Myocardial protection via coronary sinus interventions: superior effects of arterialization compared with intermittent occlusion

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ABSTRACT  It has been reported that infarct size can be reduced by several interventions, by which arterial blood is delivered retrogradely to the ischemic myocardium through the cardiac veins or alternatively the cardiac venous system is intermittently occluded. Accordingly, we studied several modalities of myocardial protection that used the cardiac venous system and compared them by means of a quantitative technique for measuring infarct size. Thus 73 anesthetized dogs with coronary arterial occlusion were randomized into the following groups: group I (n = 9), 6 hr of occlusion without any intervention; group II (n = 11), venovenous shunt (60 ml/min) to the great cardiac vein; group III (n = 11), arteriovenous shunt to the anterior interventricular vein; group IV (n = 12), high flow arteriovenous shunt to the anterior interventricular vein (60 ml/min); group V (n = 11), arteriovenous shunt to the great cardiac vein (60 ml/min); group VI (n = 10), arteriovenous shunt to the great cardiac vein (60 ml/min) combined with diastolic occlusion of the great cardiac vein; group VII (n = 9), intermittent pressure-controlled occlusion of the great cardiac vein without arterialization. The arteriovenous shunt (groups III to VI) or venovenous shunt (group II) was done by selective catheterization of the anterior interventricular vein or the great cardiac vein, advancing a catheter from the jugular vein through the right atrium and coronary sinus under fluoroscopic control. This catheter was then connected to a cannula located either in the carotid artery (groups III to VI) or in the right atrium (group II). One minute after occlusion, $^{99m}$Tc-labeled albumin microspheres (8 mCi) were injected into the left atrium for the subsequent assessment of the hypoperfused zone, which is the area at risk for infarction. After 3 min, interventions were begun and continued throughout the 6 hr of the experiment. After 6 hr, the left ventricles were cut into 3 mm thick slices. Infarct size and the hypoperfused zone were measured by planimetry after incubation of these slices in triphenyltetrazolium chloride and after autoradiography, respectively. The hypoperfused zones as percent of the left ventricle were not different between group I (controls) and groups II to VII (i.e., interventions), showing that the zones at risk for infarction in all groups were similar. The percent of hypoperfused zone that evolved to necrosis (infarct size/hypoperfused zone × 100) was 100 ± 5% in the control group (group I). In the group with venovenous shunt (group II) it was 86 ± 6% (NS vs group I). However, in groups III, IV, V, and VI it was significantly smaller than in controls: group III, 63 ± 6% (p < .01); group IV, 66 ± 11% (p < .025); group V, 54 ± 9% (p < .01); and group VI, 54 ± 9% (p < .01). In group VII, subjected to intermittent occlusion of the great cardiac vein alone, this value was not different from control (84 ± 5%; NS vs group I). Thus only dogs subjected to arterialization of the cardiac venous system (groups III to VI) had significantly less myocardium evolving to necrosis as compared with the control group. Frequent gross myocardial hemorrhage appeared only in group IV, in which high flow retroperfusion (60 ml/min) of the anterior interventricular vein was instituted. Therefore, although the various types of arterialization of the cardiac venous system reduced infarct size by 34% to 46%, pressure-controlled occlusion of the great cardiac vein and retroperfusion with venous blood did not afford myocardial protection.


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Received Sept. 27, 1984; revision accepted March 15, 1985.

THE BENEFICIAL effect of arterialization of the cardiac venous system was suggested as early as 1898 by Pratt. This concept was later used for surgical revascularization in patients with chronic coronary artery disease by arterialization of the coronary sinus or the local cardiac vein. The former procedure developed
by Beck and Makao\textsuperscript{3} was associated with unacceptable mortality and ultrastructural damage\textsuperscript{4} of the retroperfused hearts. The concept of surgical arterialization of the cardiac venous system as a method of treating myocardial ischemia was laid aside with the modern era of aortocoronary bypass grafting.

More recently, the concept of selective retroperfusion was revived, but this time as a technique to be used in a catheterization laboratory with the goal of reducing myocardial damage after a myocardial infarction.\textsuperscript{5} There are several studies\textsuperscript{5-7} in both dogs and baboons that show a reduction in infarct size after coronary retroperfusion.

However, the methods used to achieve an arteriovenous shunt varied. Thus the shunt was performed between a systemic artery and the anterior interventricular vein\textsuperscript{1, 5, 8, 9} or the great cardiac vein.\textsuperscript{5, 7, 10-12} In addition, the arterial blood was directed to cardiac veins by many different techniques: by the native pressure of the aorta,\textsuperscript{5, 9} by a pump delivering a variable volume of blood only during the diastolic phase of the cardiac cycle,\textsuperscript{5, 7} or by the latter technique in conjunction with a balloon inflated in diastole.\textsuperscript{6, 10-12} Recently, it was demonstrated that even a simple shunt from the carotid artery to the anterior interventricular vein reduced infarct size and significantly improved left ventricular ejection fraction.\textsuperscript{13}

Moreover, it has been reported that pressure-controlled intermittent occlusion of the coronary venous system without delivery of arterial blood also reduced myocardial damage.\textsuperscript{14}

The techniques used to evaluate the reduction in myocardial damage varied profoundly and therefore the reported efficacy of these different interventions could not be compared.

Accordingly, the goal of this study was to evaluate and compare the effects on the extent of myocardial infarction of various modalities of myocardial protection by means of short-term arterialization of the cardiac venous system. For this purpose the arteriovenous shunts were established to the anterior interventricular vein, which is the vena comitans of the occluded left anterior descending artery, or more proximally to the great cardiac vein. The blood was delivered into the cardiac veins by the native arterial pressure, by a pump that delivered a higher volume of blood, or, in addition to the pump, by inflating a balloon near the tip of the catheter in diastole. The pressure-controlled intermittent occlusion of the great cardiac vein, an intervention that does not use arterialization, was also performed. Moreover, a venovenous shunt was also evaluated to analyze whether oxygen delivery to the cardiac veins is essential for myocardial salvage.

**Methods**

Seventy-three mongrel dogs were anesthetized with sodium pentobarbital intravenously (25 mg/kg), intubated endotracheally, and ventilated with room air using a volume respirator (Harvard Apparatus, Waltham, MA). Polyethylene cannulas were placed in the left carotid artery and left brachial vein for monitoring arterial pressure and to administer drugs, respectively. Systemic arterial pressure (Statham P23db pressure transducer) and the electrocardiogram (lead aVF) were recorded continuously throughout the 6 hr experiments on a polygraph (Gould Instruments, Cleveland). A thoracotomy was performed in the fifth intercostal space and the hearts were suspended temporarily in a pericardial cradle. The left anterior descending coronary artery was dissected free from adjacent tissues proximal to the first diagonal branch. All dogs received heparin sodium (Elkins Sinn, Inc., Cherry Hill, NJ) in a dose of 4000 U intravenously and repeated every 3 hr.

Just before coronary arterial occlusion, the dogs were randomized into the following seven groups (all interventions were initiated after coronary artery occlusion):

- **Group I. Control group.** A 6 hr coronary arterial occlusion without any additional intervention (n = 9).
- **Group II. Venovenous shunt from the right atrium to the great cardiac vein (n = 11).** The venous blood was pumped at a constant flow rate of 60 ml/min with an external roller pump (Sarns, S10 K II Blood Pump, Sarns Inc., Ann Arbor, MI).
- **Group III. Arteriovenous shunt from the carotid artery to the anterior interventricular vein (n = 11).** The arterial blood was delivered by the native arterial pressure.
- **Group IV. Arteriovenous shunt from the carotid artery to the anterior interventricular vein with a constant blood flow of 60 ml/min provided by an external roller pump (n = 12).**
- **Group V. Arteriovenous shunt from the carotid artery to the great cardiac vein with a constant blood flow of 60 ml/min provided by an external roller pump (n = 11).**
- **Group VI. Arteriovenous shunt from the carotid artery to the great cardiac vein with a constant blood flow of 60 ml/min provided by an external roller pump.** In addition, a balloon near the tip of the retroperfusion catheter was inflated in diastole and deflated during systole (n = 10).
- **Group VII. Intermittent occlusion of the great cardiac vein without retroperfusion (n = 9).** The catheter tip was positioned in the great cardiac vein. When the balloon was inflated, meglumine diatrizoate (Renografin 76) injected through the tip of the catheter filled the anterior interventricular vein. During balloon deflation there was no dye visible in the anterior interventricular vein, and there was free reflux of contrast medium into the right atrium. The inflation of the balloon (10 mm in diameter) was maintained for 15 sec, which corresponded with the plateau of the great cardiac vein pressure tracing recorded through the central lumen of the catheter (figure 1). The deflation time was 4 sec, which was required to restore the great cardiac vein pressure to the baseline value.

In groups II to VII the double-lumen retroperfusion catheter (Datascope Corp., Paramus, NJ) was advanced via the jugular vein and right atrium into the coronary sinus and then into the appropriate portion of the cardiac venous system. The length of this catheter was 90 cm, and the external and internal diameters were 2.6 and 1.1 mm, respectively. The position of the catheter was established by fluoroscopy with injections of a radiopaque dye (Renografin 76). Figure 2 shows examples of different
positions of the retroperfusion catheter in the cardiac venous system.

One minute after occlusion, $2 \times 10^6$ (8 mCi) $^{99m}$Tc-labeled albumin microspheres (20 $\mu$m in diameter) (3M Co., St. Paul, MN) were injected into the left atrium through a polyethylene cannula for the subsequent assessment of the hypoperfused zone, as described in detail previously.\textsuperscript{15}

Three minutes after occlusion the interventions in groups II to

FIGURE 1. Example of great cardiac vein pressure (GCVP) recorded during intermittent occlusion as performed in group VII. Time of inflation was 15 sec, deflation 4 sec.

FIGURE 2. Positions of the retroperfusion catheter. A, Catheter tip is wedged in the anterior interventricular vein (AIV). This was the position used in groups III and IV. B, Balloon retroperfusion catheter with the tip in the great cardiac vein (GCV), with balloon (arrow) deflated. Dye does not reach the AIV. This was the position used in groups II and V. C, Balloon retroperfusion catheter in GCV with balloon (arrow) inflated. Dye now fills the AIV. This type of catheter and position were used in groups VI and VII.
VII, as described above, were initiated. Twenty-four dogs died in the 6 hr period after occlusion. In these dogs, only the hypoperfused zone was calculated as described below. These animals were excluded from further analysis of myocardial necrosis.

Six hours after occlusion the animals were killed with an intravenous injection of 20 meq of potassium chloride and their hearts were excised. The epicardial fat, right ventricle, atria, mitral valve annulus, and great vessels were removed from the left ventricle. The left ventricle was then frozen at −70°C and cut into 3 mm thick slices from the apex to the site of occlusion.

To assess the extent of myocardial necrosis (infarct size), all slices were incubated in a 1.5% solution of triphenyltetrazolium chloride for 10 min at 37°C, which stained the normal myocardium red and the infarcted area yellow. The slices were then immersed in a 10% solution of formaldehyde to enhance the difference in color between the normal and necrotic myocardium. These slices and their areas of necrosis were traced onto transparent plastic sheets and measured by planimetry (Apple II computer). Infarct size was expressed as percentage of the total cross-sectional area of the left ventricle.

To assess the extent of the hypoperfused zone (which is the area at risk for infarction) the same slices were then studied autoradiographically by placing them on x-ray film (Cronex 4, E.I. DuPont, Wilmington, DE) for 13 hr. The areas without blood flow were the “cold spots,” whereas the areas with blood flow were the “hot spots.” To clearly identify their borders, soft x-ray films (i.e., 25 kVp, 100 mAs) were also obtained and superimposed on the autoradiographs. The contours of the slices and the cold spots were delineated on transparent plastic sheets and measured by planimetry (Apple II). The hypoperfused zone was then calculated as a percentage of the total cross-sectional area of the left ventricle.

In each dog, the percent of the area at risk for infarction, i.e., the hypoperfused zone that evolved to necrosis, was calculated by dividing the infarct size by the hypoperfused zone and multiplying by 100.

In addition, the incidence of gross myocardial hemorrhage was recorded in each group.

**Statistical methods.** Results were expressed as mean ± SEM. The Bonferroni method was used to compare hypoperfused zone and the infarct size/hypoperfused zone ratio in treated groups (groups II to VII) with those in the control group (group I) and for comparisons of heart rate and mean arterial pressure measured before coronary arterial occlusion. The multigroup repeated measurements of heart rate and arterial pressure after occlusion were analyzed among groups comparing the mean of all measurements (i.e., overall differences in the elevations) and the slopes (i.e., differences in the trends). Student’s paired t test was used for analysis of the great cardiac vein pressures (group VII). The 2 × 7 factorial design analysis was performed to evaluate the incidence of intramyocardial hemorrhage and mortality.

**Results**

To verify whether all groups were comparable before interventions were begun, heart rate, arterial pressure, and the extent of the hypoperfused zone were analyzed. Thus, just before coronary arterial occlusion heart rate and arterial pressure were similar in the control group (group I) and in the six treated groups (II through VII) (tables 1 and 2).

Hypoperfused zone, calculated by planimetry of the autoradiographs, was 26 ± 2% of the left ventricle in the control group. In the treated groups the hypoperfused zone did not differ from that in the control group (26 ± 1%, 30 ± 3%, 31 ± 4%, 29 ± 2%, 28 ± 2%, and 30 ± 3% in groups II through VII, respectively; NS vs control group) (figure 3).

Mortality was similar in all groups. In groups I through VII mortality was 2/9, 4/11, 4/11, 5/12, 4/11, 3/10 and 2/9, respectively (NS vs controls).

The extent of the hypoperfused zone that evolved to infarction (infarct size/hypoperfused zone × 100) (figure 4) was 100 ± 5% in the control group (group I). In the group with venovenous shunt (group II) there was no significant reduction of infarct size (86 ± 6%; NS vs group I). In all groups that received arterial blood through the shunt, the percent of the hypoperfused zone that evolved to necrosis was smaller than that in the control group (63 ± 6% in group III [p < .01], 66 ± 11% in group IV [p < .025], 54 ± 9% in group V [p < .01], and 54 ± 9% in group VI [p < .01]). Furthermore, the extent of the hypoperfused zone that evolved to infarction did not differ in groups III through VI, showing that arteriolarization of the cardiac veins is effective to a similar extent independent

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**Table 1**

<table>
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<tr>
<th>Group</th>
<th>n</th>
<th>Before CAO</th>
<th>After CAO (hr)</th>
<th>Slopes&lt;sup&gt;a&lt;/sup&gt; (p value)</th>
<th>Elevations&lt;sup&gt;a&lt;/sup&gt; (p value)</th>
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<td>NS NS</td>
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<tr>
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<td>NS NS</td>
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<td>NS .05</td>
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<tr>
<td>VI</td>
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<td>151 ± 10</td>
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<td>.05 .05</td>
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<td>VII</td>
<td>7</td>
<td>136 ± 3</td>
<td>134 ± 7 132 ± 7 127 ± 7 125 ± 8 131 ± 12 126 ± 10 126 ± 10</td>
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CAO = coronary arterial occlusion.

<sup>a</sup>See Methods for description of interventions.

<sup>b</sup>All comparisons were calculated vs control group (I).
of the method of delivery of oxygenated blood (figure 4).

In the group subjected to intermittent occlusion of the great cardiac vein without delivery of arterial blood (group VII), the percent of the hypoperfused zone that evolved to infarction was not different from that in the control group (84 ± 5%; NS, figure 4). Furthermore, retrospective analysis showed that the extent of the hypoperfused zone evolving to infarction in all groups that had an arteriovenous shunt (group III through VI) was significantly lower (59 ± 4%; p < .01) than that in group VII.

There was a close linear correlation between the extent of the hypoperfused zone and infarct size in the control group. In group I it was: infarct size = 0.71 hypoperfused zone + 7.28, n = 7, r = .86 (figure 5). The groups that had an arteriovenous shunt (groups III to VI) had a smaller infarct size for the same extent of the hypoperfused zone (figure 5, left), as indicated by significant difference in elevations between the regression lines of group I and groups III to VI (p < .05). In contrast, the group with only intermittent occlusion of the great cardiac vein (group VII) and the group with venovenous shunt (group II) did not differ from control (figure 5, right). Thus this analysis again shows that the delivery of arterial blood is essential when myocardial salvage is attempted by retroperfusion of the cardiac vein.

**Hemodynamics.** The comparison of the means of all measurements (i.e., elevations) of heart rate in each group after coronary arterial occlusion showed significantly (p < .05) lower heart rate in groups II, V, and VI compared with controls (group I). The comparison of the slopes (i.e., trends) showed significantly different trends (p < .05) only in group V in comparison with controls (group I).

The comparison of the means of all measurements of arterial pressure in each group after coronary arterial occlusion showed significantly (p < .05) lower pressure only in group V in comparison with controls (group I). The comparison of the slopes showed no significant difference in trends in groups II through VIII in comparison with controls (group I).

In group VII, which was subjected to intermittent occlusions of the great cardiac vein, the pressure recorded in the great cardiac vein during systole was 15 ± 1 mm Hg before occlusion when the balloon was

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### TABLE 2
Mean arterial pressure (mm Hg)

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<th>Group</th>
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<th>4</th>
<th>5</th>
<th>6</th>
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<th>Elevations (p value)</th>
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<tr>
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<td>105±6</td>
<td>109±5</td>
<td>109±7</td>
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CAO = coronary arterial occlusion.

*See Methods for description of interventions.

All comparisons were calculated vs control group (I).

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![FIGURE 3](https://example.com/image3.png)

**FIGURE 3.** Comparison of the hypoperfused zones (HZ) between control group (I) and the treated groups (see Methods for description of interventions). The hypoperfused zone is comparable in all groups before intervention. Values shown are mean ± SEM. LV = left ventricle.

![FIGURE 4](https://example.com/image4.png)

**FIGURE 4.** Comparison of the percentage of hypoperfused zone that evolved to infarction (IS/HZ) between the control group (I) and treated groups. There is reduction in IS/HZ only in groups subjected to arterIALIZATION.
deflated. It was significantly increased during inflation of the balloon to 59 ± 4 mm Hg (p < .001) at 15 min, 54 ± 11 mm Hg (p < .02) at 3 hr, and 46 ± 9 mm Hg (p < .02) at 6 hr after occlusion. Pressure in the great cardiac vein during diastole was 6 ± 1 mm Hg before coronary arterial occlusion with the balloon deflated. Diastolic great cardiac vein pressure significantly increased during inflation of the balloon to 15 ± 2 mm Hg (p < .001) at 15 min, 14 ± 2 mm Hg (p < .005) at 3 hr, and 16 ± 2 mm Hg (p < .005) at 6 hr after occlusion. Systolic great cardiac vein pressure after occlusion with the balloon deflated did not differ from preocclusion values (20 ± 4 mm Hg at 15 min, 17 ± 3 mm Hg at 3 hr, and 15 ± 1 mm Hg at 6 hr; all values NS vs before occlusion). Diastolic great cardiac vein pressure after occlusion with the balloon deflated was also similar to preocclusion values (6 ± 2 mm Hg at 15 min, 5 ± 1 mm Hg at 3 hr, and 7 ± 1 mm Hg at 6 hr; all values NS vs before occlusion).

**Myocardial hemorrhage.** Gross intramyocardial hemorrhage was observed in none or in only one dog in each group except group IV, in which it occurred in 75% of the dogs. Thus it occurred 0/9 dogs in group I, 0/11 in group II, 1/11 in group III (NS vs controls), 9/12 in group IV (p < .025 vs controls), 1/11 in group V (NS vs controls), 2/10 in group VI (NS vs controls), and 1/9 in group VII (NS vs controls). Frequent myocardial hemorrhage occurred only in group IV, in which high flow (60 ml/min) was delivered through a catheter wedged in the anterior interventricular vein.

**Discussion**

The major findings of our study were: (1) myocardial infarction expressed as a percentage of the zone at risk evolving to necrosis was significantly reduced by various types of arterIALIZATION of the cardiac venous system (groups III to VI) by 34% to 46%, (2) pressure-controlled intermittent occlusion of the great cardiac vein did not significantly reduce the infarct size/hypoperfused zone ratio and therefore did not appear to salvage ischemic myocardium, (3) retroperfusion with venous blood did not afford myocardial protection, and (4) a high incidence of myocardial hemorrhage as a complication was found only with high flow retroperfusion, with the catheter wedged in the anterior interventricular vein.

**Previous investigations.** Hochberg et al. found that arterial retrograde perfusion of the anterior interventricular vein moderately improved regional myocardial blood flow within the ischemic zone during coronary arterial occlusion. Later it was demonstrated that an arteriovenous shunt between the aorta and the anterior interventricular vein by means of a saphenous vein graft resulted in partial restoration of transmural flow in the ischemic region as measured 3 to 5 months after surgery. Similarly, synchronized diastolic retroperfusion was reported to increase collateral flow in the acutely ischemic myocardium. This was attributed to diastolic inflation of the balloon in the great cardiac vein (as in group VI in our study), which directed retroperfused arterial blood into the anterior interventricular vein and...
the ischemic region. Thus both local surgical retroperfusion and retroperfusion by means of catheterization of the great cardiac vein resulted in improvement of regional myocardial blood flow instead of redirecting retroperfused blood through alternative venous routes (e.g., thebesian veins) into cardiac chambers.

Although regional myocardial blood flow was not measured in our study, it is reasonable to assume that effective perfusion of the ischemic zone was achieved by directing oxygenated blood either directly to the anterior interventricular vein (groups III and IV) or by arterial retroperfusion of the great cardiac vein (groups V and VI). In contrast, retroperfusion of the great cardiac vein with venous blood (group II) was ineffective, indicating that changes in pressure and/or volume in the local veins within the ischemic region were not involved in reduction of infarct size.

Farcot et al. first postulated that diastolic augmentation enhances the effect of retroperfusion. As shown in our study, diastolic augmentation in the great cardiac vein during arterial retroperfusion (group VI) is not necessary for myocardial salvage. Similar reduction of infarct size was observed when arterial retroperfusion through the great cardiac vein was carried out with and without diastolic counterpulsation (figure 4).

Early studies by Gregg and Dewald and later by Muers and Sleigh indicated that elevation of cardiac venous pressure by means of coronary sinus occlusion caused bradycardia and hypotension in experimental animals. In the present study, retroperfusion and/or brief occlusion of the great cardiac vein (groups VI and VII) resulted only in minor changes in heart rate and arterial pressure. Although it was not evaluated in the present study, other investigators reported improvement in global systolic and diastolic left ventricular function during short-term arterial retroperfusion. Furthermore, Farcot et al. reported beneficial effects of diastolic synchronized retroperfusion on regional left ventricular function shortly after coronary arterial occlusion. Although these results are encouraging, they should be confirmed in conscious animals to avoid the well-recognized effect of anesthesia on measurements of left ventricular function.

Effects of intermittent occlusion of the cardiac venous system. Several investigators have shown that coronary sinus occlusion results in reversed capillary flow, as evidenced by increased backflow from the ischemic zone. However, as shown by Gregg and Dewald in 1938, this type of retrograde perfusion could not preserve systolic function of the ischemic myocardium. More recently, however, Mohl et al. showed that intermittent pressure-controlled coronary sinus occlusion reduced experimental infarct size. In the present study, despite similar experimental conditions, we were unable to observe significant myocardial salvage during intermittent occlusion of the great cardiac vein (group VII). These results, however, should be interpreted with caution because subtle changes among study groups could be missed due to the multiple group design. The biological relevance of these subtle changes remains speculative. This finding is also consistent with the lack of myocardial protection during venous retroperfusion (group II), and it confirms the earlier hypothesis by Gregg and Dewald that regional retroperfusion with blood having a low oxygen concentration is not sufficient to protect the ischemic myocardium.

Potential side effects. Early surgical experience with long-term arterial retroperfusion was associated with coronary venous congestion and structural damage to the cardiac veins. This was later attributed to impaired drainage from the retroperfused region of the myocardium, as a consequence of permanent occlusion of the coronary sinus. Further studies documented that severe damage to venules occurs when intravascular venous pressure exceeds 60 mm Hg. The present study, where free washout of blood was permitted, showed that short-term retroperfusion by means of specially designed catheters, with frequent fluoroscopic control of the catheter position, carries only a small risk of intramyocardial hemorrhage. Only arterialization of the anterior interventricular vein with the catheter wedged and continuous high flow (group IV) resulted in an exceptionally high incidence of intramyocardial hemorrhage. This was related to excessive flow directed to the anterior interventricular vein. In other types of retroperfusion, intramyocardial hemorrhage was occasionally observed and may reflect accidental impairment of venous drainage.

Experimental technique. There are several advantages that should be pointed out concerning our experimental design. First, the zone at risk (i.e., hypoperfused zone), which was determined in vivo before implementation of the intervention, takes into account the variable degree of collateral circulation in experimental animals. As was previously shown in other studies as well as in ours (figure 5), the size of the hypoperfused zone is an important determinant of the extent of myocardial necrosis. Second, rather than comparing infarct size among different groups, the infarct size/hypoperfused zone was determined, thereby negating the influence of the variability in the degree of myocardial necrosis among animals.

In the present study, the infarct size was delineated
with a histochemical method that has been shown to correspond with the microscopically determined zone of necrosis.\textsuperscript{28} Other studies\textsuperscript{6, 10} also using this histochemical technique, indicated that arterial retroperfusion with diastolic augmentation in the great cardiac vein resulted in striking reduction of myocardial necrosis. Although the present investigation confirmed the effectiveness of such treatment (group VI), quantitative comparisons are difficult for two reasons. First, histochemical staining only 3 hr after coronary arterial occlusion,\textsuperscript{6} as opposed to 6 hr as done in our study, may underestimate the size of the myocardial infarction. Second, there were no measurements of the initial area at risk. Previous investigations\textsuperscript{29} have shown that marked reduction of infarct size is possible in treated animals with a small initial hypoperfused zone. This phenomenon reflects not only the effectiveness of the intervention but also better collateralization of the myocardium when the zone at risk is small. Therefore we excluded dogs with the hypoperfused zone smaller than 15\% of the left ventricle, to avoid overestimation of the beneficial effect of a particular intervention.

**Clinical implications.** The effectiveness of short-term transcatheter arterial retroperfusion in humans is unknown. Based on our investigation, it is postulated that different types of arterial retroperfusion (groups III, V, and VI) can be used in selected groups of patients with acute myocardial infarction or unstable angina, until antegrade flow in the left anterior descending coronary artery is restored. This technique of myocardial protection may also be useful during coronary angioplasty, especially in patients with multivessel disease or without significant collateral circulation into the potentially ischemic region. In addition, catheterization of the cardiac veins seems to be an easily accessible route to deliver substances such as cold cardioplegic solution into the ischemic region.\textsuperscript{12} In particular, it becomes relevant when antegrade cooling of the ischemic zone is not satisfactory, as in emergency bypass surgery after abrupt closure of the left anterior descending coronary artery during angioplasty or in selected patients with valvular heart disease.

On the other hand, we do not recommend high flow retroperfusion of the anterior interventricular vein (group IV). Despite myocardial salvage observed in this group, a high incidence of intramyocardial hemorrhage was noted.

In conclusion, this study demonstrates that different types of short-term arterIALIZATION of the cardiac venous system reduces the extent of infarct size as a function of the zone at risk. By contrast, an increase in cardiac venous pressure by means of intermittent great cardiac vein occlusion or venous retroperfusion are not effective in reducing myocardial damage. Deleterious effects of retroperfusion, such as intramyocardial hemorrhage, are uncommon with arterIALIZATION of the cardiac veins, except for perfusion of the local cardiac vein (anterior interventricular vein) with high flow. It is postulated that arterIALIZATION of the cardiac venous system by local retroperfusion, by means of an arteriovenous shunt or a roller pump balloon catheter system in the great cardiac vein, may be clinically useful in certain patients with acute ischemic syndromes.

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Circulation. 1985;71:1215-1223
doi: 10.1161/01.CIR.71.6.1215

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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