Experimental Studies on the Effect of Potassium Citrate for Elective Cardiac Arrest and a Trial of the Concomitant Use of Glucose and Insulin

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For the purpose of examining the effect of the elective cardiac arrest on the heart muscle, the isolated Langendorf dog's heart preparation with cross circulation was prepared for analysis of the physiological and histological reaction of the cardiac muscle induced by 30 minutes coronary occlusion with or without cardiac arrest. As the heart muscle is loaded with anoxia during cardiac arrest, glucose and insulin were added to the commonly used agents for cardiac arrest in order to accelerate anaerobic glycolysis. By this process the condition, after reperfusion, was found more stable and the histological changes less serious than when these agents were used alone. When an agent for cardiac arrest was alkalized in order to alleviate the metabolic acidosis during a period of cardiac arrest, the change that resulted was found histologically slight, but a long lasting tachycardia after reperfusion was observed.

SINCE the artificial oxygenating circuit was sufficiently improved for the clinical use by which the heart can be isolated from the general circulation, a remarkable progress has been made in the surgical treatment of various congenital and acquired heart diseases. However the blood outflow from the coronary veins and also the leakage through the aortic valve is quite an embarrassing obstruction for the proceeding of the surgical operation under the field of vision of the surgeon. Furthermore, the heart beat can not so easily overcome the strain of carrying elaborate applications of techniques. It is most desirable to avoid these obstructions for the performance of the cardiac surgery.

After the well known notion by Ringer1 on the action of various cations on heart beats, Hooker2 reported in 1929 that potassium chloride

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was effective in removing ventricular fibrillation. Montgomery et al.\textsuperscript{3)} applied it for the case of the ventricular fibrillation which occurs during hypothermia. Merlose et al.,\textsuperscript{4)} on the basis of these experiences, conducted experiments of elective cardiac arrest on animals at normal and low body temperatures with potassium citrate. The cardiac arrest induced electively by infusion of the isotonic solution of potassium citrate into the coronary artery was restored soon after recirculation and the normal sinus rhythm resumed. The Merlose's procedure was clinically applied in 1956 by Effler et al.\textsuperscript{5)} and 3 successful cases were reported. Thereafter Moulder et al.\textsuperscript{6)} also studied the cardiac arrest experimentally by acetylcholine administration with occlusion of coronary circulation under general hypothermia and extended this technique to 5 clinical cases. Lam et al.\textsuperscript{7)} obtained a clinical success independently by using acetylcholine for the intracardiac operation. Furthermore, Young et al.\textsuperscript{8)} used a mixed solution of magnesium sulfate and potassium citrate for the same purpose under general hypothermia.

Since these reports have been published, the elective cardiac arrest has come to be widely used, while some definite disadvantages were seriously criticized. At present, Effler,\textsuperscript{9)} Kirklin,\textsuperscript{10)} Blanco\textsuperscript{11)} and others favour this technique of the cardiac arrest in any possible way, but there are not a few surgeons,\textsuperscript{12),13)} who are very critical of the clinical results. While the clinical evaluation of the availability of the elective cardiac arrest on the variety of cardiac diseases is not so easy, the experimental studies on the effect of potassium citrate with coronary occlusion is helpful for the complete understanding of the complicated situation brought by potassium ion, citrate ion and the existing anoxia.

In the present paper, the authors examined first the changes in the heart rate, the coronary blood flow, the myocardial oxygen consumption, ECG and the histology of the heart muscle after recovery from elective cardiac arrest by potassium citrate using the isolated Langendorf dog's heart preparation with cross circulation. Furthermore the concomitant use of glucose with insulin to the potassium citrate solution and also the effect of alkalization of the cardiac tissue were studied.

\textbf{Method}

Twenty-eight experiments were performed on 56 mongrel dogs. The details of the experimental arrangement of the isolated Langendorf dog's heart preparation with cross circulation have already been published by the authors.\textsuperscript{14)} Here, only one principal part is described.

As is shown in Fig. 1, this method consists of a recipient animal (A), averaging 10\textsuperscript{Kg.} and anesthetized with sodium pentobarbital (30\textsuperscript{mg.}/\textsuperscript{Kg.})
Fig. 1. Diagram of the modified Langendorf dog's heart preparation.
A, isolated heart; B, donor dog; a, automatic respirator; b, blood reservoir on the arterial side; c, Dale-Schuster type perfusion pump; d, thermostat; e, filter; f, thermometer; g, air cushion; h, bubble flowmeter; i, recorder; j, reservoir on the venous side; k, pneumatic resistance; l, polyethylene catheter for administration of the test drug solution.

intraperitoneally) and the donor dog (B), averaging 16Kg. and anesthetized with morphine and urethane (morphine HCl 10 mg./Kg., urethane 1 mg./Kg., both given subcutaneously). A tracheal cannula is inserted into the donor dog through which the animal respired 100% oxygen artificially at a rate of 225 ml./Kg./min. The arterial blood drained from the common carotid artery of the donor dog was perfused by a Dale-Schuster type pump in the coronary arteries of the isolated heart of the recipient dog through the innominate artery under a constant temperature. The pneumatic resistance was placed in parallel through which the excessive amount of blood pumped out, overflowed directly to the venous blood reservoir and then to the jugular vein of the donor. In this way, the perfusion pressure of the coronary arteries of the recipient can be kept constant even though the coronary blood flow changes suddenly. The coronary venous outflow was collected through the pulmonary artery and measured by the automatic bubble flowmeter. The automatic bubble flowmeter is so constructed, that the speed of flow is recorded simultaneously with ECG without interruption. An unipolar electrode was placed on the right auricle and the apex of the left ventricle. The A-V oxygen difference is measured by the Van Slyke apparatus and the myocardial oxygen consumption is calculated from the amount of the coronary flow and A-V oxygen difference. Initially 5,000 units of heparin is given intravenously to the donor dog and 2,000 units to the recipient. After the cross circulation is established, 1,000 units per hour is added to the perfusion system successively. When the perfusion pressure and the blood temperature are kept constant, the cardiac rhythm in this preparation
Fig. 2. Heart rate, coronary blood flow and myocardial O$_2$ consumption for the isolated Langendorf dog's heart preparation with cross circulation during a course of 2 hours in the control experiment.

Fig. 3. ECG of the control experiment.
is kept fairly constant even after a lapse of 2 hours and the coronary blood flow and myocardial oxygen consumption increase only very slowly, even though there is a tendency to increase in some cases (Fig. 2). No significant change is observed on ECG (Fig. 3.), nor any marked change is seen in the myocardial tissue after 2 hours perfusion (Fig. 4). A nonspecific histological change due to blood perfusion is occasionally noticed.

![Fig. 4. Histological change of the control experiment. No marked change in the myocardial tissue.](image)

A polyethylene catheter, 1 mm. in diameter, is inserted to the subclavian artery for the administration of the test solution for the cardiac arrest, and the tip of the catheter is placed close to the aortic ostium. The effects of the drugs were tested 30 minutes after the perfusion system is completed, when the state of stability was obtained.

First the perfusion in the heart was suddenly cramped off and the solution of test drug was given immediately through the polyethylene catheter, until the disappearance of the spontaneous heart beat was affirmed by the continuous ECG recording. After a certain lapse of time of cardiac arrest, the coronary circulation was reopened.

The effect of elective cardiac arrest can be analysed in 2 categories; the effect of anoxia by coronary occlusion and the effect of the drugs for inducing the arrest. In order to examine the effect of the anoxia without the cardiac arrest, the perfusion was simply occluded for a fixed period of time. The circulation was reopened and the process of recovery observed. Five minutes coronary ischemia, repeated 5 minutes coronary occlusion with interruption of 15 minutes perfusion, and 30 minutes coronary occlusion were made.

For evaluation of the test drug, the recovery process was compared for one hour among groups of the 30 minutes occlusion, with and without drugs to induce cardiac arrest. The isotonic solution of 2.5% potassium citrate, 2.5% potassium citrate together with 500 mg. of glucose and 10 units of insulin, 2.5% potassium bicarbonate with glucose and insulin and 1.9% potassium chloride adjusted to pH 8.0 by sodium bicarbonate and added with glucose and insulin were used. Furthermore prostigmin, magnesium sulfate and potassium citrate solution recommended by Young et al. were tested. The ventricular fibrillation usually occurring by reperfusion, was set back immediately to the sinus rhythm by counter shock with 100 V AC in 0.1 sec. duration.
RESULTS

I. The coronary occlusion without drugs

1) Five minutes coronary ischemia

Three minutes after the occlusion, lowering of ST, negative T and prolongation of PQ and RR intervals were noticed on the ECG. Tachycardia was observed at the beginning of the reperfusion and it lasted thereafter throughout the observation period. Coronary blood flow decreased gradually after the reactive hyperemia was over, but even after 30 minutes, it was at a higher level than before the occlusion. Myocardial oxygen consumption increased temporarily and returned to the control level within 15 minutes (Fig. 5). Histologically, there was no noticeable change (Fig. 6).
2) Repeated 5 minutes coronary occlusion with interruption of 15 minutes perfusion

The changes in ST and T on ECG disappeared immediately after the reperfusion, but the heart rate and myocardial oxygen consumption remained at a high level. Though the coronary blood flow returned gradually to the preocclusion level, it remained high more or less. It was confirmed that the effect of double 5 minutes occlusions in 15 minutes interval acted as an additive effect in succession, as the effect of the first 5 minutes occlusion still remained after 15 minutes perfusion (Fig. 7).

Fig. 7. Changes of heart rate, coronary blood flow and myocardial O₂ consumption in the case of repeated 5 minutes coronary occlusion with interruption of 15 minutes perfusion.

3) Thirty minutes occlusion

After the occlusion, the heart rate gradually decreased and the contraction became weaker. At around 10 minutes the visible contraction was not observable but P waves were still present in atrial lead which completely disappeared within 25 minutes (Fig. 8). The ventricular fibrillation occurred after reperfusion in all cases. After it recovered to the rhythmic beat by counter shock, the persistent tachycardia was a common incidence and continued. The coronary blood flow after the reactive hyperemia gradually decreased, but it showed the persistently higher level than before the occlusion. The myocardial oxygen consumption varied nearly in parallel with the coronary flow (Fig. 9). Some significant changes in the histological study such as highly developed degeneration, necrobiosis and necrosis of the myocardial tissue were noticed (Fig. 10).

II. The coronary occlusion with the cardiac arrest induced by drugs
Fig. 8. Changes of ECG in the case of 30 minutes coronary occlusion.

Fig. 9. Changes of heart rate, coronary blood flow and myocardial O₂ consumption in the case of 30 minutes coronary occlusion.
1) 2.5% potassium citrate

The frequent heart beats after reperfusion were sometimes absent and settled to the initial value sooner or later. The coronary blood flow after a lesser degree of reactive hyperemia tended to decrease below the initial level to some extent. The characteristic depression of the myocardial oxygen consumption immediately after reopening of coronary circulation increased gradually approaching to the value before the occlusion, but it never reached that level during observation (Fig. 11). On ECG, a picture of hyperpotassemia appeared for a short period (Fig. 12). Histologically, highly developed changes of mainly myocardial necrosis were produced in all cases (Fig. 13).

2) Combination of 2.5% potassium citrate, glucose 500 mg. and insulin 10 units
The rapid heart rate was nearly restored to its original value within 30 minutes after release of the occlusion. The coronary blood flow was
Fig. 14. Changes of heart rate, coronary blood flow and myocardial O₂ consumption in the case of cardiac arrest induced by 2.5% potassium citrate with glucose and insulin.

Fig. 15. Changes of ECG of the experiment described in Fig. 14. No significant changes except hyperpotassemia which lasted for a short period.
stabilized at a certain level during 30 minutes after reactive hyperemia and maintained a high value, the same as in the 30 minutes occlusion experiment. The initial increase of myocardial oxygen consumption decreased gradually to a value lower than that before the occlusion similar to the potassium citrate experiment (Fig. 14). No significant changes appeared in ECG except hyperpotassemia which lasted for a short period of time (Fig. 15). Histological changes were apparently slight in comparison to the case of potassium citrate alone (Fig. 16).

3) Combination of 2.5% potassium bicarbonate, glucose 500 mg., and insulin 10 units

The results were subdivided in group A with comparatively slight (Fig. 17) and group B with rather severe histological changes (Fig. 18).
Fig. 19. Changes of heart rate, coronary blood flow and myocardial $O_2$ consumption in the case of cardiac arrest induced by 2.5% potassium bicarbonate with glucose and insulin (Group A, comparatively slight myocardial changes).

Fig. 20. Changes of heart rate, coronary blood flow and myocardial $O_2$ consumption in the case of cardiac arrest induced by 2.5% potassium bicarbonate with glucose and insulin (Group B, severe myocardial changes).

Both groups exhibited a prominent tachycardia as in the 30 minutes occlusion. The coronary blood flow after a reactive hyperemia decreased gradually and in group A it increased again, while in group B it never increased but rather stabilized at low level. The myocardial oxygen consumption in group A showed sustained higher rate (Fig. 19), but in group B it remained in a decreased rate even without an initial increase (Fig. 20). The ECG did not show any difference from the case of potassium citrate, glucose and insulin.
Fig. 21. Changes of heart rate, coronary blood flow and myocardial $O_2$ consumption in the case of cardiac arrest induced by Young’s solution with prostigmin.

Fig. 22. Changes of ECG of the experiment described in Fig. 21. The pattern of the sinus bradycardia.
4) Combination of 1.9% potassium chloride, sodium bicarbonate, glucose 500 mg. and insulin 10 units (pH 8.0)

Approximately the same changes were observed in this case as that of 2.5% potassium bicarbonate, glucose and insulin.

5) Young's solution and prostigmin

Bradycardia continued for a long time even after the release of the occlusion. The coronary blood flow after a temporary increase was maintained in a lower value than that before the occlusion. The myocardial oxygen consumption settled to a certain low value at an early period (Fig. 21). The ECG pattern of the sinus bradycardia was recognized (Fig. 22). Histologically, not so severe changes were observed (Fig. 23).

Discussion

Induced cardioplegia has been widely used since Effler et al.\textsuperscript{5)} reported it as an effective mean to facilitate intracardiac operation under direct vision. As agents for cardiac arrest, potassium citrate, acetylcholine, magnesium sulfate, mixed solution of potassium citrate and prostigmin (Young's solution), solution of potassium citrate and magnesium sulfate, mecholyl and potassium citrate, etc. have been used. Of these agents, potassium citrate has been most widely used as one that assures of a long cardiac arrest. Lately, not a few reports have been observed which are critical of the process of elective cardiac arrest. Cooley et al.\textsuperscript{12)} has never used this process because it prolongs the period of total extracorporeal circulation and produces frequent ventricular fibrillation. Lillehei et al.\textsuperscript{13)} states that this process accompanies a great risk, when left ventricular hypertrophy and myocardial degeneration are present. Mines et al.\textsuperscript{15)} examined the elective cardiac arrest which was induced by a solution of
potassium chloride and magnesium sulfate, and found that it was safe and recovery assured as long as the arrest lasted not more than 35 minutes, but in the cases where it lasted more than 35 minutes various disturbances occurred with high rate of mortality. The authors have noticed through experimental results (Fig. 24 and Table I), above all, histological observa-

![Graph](image-url)

Fig. 24. Changes in percent of heart rate, coronary blood flow, and myocardial \( O_2 \) consumption (summarized from total data).

tion that elective cardiac arrest by means of potassium citrate retard the recovery after reperfusion, i.e., the lesser degree of the reactive hyperemia, the depression of the oxygen consumption and the coronary flow and the absence of tachycardia and produced severe histological damages in the heart muscle. However, the heart to which a drug was given for inducing the standstill, is considered to be influenced not only by the drug itself but by anoxia. The effects of anoxia induced by the 30 minutes occlusion were the prominent reactive hyperemia, the sustained higher level of the coronary flow and the oxygen consumption, a long lasting tachycardia and vast histological damages. According to Newsholme and Randle,\(^{16}\) anaerobic heart muscle of a rat, when insulin was added to it, tends to have the phosphofructokinase-action strengthened and glycolysis accelerated. The authors, in order to alleviate the effect of anoxia, used a mixed
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<th>Drugs for cardiac arrest</th>
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<th>Grade of histological changes</th>
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Table I. Histological Changes of All Experimental Cases

* VF, Resuscitated by counter shock.
+ Necrosis.
± Degeneration.
Ed. Subendocardial layer.
M. Middle layer.
Ep. Subepicardial layer.
solution to which insulin and glucose were added to potassium citrate to make anaerobic metabolism active, that is, to accelerate the use of glucose. As a result it was found that the myocardial damages were apparently less in this case than when potassium citrate was used alone. Furthermore the toxic effect of potassium citrate, i.e., the restricted reactive hyperemia, the long lasting reduction of the coronary flow, the depression of the oxygen consumption and the absence of the tachycardia during a period of the reactive hyperemia was apparently alleviated. When the drug itself was replaced by potassium bicarbonate, the results obtained were similar to the anoxic effect induced by coronary occlusion. The myocardial damage caused by potassium chloride and Young's solution was less serious than in the case of potassium citrate.

Concerning the clinical application of the elective cardiac arrest, the authors consider that it is desirable that the natural reaction of the myocardial anoxia and the effect of not inert potassium salt are restored to the pretreated stage as early as possible. Especially the oxygen consumption and heart rate should be stabilized earlier. From this point of view, the use of glucose and insulin added to potassium citrate should be considered to produce the best result. On the other hand, it is noteworthy that when potassium citrate was added to Young's solution, myocardial oxygen consumption was stabilized early, but it is quite unpleasant that, in this case, bradycardia continued for a long time. When an agent for arrest is made alkaline in order to alleviate myocardial acidosis, it is also undesirable that rapid heart rate and an increased myocardial oxygen consumption continue in a period of recovery. The authors believe that among the agents for cardiac arrest, which are used at present, there is no very reliable one, and that potassium citrate which is most widely used leaves the severest influence on the heart muscle and it can not be recommended, although this influence on the heart muscle can be alleviated, when glucose and insulin are added to it.

Summary

The isolated Langendorf dog's heart preparation with cross circulation was arranged for studying the effect of anoxia by coronary occlusion and cardiac arrest by drugs, potassium citrate, potassium bicarbonate, and potassium chloride with or without 500 mg. of glucose and 10 units of insulin. The heart rate, coronary blood flow, myocardial oxygen consumption and histological changes were studied.

(1) The more severe and profuse histological changes, mainly irreversible myocardial degeneration, were produced when potassium citrate was used than those produced by 30 minutes coronary occlusion.
(2) The effect of anoxia, i.e., the prominent reactive hyperemia, the sustained increase of the coronary flow and the oxygen consumption and the increase of heart rate observed by the 30 minutes coronary occlusion were definitely restricted by the use of potassium citrate. The concomitant use of the glucose with insulin alleviated the toxic effect of citrate to some extent.

(3) The alkalization in order to avoid the metabolic acidosis of the heart muscle occurring during cardiac arrest left a long lasting tachycardia and thus produced an increase of myocardial oxygen consumption for a period of observation.

References