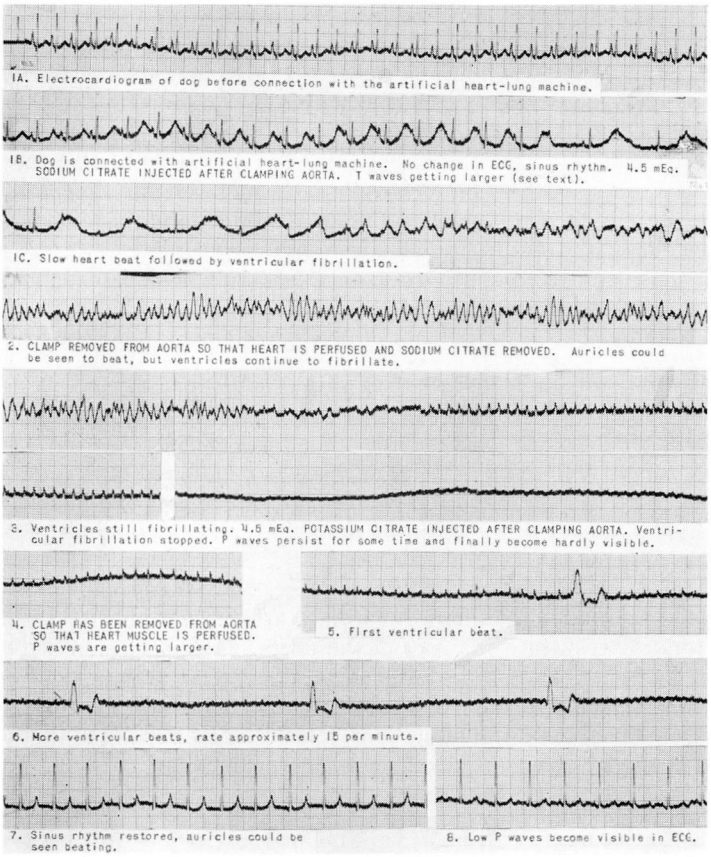

Fig. 1.

increased in voltage and duration, and the Q-T interval became prolonged. The latter change was so great that a 2:1 atrioventricular block occurred; it resulted from the fact that alternate P waves occurred before repolarization of the ventricular myocardium was complete. Similar changes recently have been described as occurring after transfusion of large amounts of citrated blood, and they were reversible with small amounts of calcium chloride.[10] The cause of the increase in the voltage and in the width of the T waves is not apparent. The change in the S-T segment is characteristic of hypocalcemia and probably is due to the citrate binding of ionized calcium. The changes in T waves in these experiments are difficult to evaluate because anoxia may be a factor, since the aorta was clamped and the heart continued to beat. Ventricular fibrillation followed a brief period of electrical alternans in dogs 1 and 2. In neither dog could fibrillation be stopped with second or third injections of sodium citrate, and release of the clamp from the aorta did not influence the rhythm. Cardiac

arrest was induced by an injection of potassium citrate, and the normal beat returned after release of the clamp from the aorta. In dog 3, 5 mEq. of sodium citrate slowed the heart rate from 90 to 40 beats per minute and P waves were not regularly seen. One gram of calcium gluconate injected into the machine increased the heart rate and restored the sinus rhythm.

It seems that the citrate ion in the amounts used for elective cardiac arrest was unable to stop heart action and appeared to promote ventricular fibrillation. We can find no support for Melrose's opinion[11] that the citrate serves a useful purpose.

Sodium lactate. To investigate the possibility that the sodium ion might have influenced the effect of sodium citrate, 5 mEq. of sodium lactate was injected into the root of the occluded aorta of dog 1. The T waves became larger and peaked and the Q-T interval increased because of increased duration of the S-T segment, but there was no fibrillation and no arrest (Fig. 2, *9*). The change in the T waves resembles that seen in mild hypokalemia. In dog 3 the injection of 10 mEq. of sodium lactate slowed the heart rate. In both experiments the injection of potassium chloride promptly stopped the heart action.

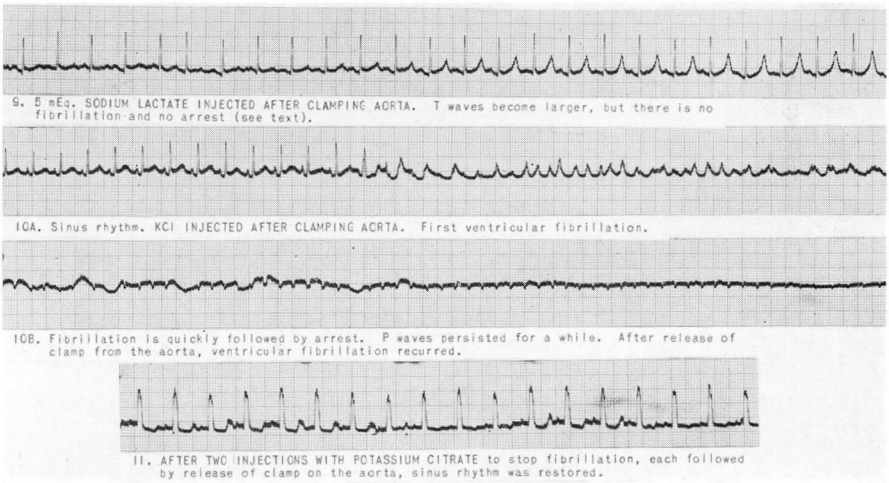

Fig. 2.

Potassium chloride. If, as seemed likely, potassium is the effective ion that arrests cardiac action, then equivalent doses either of potassium chloride or of potassium citrate should be equally effective. Potassium chloride was injected four times and each time it stopped the heart. In the first dog the ventricular arrest was preceded by a brief period of ventricular fibrillation (Fig. 2, *10A*), a sequence also commonly seen when potassium citrate is used. Ventricular fibrillation recurred after release of the clamp, but following rearrest normal rhythm was restored.

Summary

Experiments were done in dogs to demonstrate the effects of potassium and citrate ions on the heart under conditions similar to those existing clinically during elective cardiac arrest by the Melrose method. Potassium chloride seemed to be as effective as potassium citrate in producing cardiac arrest; thus, as expected, the potassium ion is responsible for this effect.

Citrate without potassium sometimes produced ventricular fibrillation which probably is a result of the binding of calcium. Since recovery from potassium citrate arrest is usually uneventful, a large series of experiments would be required to prove whether potassium chloride has less tendency to induce ventricular fibrillation than has potassium citrate.

An unusual type of 2:1 atrioventricular block was found when sodium citrate so prolonged Q-T intervals that alternate P waves occurred before repolarization of the ventricular myocardium was completed.

References

1. Effler, D. B.; Groves, L. K.; Sones, F. M., Jr., and Kolff, W. J.: Elective cardiac arrest in open-heart surgery: report of three cases. Cleveland Clin. Quart. **23**: 105-114, April 1956.
2. Melrose, D. G.; Dreyer, B.; Bentall, H. H., and Baker, J. B. E.: Elective cardiac arrest. Lancet **2**: 21-22, July 2, 1955.
3. Ringer, Sydney: Further contribution regarding influence of different constituents of blood on contraction of heart. J. Physiol. **4**: 29-42, 1 plate, 1883.
4. Hering, H. E.: Demonstration der Aufhebung des Flimmerns durch Injektion von KCl Lösungen. Deutsche med. Wchnschr. **33**: 1567, 1907.
5. Wiggers, C. J.: Editorial: Defibrillation of ventricles. Circulation Res. **1**: 191-199, May 1953.
6. Hooker, D. R.: On recovery of heart in electric shock. Am. J. Physiol. **91**: 305-328, Dec. 1929.
7. Wiggers, C. J.: Studies of ventricular fibrillation caused by electric shock; revival of heart from ventricular fibrillation by successive use of potassium and calcium salts. Am. J. Physiol. **92**: 223-239, Feb. 1930.
8. Montgomery, A. V.; Prevedel, A. E., and Swan, H.: Prostigmine inhibition of ventricular fibrillation in hypothermic dog. Circulation **10**: 721-727, Nov. 1954.
9. Kolff, W. J.; Effler, D. B.; Groves, L. K.; Peereboom, G.; Aoyama, S., and Sones, F. M., Jr.: Elective cardiac arrest by Melrose technic: potassium asystole for experimental cardiac surgery. Cleveland Clin. Quart. **23**: 98-104, April, 1956.
10. Hubbard, T. F.; Neis, D. D., and Barmore, J. L.: Severe citrate intoxication during cardiovascular surgery. J.A.M.A. **162**: 1534-1535, Dec. 22, 1956.
11. Melrose, D. G.: Discussion in Proceedings of American Society for Artificial Internal Organs, Atlantic City, New Jersey, April 15-16, 1956.