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Kyoto University
MYOCARDIAL DYSFUNCTION AFTER CARDIOPLEgia
AN EXPERIMENTAL STUDY

by

TAKURO KUSUNOKI, M. D.*
HUAN-CHEN CHENG, M. D.**
HUNTER H. McGUIRE, Jr., M. D.
LEWIS H. BOSHER, Jr., M. D.

RICHMOND, VIRGINIA

Presented before the Southern Thoracic Surgical Association, Biloxi, Mississippi, November 20-21, 1959
Present addresses : * Iwate Medical College, Morioka, Japan
** St. Francis Hospital & Sanatorium, Roslyn, Long Island, N. Y.
From the Division of Thoracic and Cardiovascular Surgery, Department of Surgery, Medical College of Virginia, Richmond, Virginia

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Today cardioplegia achieved with potassium citrate (the Melrose technique) (1, 2) is condemned as vociferously as it was enthusiastically acclaimed four years ago. Other cardioplegic agents and techniques have since been introduced and in turn received with varying degrees of enthusiasm. We share the clinical impression of others that induced cardiac arrest has often produced serious impairment of myocardial function. However, hypotension and circulatory failure cannot be ascribed solely to cardioplegia. The ventriculotomy and the hemodynamic adjustment required of the heart are important determinants. Because of the many factors involved in the success of a complicated open heart procedure the survival of the animal or patient has proved to be an unreliable or inadequate measure of the safety and relative value of a cardioplegic agent. Our investigation was undertaken in order more accurately to evaluate and quantitate different methods of elective cardiac arrest.

Sarnoff and Berglund (3) have shown that ventricular performance can be expressed as a function curve in which ventricular stroke work is plotted against the corresponding mean atrial or ventricular filling pressure. In their experiments, which did not involve extracorporeal circulation, the data were obtained by progressively elevating the atrial pressure with increments of blood transfused into the experimental animal. The resulting cardiac output was measured by means of a flow meter. Stirling, Stanley and Lillehei (4) studied the effects of ventriculotomy upon right ventricular function using Sarnoff curves. They collected the necessary data by controlled venous inflow. We have employed a similar technique in our own studies.
Fig. 1

PERFUSION

FUNCTION CURVE
METHODS

Twenty-six mongrel dogs, averaging 9.5 kg, were medicated with 4 mg/kg morphine sulfate, induced with sodium pentothal and anesthetized with alpha chloralose and urethane. They were anticoagulated with heparin, 5 mg/kg. Extracorporeal circulation with total perfusion was established for 15 minutes with rotary pump and homologous lung oxygenator (Fig. 1). The perfusion circuit was then modified for controlled venous inflow and at increasing flow rates from 600 to 3000 cc/min. The mean right atrial, pulmonary artery, left atrial and aortic pressures were recorded. With pressures converted to centimeters of water the following formulae yield ventricular stroke work:

\[
\text{RV Stroke Work (gm.-meters)} = \frac{\text{Flow (cc/min) \times (PA-RA pressure)}}{\text{Pulse Rate \times 100}}
\]

\[
\text{LV Stroke Work (gm.-meters)} = \frac{\text{Flow (cc/min) \times (Ao-LA pressure)}}{\text{Pulse Rate \times 100}}
\]

Fig. 2

CARDIAC ARREST – Aortic Occlusion – 15 min.

LEFT HEART 6–12–59

RIGHT HEART

I – Control
IV – Stellate Stimulation

Supported by NIH Grant (H-3065 (C2), and by Heart-Lung Project.
All function curves were determined at 35°C. The average maximum control stroke work for all left ventricles was 28.8 gm.-meters, and for all right ventricles was 5.2 gm.-meters. Function curves for each normal ventricle were constructed by plotting each filling pressure (mean atrial pressure) against the stroke work which it produced (Curves I for Figs. 2, 3, 4).

Total perfusion was then reinstituted and the heart arrested by one of the five techniques described below. After a 15 minute period of cardiac depression or arrest the heart was released and cardiac action resumed (with defibrillation in 2 cases). Both atria were decompressed until cardiac action was adequate to prevent distention of the heart. Function (Curve II) was studied after 15 minutes of recovery perfusion, and again (Curve III) after an additional perfusion of 15 minutes (approximately 1 hour after arrest). (In some experiments the effect of stimulating the isolated right stellate ganglion was evaluated (Curve IV)). The function curves thus obtained were then plotted together to form a family of curves produced by a single heart (Figs. 2, 3, 4).

Fig. 3
Heretofore function curves of variously treated hearts have been compared by gross visual impression in regard to maximum peak, slope, and displacement along the abscissa (1-6). This comparison "by impression" does not allow statistical integration of several experiments. Every function curve represents its heart's functional capacity over the wide range of filling pressures by which it might be challenged. It is impossible by any single formula to assign to every function curve a numerical value which is quantitatively significant of function. However, the relative values of 2 curves in the same family may be expressed numerically as the average ratio between their stroke works over a range of atrial pressures. This average ratio is accurately expressed by relating the areas under curves delimited by properly selected ordinates (Fig. 5). In these experiments control curves are considered 100% of ventricular function, and post-arrest curves are related to
the control curves in terms of per cent.

**Fig. 5**

**HYPOTHETICAL EUNCION CURVES DEMONSTRATING METHOD OF DERIVING CURVE AREA AND PERCENT OF FUNCTION**

**RESULTS**

*Acetylcholine* (10mg/kg) achieved arrest promptly when injected into the proximal, clamped aorta of normothermic dogs. In 3 dogs the aorta was released after a 3 minute arrest, and in 4 dogs arrest was maintained for 15 minutes. Cardiac contraction returned promptly upon release of the aorta in all cases. Post-arrest function curves are expressed as per cent of control function as shown in Table I. The average values for per cent function shown in Table 1 are plotted in Fig.6. Significant is the finding that marked depression of both ventricles occurs after acetylcholine arrest of either duration, but a more rapid recovery is found after the shorter arrest (Fig. 6).

<table>
<thead>
<tr>
<th>Experiment Number</th>
<th>Maximum Stroke Work (GM-M)</th>
<th>% Function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td></td>
<td>1 2 3</td>
<td>1 2 3</td>
</tr>
<tr>
<td>AC-3 min-1</td>
<td>3.5 3.9 4.4</td>
<td>30.0 25.1 24.6</td>
</tr>
<tr>
<td>AC-3 min-2</td>
<td>5.3 3.9 4.6</td>
<td>23.9 10.3 13.3</td>
</tr>
<tr>
<td>AC-3 min-3</td>
<td>4.0 3.2 3.7</td>
<td>22.2 13.4 16.0</td>
</tr>
<tr>
<td>AC-3 min-Aver.</td>
<td>4.3 3.7 4.2</td>
<td>25.0 16.2 18.0</td>
</tr>
<tr>
<td>AC-15 min-1</td>
<td>3.2 1.5 2.0</td>
<td>27.1 12.5 11.1</td>
</tr>
<tr>
<td>AC-15 min-2</td>
<td>6.6 3.7 5.1</td>
<td>25.2 16.5 19.4</td>
</tr>
<tr>
<td>AC-15 min-3</td>
<td>2.6 1.2 2.1</td>
<td>21.4 15.4 20.0</td>
</tr>
<tr>
<td>AC-15 min-4</td>
<td>5.0 3.2 3.0</td>
<td>24.6 11.0 19.8</td>
</tr>
<tr>
<td>AC-15 min-Aver.</td>
<td>4.4 2.4 3.1</td>
<td>21.6 16.6 17.6</td>
</tr>
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</table>
Potassium Citrate (2.5%) produced immediate arrest in 7 normothermic dogs. In 3 animals the aorta was released after a 3 minute arrest, while in 4 the arrest was maintained for 15 minutes. In all cases cardiac action resumed promptly. Function curves derived from these experiments were converted to areas and percent of controls, and results are shown in Table 2. Technical errors in the 3 minute arrest experiments produced inexplicable results, while 15 minute arrest experiments resulted in marked depression of both ventricles with partial, but very incomplete, recovery occurring during the 15 minute additional perfusion. The results of Experiment No. KC-15-2 are plotted in Fig. 2 as an example of this severe myocardial depression.

Hypoxic Arrest was achieved by simple aortic occlusion in 4 normothermic dogs. Cardiac action ceased on an average of 6 minutes after occlusion. After 15
Aortic Occlusion at 25°C. for 15 minutes (during which time the animal was rewarmed and the heart remained below 29°C.) was performed in 4 experiments. As in the other experiments myocardial function was measured at 35°C. In each case the heart moved quietly until release of the aorta, when good cardiac action resumed immediately. Post-arrest function curves were converted to per cent of control of function (Table 4). In this series of experiments both ventricles showed less depression and more rapid recovery than was found in any of the three previously tested methods of cardioplegia. Figure 4 illustrates the favorable influence of hypothermia as determined in Experiment No. 25-15-2.

Results of the four techniques considered thus far are summarized in Fig. 7. Approximately 50% loss of function occurs in both ventricles after 15 minute car-

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**Table 3** Hypoxia (Aortic Occlusion)

<table>
<thead>
<tr>
<th>Experiment Number</th>
<th>Maximum Stroke Work (GM-Meters)</th>
<th>% Function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
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<td></td>
<td>1 2 3</td>
<td>1 2 3</td>
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<tr>
<td>X-15 min-1 *</td>
<td>3.6 0.9 0.9</td>
<td>100 29 25</td>
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<tr>
<td>X-15 min-2</td>
<td>5.0 2.4 3.0</td>
<td>100 52 60</td>
</tr>
<tr>
<td>X-15 min-3</td>
<td>5.6 3.1 3.4</td>
<td>100 50 54</td>
</tr>
<tr>
<td>X-15 min-4</td>
<td>8.6 3.8 5.6</td>
<td>100 48 66</td>
</tr>
<tr>
<td>X-15 Aver.</td>
<td>5.7 2.6 3.2</td>
<td>100 45 51</td>
</tr>
</tbody>
</table>

**Table 4** Hypoxia (Aortic Occlusion) -25°C.

<table>
<thead>
<tr>
<th>Experiment Number</th>
<th>Maximum Stroke Work (GM-Meters)</th>
<th>% Function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td></td>
<td>1 2 3</td>
<td>1 2 3</td>
</tr>
<tr>
<td>25-15-1</td>
<td>10.4 6.1 7.5</td>
<td>100 82 87</td>
</tr>
<tr>
<td>25-15-2</td>
<td>7.5 5.1 6.1</td>
<td>100 87 115</td>
</tr>
<tr>
<td>25-15-3</td>
<td>11.1 8.1 6.7</td>
<td>100 68 69</td>
</tr>
<tr>
<td>25-15-4</td>
<td>2.9 1.9 3.6</td>
<td>100 43 158</td>
</tr>
<tr>
<td>25-15-Aver.</td>
<td>7.8 5.3 6.0</td>
<td>100 70 108</td>
</tr>
</tbody>
</table>

* Electrical Defibrillation
dioplegia by each technique except for aortic occlusion at 25° C., where 70% of function is retained by both ventricles. After an additional 15 minute perfusion further recovery occurs in all cases: to 51% and 55% in the right and left ventricles respectively after simple aortic occlusion, 64% and 64% after acetylcholine, 78% and 76% after potassium citrate and 108% and 82% after hypothermic aortic occlusion. The last method appears to be the least harmful.

**Sympathetic stimulation**: In 12 dogs a fourth function curve was derived immediately after obtaining Curve III (on an average of 80 minutes post-arrest). During this phase of the experiment the isolated right stellate ganglion was stimulated continuously with 20 to 30 volts at 25 cycles per second. The purpose of this maneuver was to determine whether elective cardiac arrest impaired the heart's responsiveness to sympathetic stimulation. In 75% of cases (see Fig. 3), Curve IV revealed improvement over Curve III, but because control stimulation curves were not made, it is not known whether the additional improvement was spontaneous or induced. More conclusive studies are now in progress.

**Total Body Hypothermia to 15° C.** with interruption of perfusion for 15 minutes was performed in 3 dogs. Cooling and rewarming was effected by a heat exchanger in the extracorporeal circuit. In each experiment a quiet but tonic heart was produced, and in only 1 case was defibrillation necessary upon recovery. The results shown in Table 5 reveal wide discrepancies with a general tendency towards delayed loss of function. These findings may represent the delayed effect of hypo-
thermia and rewarming. Since no metabolic studies were performed in this series of experiments, the data allow no conclusions.

<table>
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<th>%Function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>15-15-1</td>
<td>3.6</td>
<td>2.9</td>
</tr>
<tr>
<td>15-15-2*</td>
<td>2.8</td>
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<tr>
<td>15-15-3</td>
<td>9.8</td>
<td>2.7</td>
</tr>
<tr>
<td>15-15-Aver.</td>
<td>5.4</td>
<td>3.3</td>
</tr>
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</table>

* Electrical Defibrillation

**DISCUSSION**

Investigations on cardioplegic agents have been carried out by a variety of methods. These include observations on the recovery and contractility of the isolated heart or on the isolated heart metabolically supported by a donor animal. Studies have been reported on the period of time for pump support following cardiac arrest in order to achieve a satisfactory and stable arterial pressure. Other investigations concern the oxygen consumption of the arrested heart or the developing tissue acidosis. Survival statistics have been compared between animals undergoing cardiac arrest and those in which coronary perfusion was uninterrupted, or interrupted by simple aortic occlusion. Finally, histologic changes in the myocardium of surviving animals have been reported. As compared to these methods, ventricular function studies by the Sarnoff technique have the distinct advantage of stressing the heart to the point of maximum performance while allowing a rough quantitation of this performance. Moderate or even minor impairment of myocardial function is thus revealed.

In a series of recent reports Hanlon and his associates (5, 6) have shown marked depression of left ventricular myocardial function after a 30 minute arrest with either potassium citrate, acetylcholine, a mixture of prostigmine, magnesium sulfate and potassium citrate, or aortic occlusion. There was reduction in maximum stroke work performance from the control value of 25-50 to less than 10 gm.-meters of work, when measured 10 minutes or 2 hours post-arrest. Less depression was noted after potassium arrest for 20 minutes. Partial protection of the heart was provided by previous digitalization or cooling to 28°C, and partial recovery was effected by administration of Wyamine. Weirich and Burke (7) have noted a roughly similar effect on myocardial function with increasing deterioration as the period of arrest was prolonged from 5 to 20 minutes. The effect of potassium citrate, acetylcholine, or simple aortic occlusion was roughly the same.

Braunwald and Morrow (8) found severe depression in myocardial function after 20-30 minutes of arrest with either potassium citrate or acetylcholine. Using
interrimt aortic occlusion, however, with 4 minutes of occlusion and 1 minute
of release alternatively over a period of 30 minutes they found no significant depression.

The ventricular function studies reported in this paper were commenced before the
city of the above investigators was known to us. Our methods and our results
are closely similar to those of the above authors. However, a valid method of
integrating the data of identical experiments has been devised, permitting us to
compare statistically the results of any given type of arrest in a series of exper-
iments (Fig. 5). The data obtained were thus analyzed and justify the following
conclusions.

CONCLUSIONS

1. Cardiac arrest for 15 minutes by any of the techniques studied results in
depression of myocardial function to 50-70% of control function when measured 15
minutes post-arrest.

2. Partial recovery of myocardial function occurs with an additional 15 minute
perfusion.

3. At normal body temperature, 15 minute cardiac arrest by potassium citra-
te and by acetylcholine, and 15 minute aortic occlusion, cause similar degrees of
depression, although recovery appears to be most rapid after potassium citrate and
most delayed after hypoxia.

4. Prolongation of cardioplegia results in greater depression of myocardial
function, and further delay in recovery of function.

5. Hypothermia to 25°C, partially protects the heart rendered hypoxic for 15
minutes, and in comparison to other methods studied, cardioplegia by this technique
resulted in least depression and best recovery of myocardial function.

Acknowledgment

We are indebted to Dr. Stanley Sarnoff for his suggestions, which have aided
in the conduct of these experiments and in the preparation of this manuscript.

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和文抄録
任意心搏停止法の心機能曲線に及ぼす
影響に関する実験的研究
楠 卓 郎・鄭 燦 陈

26匹の犬を使用し，同種肺利尿による体外循環を行って，Sarnoffの心機能曲線を描き，Acetylchoine又はK-citによる心停止，Hypoxiaによる心停止等の各種心搏停止の心機能曲線に及ぼす影響を調査した。
その結果次の如き結果を得た。

1) 15分間の心搏停止を行うと，如何なる方法を用いても，心搏停止解除後15分間体外循環を行っても，何れも50～70％の心機能低下が認められる。

2) その後15分間の体外循環を行うと，心機能曲線では部分的な恢復の傾か認められる。

3) 15分間の心搏停止は，Acetylcholine, K-cit, Hypoxia，何れの場合でも略々同程度の心機能抑制をもたらすが，その恢復はK-citが一番良好で，Aortic occlusionによる Hypoxia の場合が最も遅れる傾である。

4) 心搏停止の時間が長くなればなる程，心機能は低下し，更にその後恢復が遅延する。

5) 25℃の低体温を併用すると，心搏停止による心機能低下は軽減され，恢復も良好である。