Coronary Venous Perfusion of the Ischemic Myocardium during Acute Coronary Artery Occlusion in Isolated Rat Hearts

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SUMMARY. Effects of retrograde coronary venous perfusion on oxygen supply and energy metabolism of ischemic myocardium of the isolated perfused rat heart were examined by means of NADH fluorescence photography. Occlusion of the left coronary artery produced regional ischemia of the left ventricular free wall, as evidenced by the sharply demarcated increase in NADH fluorescence. During ischemia, a narrow area of minimal fluorescence (140 ± 10 μm), indicating sufficient oxygenation for oxidative phosphorylation, was observed around the epicardial coronary veins in the ischemic lesion. Retrograde perfusion was introduced through the coronary vein (left cardiac vein) that drained off the ischemic area, which resulted in a marked reduction of the area of increased NADH fluorescence in the epicardial surface. In the cross-sectional view, although the myocardium of the entire ischemic area induced by left coronary artery occlusion could be perfused by venous retroperfusion, the effect on reduction of the area of increased NADH fluorescence was seen only in the epicardial half of the myocardium. Retrograde coronary venous perfusion also resulted in a small increase in tension development (P < 0.05), a decrease in resting tension (P < 0.01), and partial preservation of myocardial high energy phosphate content (P < 0.01). We propose that coronary venous retroperfusion improves oxygenation, partially preserves oxidative phosphorylation in the epicardium, and improves contractile function in the ischemic region. (Circ Res 56: 666-675, 1985)

EXPERIMENTS involving retrograde perfusion on arterIALIZATION of the coronary veins were first reported by Pratt (1893), who was able to sustain the contraction of the cat heart for several hours by coronary sinus perfusion. Since then, attempts have been made to restore the impaired myocardial circulation in cases of ischemic heart disease. The first clinical application of this attempt was accomplished by Beck (1948). He performed a carotid-coronary sinus anastomosis or an aortocoronary sinus anastomosis, using a vein graft. However, the mortality with the procedure remained high. These studies have been overshadowed by the development of direct coronary artery revascularization (Berger and Stary, 1971). Recently, there is renewed interest in retrograde coronary venous perfusion, in selective situations such as diffuse coronary arteriosclerosis, and in cases of temporal support for patients with acute myocardial infarction. Recent efforts of Meerbaum et al. (1976) showed the usefulness of a synchronized diastolic retroperfusion system to decrease damage in the acutely ischemic myocardium. There have been numerous studies on the usefulness of retrograde coronary venous perfusion; yet, metabolic events associated with the possible increase in oxygenation to the tissue are poorly understood. The objective of our study was to obtain evidence for direct oxygen delivery to the ischemic lesion, by retrograde coronary venous perfusion (RCVP), using NADH fluorescence photography (Barlow and Chance, 1976; Steenbergen et al., 1977; Harken et al., 1978). Nicotinamide adenine dinucleotide, reduced form (NADH), fluorescence increases when the oxygen supply is deficient, and, as a result, oxidative phosphorylation is inhibited (Chance, 1976). Fluorescence photography was used to determine the area involved by antegrade aortic perfusion and RCVP, and for this, a fluorescent dye was added to the perfusate.

Methods

Perfusion Technique

Male Wistar rats weighing 250–350 g were given free access to a commercial diet and tap water. Thirty minutes before excision of the hearts, 500 U of heparin were given intraperitoneally. The isolated hearts were perfused at a pressure of 80 cm H2O by the Langendorff procedure (Langendorf, 1895), with a minor modification. The perfusate was Krebs-Ringer bicarbonate buffer solution containing 2.5 mM calcium and 5.5 mM glucose, aerated with a 95% O2–5% CO2 mixture for the aerobic perfusion and a 95% N2–5% CO2 mixture for the anaerobic perfusion. The perfusate was allowed to pass through the heart only once. The hearts were perfused at 30°C and were paced electrically at 200 beats/min. Under these conditions, we obtained a stable preparation for almost 60 minutes. Myo-
cardial oxygen consumption under these conditions was $1.08 \pm 0.08 \text{ mmol O}_2/\text{hr per g}$.

A strain gauge (SB-IT, Nihon Kohden) was attached via a nylon ligature to the ventricular apex for the measurement of tension development of the whole heart. At the start of each experiment, the resting tension was set at about 1 g.

To induce regional ischemia in the left ventricular wall, we surgically occluded the left coronary artery (LCA) at a point 5 mm from its origin, using the techniques developed by Selye et al. (1960).

Arterial and venous effluent Po$_2$ during the perfusion in aerobic, anaerobic, and LCA occlusions was measured with a Corning blood gas analyzer. Coronary flow rates (flow rates of venous effluent) were measured with a drop counter.

In all experiments, preconditioning of the preparation involved a 20-minute perfusion to wash out the red blood cells and to stabilize the heart rate and coronary flow.

**Coronary Venous Retroperfusion**

For retrograde coronary venous perfusion (RCVP), a polyethylene catheter, 300 µm in diameter, was inserted into the left cardiac vein (Halpern, 1953) via the right atrium. The distal end of the catheter was carefully located near the margin of the ischemic region, and retrograde flow rate through the catheter was controlled by a roller pump. To diminish the possible fluctuation of the flow rate, a 10-ml air space was made within the perfusion route. Since the outside diameter of the catheter was less than the inside diameter of the vein, obstruction of antegrade venous drainage of the perfusate from the heart during systole and resultant possible tissue edema was prevented (Farcot et al., 1978). Since coronary flow rates during the aerobic control period and during LCA ligation were $8.8 \pm 0.3 \text{ ml/min}$ and $5.7 \pm 0.4 \text{ ml/min}$, respectively (indicating that there was a reduction of at least 3 ml/min during ischemia), retrograde flow rate was set at 3 or 5 ml/min; with these flow rate levels, there was no tissue edema. To monitor pressure in the retrograde-perfused vein, we punctured a branch of the vein near the ischemic margin, inserted a polyethylene catheter 300 µm in diameter, and connected it to a catheter-tip transducer (Millar; pc-350). For simultaneous determination of the area of arterial antegrade perfusion and the area of venous retrograde perfusion by fluorescence photography, fluorescein sodium (Wako-Junyaku) and thioflavin S (Chroma) were perfused from the aortic and venous roots, respectively.

**Fluorescence Photographs**

Photographs of NADH fluorescence were obtained by a system we developed in collaboration with the Union Giken Company, Osaka, Japan, the principles and the techniques of which were described initially by Barlow and Chance (1976). A Canon A-1 camera with a 50-mm focal length microlens and extension tube (FD-25) was used. Toshiba Y-45 and B-46 filters were placed before the camera lens to allow for transmission in the 440- to 500-nm region. NADH excitation was provided by two 300J xenon flash tubes (FS-403, Union Giken), one mounted on either side of the camera lens, to provide fairly uniform illumination on the left ventricular free wall. The xenon flash tubes were covered with Toshiba UV-D36C and UV-35 filters to provide 340-380 nm excitation. To avoid possible fluctuations of fluorescence during the cardiac cycle, the flash was synchronized to occur during diastole, with an electrical pacing spike as a trigger.

All heart preparations for the cross-sectional NADH fluorescence photography were immersed immediately in liquid nitrogen, and then freeze-dried. Cross-sectioning was performed with a razor blade, at a right angle to the long axis of the freeze-dried heart, at a level 10 mm from the apex. For detailed microscopic examinations of the cross-sectional distribution of NADH fluorescence, fluromicrophotography was carried out with a reflected fluoromicroscope (Zeiss-standard 18F, filter set 01).

For the fluorescence photography of both thioflavin S (emission: 440 nm) and fluorescein sodium (emission: 530 nm), 340- to 380-nm wavelength was also used for excitation. Both thioflavin S and NADH emit at 440 nm.

**FIGURE 1.** Epicardial NADH fluorescence photographs under conditions of aerobic perfusion (panel A), hypoxia (panel B), and regional ischemia (panel C).
When we examined the distribution of NADH and thioflavin S fluorescence in the same heart, NADH fluorescence was photographed before the venous retroperfusion of thioflavin S. The fluorescence intensity of thioflavin S is so high that the photographic condition required to detect the fluorescence of added dyes is not sensitive enough to be disturbed by NADH fluorescence of low intensity. Fluorescence of NADH and added dyes was clearly recorded in characteristic color (emission) on Kodak Tri X film (ASA 400, monochrome) and Kodak color negative film (ASA 400).

**Biochemical Analysis**

After 20 minutes of regional ischemia, with or without venous retrograde perfusion, the left ventricular free wall subjected to ischemia assessed by NADH fluorescence was quickly excised and frozen, using a Wollenberger's tong precooled in liquid nitrogen. In addition, the control left ventricular free wall was obtained from the heart perfused with aerobic solution for 20 minutes, following 20 minutes of perfusion for preconditioning (control). Tissue concentrations of adenosine 5'-triphosphate (ATP) and creatine phosphate (CP) were assayed according to the method of Lamprecht et al. (1975). Adenosine diphosphate (ADP) and adenosine monophosphate (AMP) were assayed by the procedures described by Jaworek et al. (1975). Tissue concentrations of nicotinamide adenine dinucleotide (NAD) and its reduced type (NADH) were assayed according to the method of Williamson and Corkey (1969).

**Statistical Analysis**

Results were expressed as mean ± SEM. Statistical significance was determined by analysis of variance. Values of $P < 0.05$ were considered significant.

**Results**

**The Area of Increased NADH Fluorescence Induced by LCA Occlusion**

All control photographs of each normoxic-preischemic heart showed uniform distributions of minimal NADH fluorescence (Fig. 1A). When the heart, initially perfused with aerobic perfusate (Fig. 1A), was perfused with an anaerobic one, the entire heart...
showed an increase of epicardial NADH fluorescence that was relatively uniform in intensity (Fig. 1B). Upon occlusion of LCA, increased NADH fluorescence was clearly visible distal to the occlusion (Fig. 1C). The ischemic myocardium showed a zone of NADH fluorescence relatively low in intensity around the epicardial vein, which was broader (1.4 times) than that observed under conditions of anaerobic perfusion. Figure 2A also shows a typical NADH fluorescence photograph of regional ischemia induced by LCA occlusion. In this experiment, the relatively distal portion of the LCA was ligated to demonstrate clearly the border between the ischemic and normal areas, in a photograph of the left ventricular free wall. Because of the minimum NADH fluorescence, both in and around the epicardial veins, the areas appeared distinctly as networks of dark lines in the ischemic area of increased fluorescence. When fluorescein sodium was perfused by admixture with the aortic perfusate following LCA ligation, we obtained a photograph of fluorescein sodium with a reversed impression of the NADH fluorescence photograph (Fig. 2B). The area of minimal NADH fluorescence in Figure 2A coincided with the area of fluorescein sodium in Figure 2B. The epicardial veins in the ischemic area clearly showed evidence of fluorescein sodium, which may have derived from the perfused normoxic area because the dye was absent in the ischemic area and was present only in the epicardial veins.

Figure 2C shows a cross-sectional fluorescence photograph of both NADH and fluorescein sodium perfused from the aorta during LCA occlusion. NADH fluorescence (blue color) demonstrates an anoxic area in regional ischemia, and fluorescein sodium (green color) demonstrates a perfusion area from the aorta. Between these two fluorescent areas, there was a narrow band of no fluorescence approximately 180 ± 30 μm wide. It is emphasized that the NADH fluorescence area was clearly demarcated, and transition from minimal to full NADH fluorescence was abrupt.

Cross-sectional fluoromicrophotographs of

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**Table 1**

Changes in Coronary Flow and Po2 during Normoxia, Anoxia, and Regional Ischemia

<table>
<thead>
<tr>
<th></th>
<th>Normoxia</th>
<th>Anoxia</th>
<th>Regional ischemia</th>
</tr>
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<tbody>
<tr>
<td>Coronary flow (ml/min)</td>
<td>8.8 ± 0.3</td>
<td>17.5 ± 0.5</td>
<td>5.7 ± 0.4</td>
</tr>
<tr>
<td>Arterial Po2 (mm Hg)</td>
<td>595 ± 12</td>
<td>39 ± 2</td>
<td>597 ± 13</td>
</tr>
<tr>
<td>Effluent Po2 (mm Hg)</td>
<td>273 ± 27</td>
<td>23 ± 2</td>
<td>251 ± 12</td>
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**Figure 3.** Fluoromicrophotographs around the epicardial large vein under conditions of hypoxia (panel A) and regional ischemia (panel B). Panels A and B: cross-sectional views.
NADH of the subepicardial myocardium in the perfusional anoxia and regional ischemia are shown in Figure 3. In cases of global anoxia, an increase in NADH fluorescence around the subepicardial vein was fairly uniform (Fig. 3A), whereas there was a narrow less-fluorescent zone (140 ± 10 μm in 10 heart experiments) around an epicardial vein of a size approximately equal to that in Figure 3A in regional ischemia (Fig. 3B).

Changes in coronary flow rate, arterial Po₂ in aerobic perfusion, hypoxic perfusion, and perfusion under LCA occlusion are shown in Table 1. There was an increase in coronary flow rate in cases of hypoxic perfusion and a decrease in regional ischemia. Venous effluent Po₂ in LCA occlusion was 251 ± 12 mm Hg, which is significantly lower than in aerobic control perfusion, but much higher than in cases of perfusional anoxia.

**Effect of RCVP on Venous Pressure**

Figure 4 shows changes in the pressure of the distal branch of the epicardial vein, under conditions of RCVP. The mean venous pressure in the aerobic control perfusion was 8.2 ± 0.2 mm Hg. Venous pressure decreased by LCA occlusion to 3.6 ± 0.4 mm Hg. During RCVP, there was a flow-dependent increase in the venous pressure. We observed an almost direct correlation between the RCVP flow rate and the venous pressure.

**Perfusion Area of RCVP**

Assessment of the area perfused by RCVP (5 ml/min) during LCA occlusion was carried out by admixing thioflavin S with the venous-retroperfusate. We found that the area of increased NADH fluorescence (Fig. 5A) during occlusion coincided almost completely with the area perfused by RCVP (Fig. 5B). In the normally perfused normoxic area, however, only a network of large epicardial veins was stained with thioflavin S of RCVP (Fig. 5B). Thus, the dye had reached the normoxic area by RCVP, but it remained at the large epicardial veins and did not enter the smaller veins or capillaries and, as a result, no area of thioflavin S was observed in the normoxic area. A cross-sectional view of the distribution of the thioflavin S and fluorescein sodium, indicating the area of RCVP and the area of arterial antegrade perfusion, respectively, is shown in Figure 5C. The area of thioflavin S and the area of fluorescein sodium adjoined, and both the border zone and the overlapping of the two fluorescent dyes were negligible.

**Effect of RCVP on the Area of Increased NADH Fluorescence during LCA Occlusion**

Figure 6 represents a typical sequence of epicardial NADH fluorescence photographs taken during aerobic perfusion, LCA occlusion, and LCA occlusion with subsequent RCVP at 3 ml/min and 5 ml/min. When LCA of the aerobic perfused heart (Fig. 6A) was ligated at 5 mm from its origin, a sharply demarcated area of the increased NADH fluorescence, relatively uniform in intensity, was observed in the left ventricular free wall (Fig. 6B). Upon RCVP at 3 ml/min, a heterogeneous reduction in the intensity of NADH fluorescence occurred, especially around the epicardial veins, and the NADH fluorescence had a patchy appearance (Fig. 6C). When the RCVP flow rate was increased to 5 ml/min, reduction in the area and intensity of NADH fluorescence became more prominent (Fig. 6D).

Typical cross-sectional NADH fluorescence photographs of aerobic control, LCA occlusion, and LCA occlusion with subsequent RCVP (5 ml/min) of separate hearts are shown in Figure 7. There was minimal NADH fluorescence in the aerobic control heart (Fig. 7A). Upon LCA occlusion, a transmural involvement of an increase in NADH fluorescence was observed in the left ventricular free wall (Fig. 7B). In accordance with a heterogeneous reduction of increased epicardial surface NADH fluorescence, RCVP after LCA occlusion induced patchy areas of reduced intensity in NADH fluorescence in the left ventricular free wall, especially in the myocardium adjacent to the epicardium (Fig. 7C). These patchy areas were clearly demarcated from the surrounding areas with increased NADH fluorescence, because
the intensities of the NADH fluorescence of these areas were almost equal to those of oxygenated areas of the heart. We divided the left ventricular wall into endo- and epicardium of an equal width by drawing a line along the midpoint between the endo- and epicardial margin. When the areas of increased NADH fluorescence in an epicardial half and an endocardial half of the myocardium of the left ventricular wall were measured separately (the values in the ischemic state prior to RCVP being about 50% for each), RCVP induced a decrease in the area of an increased NADH by 15% in the epicardial half (P < 0.01 vs. no-RCVP) and a negligible change in the endocardial half (Fig. 8).

Effects of RCVP during LCA Occlusion on the Myocardial Function and Metabolic Intermediates

Changes in developed tension and resting tension of aerobic control, and in LCA occlusion, with and without subsequent RCVP, are shown in Figure 9. LCA occlusion produced a rapid decrease in developed tension and a gradual increase in the resting tension. Subsequent RCVP resulted in prevention of these deleterious changes induced by LCA occlusion (P < 0.05 in developed tension, P < 0.01; resting tension).

Tissue concentrations of adenine nucleotides, creatine phosphate, and pyridine nucleotides after 20 minutes of regional ischemia, with or without RCVP (5 ml/min), are shown in Figure 10. Upon LCA ligation, myocardial stores of ATP, total adenine nucleotides, creatine phosphate (CP), and NAD+ markedly decreased (vs. normal control; P < 0.01). RCVP had a significant preserving effect on the reduction of these constituents (P < 0.01). The myocardial concentrations of AMP and NADH which significantly increased during LCA occlusion (vs. normal control; P < 0.01), were partially prevented by RCVP (vs. no-RCVP, P < 0.01).

Discussion

In the present study, the effect of RCVP on myocardial oxygenation was evaluated by both epicar-
Barlow and Chance (1976) first used NADH fluorescence photography to evaluate regional ischemia. When most of the NADH fluorescence was attributed to mitochondrial NADH (Chance, 1976), there was a linear relation between increase of epicardial surface fluorescence and increase of tissue NADH content (Chance, 1976; Kanaide et al., 1982), and the oxidation-reduction potential of NADH was proportional to the state of phosphorylation (Owen and Wilson, 1974). If the intensity of NADH fluorescence under conditions of anaerobic perfusion was taken as 100%, and that of the aerobic perfusion as 0%, the increase in NADH fluorescence reportedly reached a 50% increase at approximately $10^{-8}$ M intracellular oxygen tension (Chance, 1976). Thus, it is well accepted that NADH fluorescence is an excellent indicator of tissue anoxia (Chance et al., 1965). In the present study, in addition to the surface fluorophotography, cross-sectional observations of the rapidly freeze-dried tissues were made, by both fluorophotography and fluoromicroscopy, to evaluate three-dimensional changes in the ischemic areas and the NADH fluorescence of the perfused rat hearts. The propriety of the freeze-drying technique was supported by the following findings obtained from preliminary studies: the global shapes of the...
heart were not changed by freeze-drying and tissue concentrations of pyridine nucleotides before and after freeze-drying were equal.

In contrast to the homogeneous increase in surface

NADH fluorescence in perfusional global anoxia, occlusion of LCA 5 mm from its origin under aerobic perfusion induced a nonfluorescent zone about 140 μm wide around the epicardial large veins in the ischemic region of increased NADH fluorescence. We mixed the fluorescent dye with aerobic-aortic perfusate and found that the epicardial large veins

**FIGURE 7.** Typical cross-sectional NADH fluorescence photographs in (panel A) aerobic perfusion, in (panel B) regional ischemia, and in (panel C) regional ischemia with coronary venous retroperfusion at 5 ml/min, in separate hearts.

**FIGURE 8.** Relative areas of increased NADH fluorescence in the epicardial half and endocardial half of the myocardium. The left ventricular wall was divided by drawing a line along the midpoint between endo- and epicardium. Percent NADH fluorescence area was calculated separately. Each column represents data on 10 heart preparations; no-RCVP: LCA occlusion only; RCVP: LCA occlusion with subsequent coronary venous retroperfusion (5 ml/min). **P < 0.01 vs. epicardial half in no-RCVP.

**FIGURE 9.** Changes in developed tension (above) and resting tension (below) with aerobic perfusion (O), regional ischemia (□), and regional ischemia with subsequent coronary venous retroperfusion (○). Coronary venous retroperfusion was introduced (5 ml/min) at the time indicated by the arrow (↓). (n = 8 heart preparations in each group). *P < 0.05, **P < 0.01 vs. no-RCVP.
Regional ischemia (left cardiac vein) in the ischemic area seem to drain away perfusate, not only from the ischemic area, but also from the area of normal perfusion. A narrow zone 140 µm wide around the epicardial veins, which receives an oxygen supply from these veins, may maintain myocardial oxygenation; hence, there would be no increase in NADH fluorescence. The maintenance of myocardial oxygenation may contribute to the preservation of a thin layer of intact myocardium adjacent to the epicardial large veins as reported in the studies of myocardial infarction in rats (Seyle et al., 1960; Fishbein et al., 1978).

The vascular system of the rat heart differs anatomically from those of dogs or humans. The left circumflex artery is poorly developed, and the left coronary artery is not accompanied by large veins (Selye et al., 1960). The drainage of most of the left ventricular free wall is through the left cardiac vein, which traverses the left ventricular surface and opens in the right atrium or right anterior vena cava without forming a coronary sinus (Halpern, 1953). In the present study, RCVP was carried out through the left cardiac vein cannulated with a fine polyethylene tube via the right atrium. The area of RCVP estimated by admixing thioflavin S with the retroperfusion fluid coincided fairly well with that of NADH fluorescence, both in the epicardial surface and cross-sectional views. These findings are similar to those of Gardner et al. (1974), who used 131I macroaggregated albumin in retrograde perfusion to assess the effects of coronary circulation and concluded that the retrograde flow was largely distributed in the ischemic zone in the in situ dog heart.

Coronary venous retroperfusion under conditions of regional ischemia demonstrated the improvement of S-T changes in epicardial electrocardiograms (Bhayana et al., 1974) and a reduction in the infarcted area (Chiu and Mulder, 1975). Meerbaum et al. (1976) developed a synchronized diastolic coronary venous retroperfusion system with a ECG triggered balloon pumping unit, and noted the improvement of myocardial force, decrease in epicardial S-T elevation, and increase of O₂ uptake, as assessed from blood samples. Using ultrasonic crystals to measure myocardial contractility and an endocardial electrocardiogram to assess changes in the subendocardium, Gundry (1982) demonstrated the beneficial effect of coronary venous retroperfusion on myocardial contractility and also ECG changes in the subendocardium, both in normal and hypertrophied canine hearts. More recently, Meerbaum et al. (1982) applied hypothermic synchronized retroperfusion in the closed-chest dog after acute coronary occlusion and demonstrated a favorable effect on cardiac function after reperfusion. Despite the increasing number of reports indicating the beneficial effects of RCVP, its effect on the nutritional supply to the ischemic region has not been determined.

In the present study, oxygen delivery by RCVP to the ischemic area was assessed directly by NADH fluorescence photography. RCVP induced a marked reduction of the area of increased epicardial NADH fluorescence during LCA occlusion. Although the RCVP flow was distributed over the entire ischemic area, oxygen delivery and the resultant restoration of oxidative phosphorylation were limited to the epicardial half of the myocardium. Inhibition of diastolic tissue pressure reduction in the subendocardial myocardium in acute ischemia (Sabbah and Stein, 1982) or high rate of energy utilization and resultant high rate of oxygen consumption in the subendocardial myocardium in the reversible phase of ischemia (Dunn and Griggs, 1975), or both, may explain the insufficient oxygen supply to the subendocardial layer by RCVP.

When Chiu and Mulder (1975) included 15-µm microspheres in the retrograde perfusate and estimated flow distribution, only a small portion of
retrograde flow, even in the excised heart, provided nutritional benefits to the ischemic lesion. Since the retroperfusion technique of their study is similar in principle to ours, the small microsphere flow increases in their study may be related to the patchy and modest epicardial increases in "oxygenation" in the present study.

Although we used a relatively low work heart with a high flow rate, and the perfusion medium for antegrade arterial perfusion and for RCVP was of low viscosity, RCVP resulted in a relatively modest increase in tension development, a decrease in resting tension, and a partial preservation of myocardial high energy phosphate content. Thus, we propose that RCVP improves oxygenation, partially preserves oxidative phosphorylation in the epicardium, and improves contractile function in the ischemic region.

Farcot et al. (1978) reported that, in addition to the oxygenation of the tissue, one of the important effects of RCVP is the acceleration of secretion of toxic metabolites in the ischemic lesion. This factor was not given attention in the present study.

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We refer to the following references for the methodology and techniques used in this study:


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