Hypothermic Coronary Venous Phased Retroperfusion: A Closed-chest Treatment of Acute Regional Myocardial Ischemia

Samuel Meerbaum, Ph.D., Roberto V. Haendchen, M.D., Eliot Corday, M.D., Moysey Povzhitkov, M.D., Michael C. Fishbein, M.D., Jacob Y-Rit, M.D., Tzu-Wang Lang, M.D., Takahisa Uchiyama, M.D., Noboru Aosaki, M.D., and Jeffrey Broffman, B.A.

SUMMARY Hypothermic synchronized retroperfusion (HSRP) was applied in closed-chest dogs after acute coronary occlusion to determine whether this intervention can significantly retard the otherwise rapidly developing irreversible ischemic injury. The left anterior descending coronary artery (LAD) was occluded for 3 hours in 22 dogs and for 6 hours in 16 dogs. Starting 30 minutes after occlusion, HSRP was applied during maintained coronary occlusion in 21 dogs. The remaining dogs served as untreated controls. Arterial blood was cooled to 20°C and retroperfused in diastole into the regional coronary veins. Hemodynamics, contrast cineangiography and two-dimensional echocardiography were measured sequentially. Glycogen-depleted ischemic areas and necrotic zones were delineated in transverse slices of the left ventricle.

Untreated control dogs further deteriorated; in contrast, HSRP between 30 minutes and 3-6 hour LAD occlusion significantly reduced the rate-pressure product (21.3 ± 4.0% vs 26.8 ± 8.2%) and left ventricular end-diastolic pressure (39.5 ± 9.5% or 51.4 ± 7.7%) and increased ejection fraction (28 ± 17% and 33 ± 2.0%). HSRP caused no arrhythmias and led to much less necrosis of ischemic myocardium in the treated 3-6 hour occlusion series (7.4 ± 2.7% or 28.9 ± 12.6%) than in respective untreated controls (47.1 ± 8.9% and 72.3 ± 5.9%).

Moderately hypothermic closed-chest phased retroperfusion appears to protect reversibly injured ischemic myocardium and improve cardiac function. Such treatment may be particularly suitable in the earliest stages of evolving myocardial infarction, when maintenance of myocardial viability is essential for preservation of jeopardized myocardium while awaiting coronary bypass revascularization or nonsurgical thrombolytic reperfusion.

APPLICATION of hypothermia during periods of ischemia or anoxia is a well-established procedure in cardiac surgery. Surgical research suggests that hypothermia, often combined with cardioplegia, represents an appropriate perioperative treatment capable of extending myocardial viability if it is instituted before irreversible damage ensues. Modes of global or regional application, the degree of hypothermia, and its effectiveness alone or in conjunction with various infusion protocols have been investigated.

Although cooling-induced slowing of cellular metabolism may be beneficial during acute myocardial ischemia, prompt clinical application of regional cardiac hypothermic treatment presents difficulties, and methods have not been adequately evaluated. Stable levels of myocardial cooling can be achieved in the closed chest after a cool-down period of 2-3 hours, using externally applied or systemically administered whole-body hypothermia, and recent investigations reported that such an approach improved cardiac function and reduced infarct size. However, a delay of even 2 hours after an acute coronary occlusion may result in substantial irreversible damage. Therefore, we examined closed-chest intracoronary techniques aimed at rapidly instituted regional hypothermia to an acutely underperfused ischemic zone.

Antegrade intracoronary delivery of cooled arterial blood beyond a coronary obstruction is one method for extending ischemic tissue viability. We chose the more practicable coronary venous retrograde route to promptly produce hypothermia in an acutely ischemic segment of the left ventricle, hoping to enhance the safety and effectiveness of closed-chest synchronized retroperfusion. Our objective has been to develop a prompt hypothermic assist capable of significantly extending viability and enhancing function of jeopardized acutely ischemic myocardium. We report an exploratory experimental study of hypothermic retroperfusion applied in the earliest stage after acute coronary occlusion.

Methods

The study was performed in 38 healthy closed-chest mongrel dogs that weighed 25-35 kg. Each dog was placed on a special table to facilitate echocardiographic, fluoroscopic and cineangiographic studies.
Anesthesia was induced by administering sodium pentobarbital (35 mg/kg i.v.) 20 minutes after 1 mg/kg of i.m. morphine sulfate. Heparin (10,000 IU i.v.) was given before instrumentation, followed by 3000 IU every 3 hours. Supplemental pentobarbital was administered when required. Saline was drip-infused at a rate of 150 ml/hour.

A #4F intracoronary double-lumen balloon catheter was introduced under fluoroscopic control into the left anterior descending coronary artery (LAD), and the balloon was inflated for acute coronary occlusion at a site distal to the first diagonal branch of the LAD. After catheterization and completion of instrumentation, the preparation was allowed to stabilize for 30 minutes. Before occlusion and subsequently at regular postocclusion intervals up to 3 or 6 hours, aortic root, left ventricular (LV) and distal LAD coronary pressures were measured with Statham P23Db transducers. ECGs and blood pressures were recorded (Model V12, Electronics for Medicine, Honeywell). Magnified LV end-diastolic pressure, along with LV dP/dt derived by electrical differentiation, were also monitored. Cardiac output was measured by thermodilution (American Edwards Laboratories). Blood Po2, PCO2 and pH were monitored by sampling from the aortic root and through the central lumen of the LAD catheter. Temperatures were recorded in the closed-chest dog study at three sites: at the extracorporeal synchronized retroperfusion (SRP) pump, in the dog's rectum and within the LAD distal to the balloon occlusion.

**Synchronized Retroperfusion System**

An experimental closed-chest SRP system7 was modified to incorporate cooling of the pumped blood (fig. 1). Arterial blood was shunted from the dog's brachial or carotid artery into a phased gas-actuated balloon pump synchronized by conventional counterpulsation ECG-triggering (Phased Shift Balloon Pump, A. Kantrowitz). The arterial blood was propelled forward in diastole for ischemic zone retroinfusion, and flow was stopped in systole to facilitate normal coronary venous drainage. A single-lumen autoinflatable balloon catheter was used to achieve retrograde diastolic infusion through the regional great cardiac vein subserving the occluded LAD. The balloon inflated rapidly when catheter intraluminal pressure was generated during diastolic retroinfusion; this compartmentalized the great cardiac vein in diastole, so that retroinfusate was effectively directed to the ischemic region, with minimal bypassing to the coronary sinus. The balloon collapsed promptly when retroinfusion ceased at the onset of systole to permit coronary venous blood drainage around the retroperfusion catheter into the coronary sinus. Coronary contrast venography confirmed the rapidity of this phasic action; it demonstrated extensive diastolic penetration of retroinfusate into the plexus of small coronary veins located within the region distal to LAD occlusion, as well as effective emptying in systole through the major coronary veins.

Arterial blood was cooled by passing a coiled cannula through ice water to maintain an infusion temperature of 20°C at the external SRP pump (fig. 1). Resulting myocardial temperatures were not measured directly in this closed-chest dog study, but intracoronary blood temperature distal to the LAD occlusion was monitored by a thermistor passed into the ischemic zone through the central lumen of the intracoronary balloon catheter. Retrograde blood flow rate was measured with an electromagnetic flowmeter (model ABC-1000B, Omnicraft). To maintain regional coronary venous pressures well below 50 mm Hg at any time, a requirement derived from previous experience,9,7 mean retroperfusion flow rate was kept in the range of 60–80 ml/min, as measured with an electromagnetic probe in the hypothermic synchronized retroperfusion (HSRP) system (fig. 1).

**Measurement of LV Function**

LV ejection fraction was measured by contrast cineangiography or two-dimensional echocardiography (2D echo) (model 850A, Advanced Technology Laboratories). Because of its noninvasive character and comprehensive imaging of the left ventricle, 2D echo was also used to sequentially quantitate changes in global and regional cardiac function resulting from the HSRP intervention. Several short-axis and one long-axis 2D echo sections of the left ventricle were imaged. LV volumes and ejection fractions could be reconstructed from 2D echo section areas and LV length, in a manner described and validated.10 Endo-

---

**Figure 1.** Hypothermic synchronized retroperfusion (HSRP). Arterial blood is shunted from the aortic arch and then cooled and delivered into the synchronized bladder pump. In diastole, blood is propelled into the balloon-tipped synchronized retroperfusion (SRP) catheter and through it into the regional coronary veins. Forward flow stops in systole, causing the balloon of the SRP catheter to promptly collapse and allowing coronary venous drainage around the catheter into the coronary sinus. The system also provides measurement of infusedate pressure and flow. SRP treatment is applied through the great cardiac vein and the anterior interventricular (AI) vein to perfuse myocardium made acutely ischemic by intracoronary balloon occlusion of the left anterior descending (LAD) coronary artery. EM = electromagnetic.
Cardiac outlines of the ventricular lumen were planimetroed to compute the sectional systolic fractional area change (FAC), an index of regional contractile function. Further subdivision of sections into eight sectors was carried out in a standardized manner using the center of the lumen and internal landmarks of the left ventricle. FAC was then computed for each of the eight segments to assess function in ischemic and nonischemic zones.

Pathologic Study
At the time of sacrifice, the hearts were promptly (less than 60 seconds) excised, and cut as rapidly as possible from apex to base into five to seven transverse slices (of 0.8–1.0 cm thick). Alternate slices were either incubated in triphenyl tetrazolium chloride (TTC) or immersed into Carnoy’s solution, a nonaqueous, volatile fixative that preserves tissue glycogen. TTC served for macroscopic determination of infarct size, and periodic Acid-Schiff (PAS)-stained sections of myocardium fixed in Carnoy’s solution demonstrated glycogen loss, characterizing anaerobic metabolism and ischemic injury. The TCC-stained slices were fixed in formalin and photographed. Carnoy-fixed slices were cleared in cedar-wood oil and embedded in paraffin. Then whole mount giant histologic sections of each slice were cut from the slab surface adjacent to that of the neighboring TTC-stained slice. This section was stained for glyogen by the PAS method. The regions that are glycogen-depleted (i.e., ischemic) fail to stain. The extent of both the necrotic zone in TTC-stained slices and the ischemic zone in adjacent PAS-stained sections were measured by planimetry. Thus, the extent of necrosis could be compared with the extent of ischemia in both control dogs and in treated dogs. Electron microscopic study of TTC-delineated zones in LV slabs has confirmed that this macroscopic technique appropriately defines irreversible injury at 3 hours after occlusion or even earlier. In selected animals, coronary venous retroinfusion of colloidal carbon was used to check whether the retroperfusate entered into the ischemic zone microvasculature.

Data Analysis
Statistical evaluation was applied by unpaired t tests to compare the changes induced by HSRP (between 30 minutes and 3 or 6 hours after LAD occlusion) vs the spontaneous alterations during the same periods of untreated coronary occlusion.

Results
Effects of HSRP Applied from 30 to 180 or from 30 to 360 Minutes After LAD Occlusion

Hemodynamics
In the 3-hour series, there were no significant differences in hemodynamics between treated and untreated dogs before or 30 minutes and 3 hours after occlusion. Compared with the untreated controls, which exhibited a further drop in LV stroke volume and increased the rate-pressure product, LV end-diastolic pressure and systemic vascular resistance, HSRP applied between 30 and 180 minutes significantly lowered the double product (21.3 ± 4.0%), LV end-diastolic pressure (39.4 ± 9.5%) and systemic vascular resistance (12.5 ± 5.9%), while increasing LV stroke volume (4.5 ± 8.3%). Other differences were nonsignificant.

Comparing HSRP vs controls in the extended series, heart rate decreased 8.1 ± 7.0%, vs an increase of 27.1 ± 5.8%; mean aortic pressure was reduced by 21.5 ± 3.6%, vs a decrease of 12.1 ± 6.3%; the double product dropped 26.8 ± 8.2%, vs an increase of 16.8 ± 9.2%, and LV end-diastolic pressure dropped 51.4 ± 7.7%, vs a slight reduction of 6.3 ± 13.7% (fig. 2). Differences in other measurements were not significant.

HSRP caused no arrhythmias. The only instances of premature ventricular complexes occurred in both treated and untreated dogs very early after the coronary occlusion (within the 30-minute LAD occlusion period).

Closed-chest Temperature Measurements
After a reduction of 0.67 ± 0.22°C during the first 30 minutes of LAD occlusion, temperature distal to the balloon occlusion dropped rapidly with HSRP by 4.85 ± 0.79°C. This was significant compared with a gradual decrease by 2.04 ± 0.42°C measured rectally. The LAD temperature level remained substantially above the 20°C level instituted at the extracorporeal HSRP pump, indicating moderate myocardial hypothermia. Recent measurements with implanted thermistors in two dogs indicated that during the HSRP treatment, subepicardial temperatures in the ischemic and nonischemic zones decreased at most by several degrees, and did not drop below 30°C. These measurements appear consistent with moderate hypothermia and small myocardial temperature gradients.

LV Function
Figure 3 shows the sequential cineangiographic measurements of LV ejection fraction in untreated and treated dogs with a 3-hour LAD occlusion. There were no differences between the series before and 30 minutes after LAD occlusion, but HSRP resulted in a significant (though partial) return of global LV function.

Figure 4 illustrates the type of computer-assisted 2D echo quantitation of papillary level LV short-axis cross sections performed in the control state and after coronary occlusion. Normal contraction with uniform inward wall motion, evident before coronary occlusion, changed promptly to distinctly deranged (akinetic or dyskinetic) anterior and anteroseptal wall motion, with some hypofunction in more remote segments. This dysfunction persisted in the absence of treatment, whereas in the HSRP-treated dogs, contraction tended to return toward normal despite maintained LAD occlusion.

Sequential reconstructive 2D echo studies of LV volumes, stroke volumes and ejection fraction were performed in all dogs with a 6-hour LAD occlusion. Figures 5 and 6 are a comparison of HSRP vs control...
series and show a major reduction of both end-diastolic and end-systolic LV volumes by the HSRP treatment, resulting in a significant increase in LV ejection fraction between 30 minutes and 6 hours. In contrast, volumes remained elevated and ejection fraction decreased further in untreated controls.

Detailed analysis of 2D echo short-axis cross-sections at different levels of the left ventricle yielded further data on HSRP effects. At the higher level of the left ventricle, sectional cardiac function was returned to normal by the HSRP treatment. At the lowest level, function was improved, but remained below control (fig. 7). In untreated dogs, 6 hours of coronary occlusion led to progressively more functional derangements. Segmental analysis of the low papillary muscle level 2D echo section showed that HSRP distinctly improved contraction in the anterior ischemic region, in sharp contrast with persisting dyskinesia in untreated controls (fig. 8A). The remote nonischemic posterior wall, which showed hypokinesia in control occlusions, demonstrated significantly improved contraction with HSRP (fig. 8B). Thus, cardiac function in the HSRP series was significantly enhanced between 30 minutes and 6 hours, but deteriorated further in the untreated controls. However, LV function was usually not fully restored by HSRP to the preocclusion level.

Pathology

Sample photographs of LV slabs studied for ischemia and necrosis are presented in figures 9 and 10. Figure 9 illustrates the extent of both glycogen-depleted and necrotic zones in adjacent low papillary muscle level slabs of an untreated control dog, sacri-

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** (top) Heart rate (HR), the product of HR and mean aortic blood pressure (HR × AoPm) and systemic vascular resistance (SVR) vs time for eight dogs with untreated (open circles) and hypothermic synchronized retroperfusion (HSRP, solid circles)—treated 6-hour coronary occlusions. There were no statistically significant differences in the control state or 30 minutes after occlusion. HSRP, initiated after the 30-minute coronary occlusion measurements, and maintained throughout the 6-hour occlusion period, significantly lowered heart rate and HR × AoPm. SVR was significantly lower in the treated series at 4.5 hour after occlusion. (bottom) Left ventricular end-diastolic pressure (LVEDP), LV stroke work (SW) and maximal LV rate of rise (LV dP/dt) vs coronary occlusion. HSRP caused a significant drop in LVEDP compared with untreated dogs. There were no statistical differences in SW and LV dP/dt.

![Figure 3](http://circ.ahajournals.org/)

**Figure 3.** Left ventricular (LV) ejection fraction (%) in untreated and hypothermic synchronized retroperfusion (HSRP)—treated dogs with 3 hours of coronary occlusion (LV angiography). There were no statistical differences in ejection fraction in preocclusion control and 30 minutes after occlusion (before HSRP in treated dogs). In control dogs, ejection fraction remained depressed or decreased further between 30 minutes and 3 hours, while HSRP significantly increased global LV performance.
There is marked difference in that necrosis is minor and limited to subendocardium, while the zone of glycogen depletion exhibits a patchy character. HSRP appeared to protect most of the ischemic myocardium over the experimental coronary occlusion periods, whereas absence of treatment resulted in extensive necrosis within the ischemic zone. Statistical evaluation of the 3-hour occlusion pathologic data is shown in figures 11 and 12, which are comparisons of untreated controls with HSRP-

**FIGURE 4.** Computer-assisted two-dimensional echocardiographic quantitation of left ventricular (LV) function in a short-axis cross-sectional image at the low LV level. In this view, the septum is on the left and top, and anterior wall at the bottom, and the posterior aspect on the right. Analysis was performed both before and 30 minutes after acute occlusion of the left anterior descending (LAD) coronary artery. EDA = diastolic intraluminal section area; ESA = systolic area; and FAC = percent systolic fractional area change. Diastolic and systolic area centers are close to each other in the control state in the presence of essentially uniform inward wall motion, but deviate during coronary occlusion in view of major segmental dyssynergy. Using standardized subdivision into eight sectors, analysis of segmental FAC shows dyskinesis in the anteroseptal ischemic region, with progressively less regional dysfunction in more distant segments. Hypokinesis appears to be due to the broad impact of LAD occlusion on function at the low level of the ventricle.

**FIGURE 5.** Two-dimensional echocardiographic analysis of left ventricular end-diastolic volume (EDV), end-systolic volume (ESV) and stroke volume (SV) throughout the 6-hour experiments. There are no statistical differences between the untreated and treated series either before or 30 minutes after occlusion. In contrast with untreated dogs, significant differences developed after 1.5 hours, with hypothermic synchronized retroperfusion (HSRP) sharply reducing both EDV and ESV. SV increased at 6 hours.

**FIGURE 6.** Left ventricular (LV) volumes determined by two-dimensional echocardiography were used to compute the global percent ejection fraction (LVEF). Over 6 hours of untreated coronary occlusion, LVEF dropped progressively and substantially. Hypothermic synchronized retroperfusion (HSRP) begun after 30 minutes of occlusion led to a significant improvement in LVEF.
treated dogs. While the difference in the overall size of ischemic zones at the low papillary level was not significant (fig. 11), treated dogs did show a smaller and more patchy glycogen depletion. In sharp contrast with untreated controls, HSRP-treated dogs showed less necrosis, expressed either as percent of respective ischemic area (fig. 11) or as percent of left ventricle (fig. 12). Similar pathologic data were obtained in the 6-hour occlusion series (figs. 13 and 14). Myocardial necrosis was not fully averted by HSRP (particularly at the apex of the left ventricle), but salvage or extension of myocardial viability was highly significant compared with 6-hour untreated coronary occlusion (fig. 14).

Figure 15 illustrates the penetration of retroinfused colloidal carbon into capillary vessels within the ischemic region, confirming prior indications that SRP does indeed provide retrograde delivery of perfusate to the severely jeopardized myocardium.23

Comparison Between HSRP and SRP

Even though substantial experience with SRP has been reported,4,7 additional comparative data were obtained in the current study in five dogs applying SRP alone (without hypothermia) from 30 minutes to 6 hours after coronary occlusion. Intermediate effects between untreated control and HSRP were generally noted. Thus, SRP alone differed from HSRP between 30 minutes and 6 hours: LV ejection fraction increased 5.2 ± 17.4% vs 32.6 ± 2.0% (decrease by 31.6 ± 6.9% in untreated controls); double product decreased only 9.1 ± 13.7% vs 26.8 ± 8.2% (16.8 ± 9.2% increase in controls); LV end-diastolic pressure was reduced 18.3 ± 10.2% vs 51.4 ± 7.7% (6.3 ± 13.8% in controls); systemic vascular resistance decreased 1.5 ± 12.2% vs an increase of 22.4 ± 12.9% in HSRP (25.0 ± 11.4% increase in controls). Hypothermia appeared to counteract the often observed reduction in vascular resistance with SRP. Infarction with SRP alone was substantially less than in untreated controls, but substantially greater than in the HSRP series (58.2 ± 42.8% vs 28.9 ± 12.6% of ischemic zone).

Discussion

SRP per se is associated with distinct benefits,4,7 but HSRP was more effective in extending the viability of severely jeopardized myocardium and significantly improving cardiac function. These benefits probably...
HYPOTHERMIC RETROPERFUSION/Meerbaum et al.

FIGURE 9. Control dog killed 6 hours after coronary occlusion. Giant histologic section stained with PAS for glycogen (A), and surface of adjacent gross slice of myocardium stained with triphenyltetrazolium chloride (TTC) to demonstrate necrosis (B). The necrotic zone, which fails to stain with TTC, is almost as large as the glycogen-depleted ischemic zone (A).

FIGURE 10. Treated dog killed 6 hours after coronary occlusion. Giant histologic section stained with PAS for glycogen (A), and surface of adjacent gross slice of myocardium stained with TTC to demonstrate necrosis (B). There is no myocardium that fails to stain, indicating that no necrosis is present. In this example, when compared to the previous control, glycogen loss is also less extensive and patchy.

The hemodynamic changes and improvements in LV function with HSRP are generally in accord with previous investigations of SRP,6, 7 except that the significant drop in systemic vascular resistance usually observed with SRP alone appeared to be reduced or absent with HSRP. The addition of hypothermia was beneficial and had no deleterious effects.

Coronary venous retroperfusion is a particularly attractive approach when there is poor access to an acutely ischemic region of the heart.27-30 Global interruption of coronary venous drainage can be deleterious and cause a high degree of tissue edema, which impedes the retrograde retroperfusion.31, 32 Several investigators have used a regionally administered retroperfusion;33-36 however, the infusion still required permanent occlusion of the regional coronary vein, precluding appropriate drainage flow. To resolve this limitation, our SRP system applies retroperfusion in diastole while facilitating coronary venous drainage during systole.6, 7 This phasic system appears to minimize vascular congestion, myocardial edema and

reflect synergistic effects of enhanced ischemic tissue perfusion by SRP,24 along with reduction of cellular metabolism and oxygen demands due to lowering of myocardial temperatures.25, 26

Although not systematically measured in this closed-chest preparation, limited data with implanted myocardial thermistors indicated that the retrogradely applied hypothermia was distributed and did not reduce regional myocardial temperature below 30°C. The resulting relatively small temperature gradients may explain why no arrhythmias were encountered in our study. Intravascular temperature distal to the coronary artery occlusion provided indirect data suggesting an early but moderate degree of regional myocardial cooling when the retrogradely delivered blood temperature was lowered to 20°C at the extracorporeal SRP pump.

The hemodynamic changes and improvements in
hemorrhages. The benefits demonstrated in our SRP studies, have been corroborated37,38 and revealed that ischemic zone myocardial perfusion is significantly increased.39 Retroinfusate penetration into the capillary microcirculation was also demonstrated in our study using colloidal carbon.

The rationale for supplemental myocardial hypothermia was to maintain viability and protect jeopardized tissue by reducing cellular metabolism.40-42 The effects of myocardial cooling on perfusion, function and tissue viability have been the subject of intensive study, primarily in the arrested heart, in relation to established cardiac surgical procedures without or with cardioplegic solutions. Profound cooling could lead to arrhythmias or result in ventricular fibrillation.43 With moderate cooling, heart rate and myocardial oxygen consumption are reduced.44,45 Contractility and systemic vascular resistance might increase as a result of

---

**Figure 11.** Pathologic data on ischemic and necrotic zones in a midpapillary level left ventricular slab after 3-hour left anterior descending coronary artery occlusion without and with hypothermic synchronized retroperfusion (HSRP). Expressed as percent of the slab area, the ischemic zone after 2½ hours of HSRP was only slightly reduced but generally of a patchy character, compared with a contiguous ischemic zone in untreated dogs. Note the dramatic difference in extent of necrosis, only 7.4 ± 2.7% with HSRP compared with 47.1 ± 8.9% in untreated control occlusions.

**Figure 12.** Infarct size after 3 hours of left anterior descending coronary artery occlusion was 9.3% of the left ventricle in the absence of treatment and presented often as new transmural necrosis. With hypothermic synchronized retroperfusion (HSRP) applied between 30 minutes and 3 hours after occlusion, the size of infarction was less than 1% of the left ventricle, mostly in the subendocardial region.

**Figure 13.** Extent of necrosis as percent of ischemic areas in middle and apical left ventricular (LV) slabs, as well as in the total left ventricle, after 6 hours of untreated or hypothermic synchronized retroperfusion (HSRP)-treated coronary occlusion. HSRP reduced necrosis significantly in the mid-LV slab and in the left ventricle as a whole. Reduction in necrosis by HSRP did not reach significance (compared with untreated dogs) in the apical slab.

**Figure 14.** Size of ischemic and necrotic areas expressed as percent of the left ventricle (LV). As was the case after 3-hour occlusion (fig. 15), the ischemic zone was generally patchy after hypothermic synchronized retroperfusion (HSRP) but not significantly decreased in extent. In contrast, a significant reduction in necrosis was noted after 6-hour HSRP-treated coronary occlusion. The relatively small infarct size in the 6-hour control series (10% of LV) is attributable to the site of left anterior descending coronary artery occlusion and dog-to-dog variability, emphasizing the need to relate necrosis to the ischemic zone.
hypothermia, myocardial perfusion increase or decrease, depending on whether the physiologic state was normotensive, or else exhibited high heart rates and severely depressed blood pressure.  

To clarify the contribution of hypothermia in HSRP, we repeated, during the course of this investigation, a limited SRP study without the cooling. Significant lowering of heart rates and double product by hypothermia further improved LV function and decreased myocardial necrosis. The optimal level of regional hypothermia and mode of retrograde cooling application are not known. Treatment effectiveness depends, of course, on the time it is begun relative to the progression from reversible to irreversible myocardial injury.

System Limitations and Need For Development

SRP catheterization of the coronary sinus and great cardiac vein is usually completed within 10–15 minutes, and no serious problems were encountered in studies in about 500 dogs. Insertion of the SRP catheter into the regional anterior interventricular vein was avoided, in view of acute angles and potential trauma. Practical anatomic considerations somewhat limit the specificity of location of the retrograde coronary venous infusions. But, while the efficiency of retrograde delivery to a specific region of the heart is inherently limited, the existence of coronary venovenous shunting is useful in distributing flows to different regions of the heart and minimizing potentially damaging buildup of intravascular pressure. An ischemic zone distal to the left circumflex coronary artery occlusion can be treated by coronary sinus HSRP. Right coronary occlusions were not studied.

The maximal possible efficiency of SRP delivery is believed to be 50–60%. As long as the induced pressure and flow within the coronary veins do not exceed 30 mm Hg and 80 ml/min, respectively, experience in our laboratory indicates insignificant damage to the heart from SRP. Long-term application of nonsynchronized retroperfusion may require maintenance of even lower pressures within the coronary veins. The mean regional coronary venous pressure during our studies was generally less than 30 mm Hg. While coronary venous retroinfusion pressures and flows must be limited, several investigators have noted a preferential retroinfusate delivery to the ischemic region and endocardium.

Effective diastolic retrograde delivery of hypothermia into the ischemic myocardium might be achieved through intramural channels even in the absence of transcapillary perfusion. Because of the distributing effects of coronary venovenous shunts, the cooled myocardium encompasses portions of the nonischemic zone, and ventricular temperature gradients are thus minimized. Profound HSRP cooling might have to be avoided to exclude arrhythmias. Further experimental study should evaluate retrograde hypothermia applied after longer periods of coronary occlusion and during only partly effective interventions.

Adequacy of Measurements For Assessment of the Intervention

One of the principal end points of this study was the extent of necrosis developed within the induced acutely ischemic territory. Recent histologic and electron microscopic validations in our laboratory confirm the ability of quantitating the zone of irreversible injury with TTC after coronary occlusion periods of 3 hours or shorter. Compared with untreated controls with a similar period and level of coronary occlusion, HSRP generally resulted in only minor necrosis.

To avoid dog-to-dog variability and erroneous conclusions from experimental studies of proposed treatments of acute ischemia, myocardial infarction must be related to a zone at risk, usually defined as the area with a severe perfusion deficit due to coronary obstruction. The TTC-delineated area of necrosis in LV sections was related to a posttreatment area of myocardial glycogen depletion in equivalent adjacent surfaces. This zone depends on the primary underperfusion as well as on spontaneous or imposed alterations in oxygen demands. Glycogen loss is an early and reliable index of acute myocardial ischemia and a return of glycogen is delayed substantially even when perfusion is reestablished. A practical experimental method has been devised to delineate the zone of glycogen depletion in LV slabs obtained from treated or untreated dogs. This method is admittedly new and has not been fully explored. A particular limitation,

---

**FIGURE 15.** Glycogen-depleted ischemic myocardium after infusion of colloidal carbon by means of hypothermic synchronized retroperfusion. Microscopic sections show colloidal carbon within veins (short arrows) and capillaries (long arrows), providing morphologic confirmation of entry of retroperfusate into the ischemic zone. PAS stain; original magnification × 160.
shared by some other methods, is that measurements are performed only at the end of the experiment. Our observations of a patchy treated vs contiguous untreated zone of glycogen depletion illustrated that such a delineation may well change due to alterations in myocardial perfusion or oxygen demands, occurring spontaneously or as a result of treatment. If these changes differ widely from dog to dog, then the method may have serious limitations. In acute experiments such as those of the current study, changes in the supply zone and oxygen demands are relatively small, but an optimal technique would establish changes in the risk zone throughout the study of the treatment.

Sequential single-plane contrast cineangiography appeared satisfactory for global measurements of LV function. However, the echocardiographic method was preferred because it is noninvasive and provides comprehensive imaging of the left ventricle for computer-assisted analysis of ischemic and nonischemic segments. HSRP significantly improved global LV function, although the dysfunction caused by coronary occlusion was not fully reversed in the 3- or 6-hour period. Ischemic segmental function was enhanced by HSRP, whereas in untreated dogs similar segments usually remained severely depressed. These 2D echo studies of the extent of dysfunction were compatible with autopsy findings.

The primary hemodynamic effect of HSRP was to decrease heart rate and rate-pressure product, as might be expected with hypothermia alone. HSRP did not cause arrhythmias, and transient premature ventricular complexes encountered in the dogs usually occurred shortly after the coronary occlusion, before treatment.

Clinical Implications

At this stage of development, HSRP might best be viewed as an important adjunct of either surgical or nonsurgical reperfusion techniques, which critically depend on support of circulation and myocardial preservation during the earliest phase of acute myocardial infarction. An example of the latter is the recently introduced coronary thrombolytic procedure, which may benefit from effective interim support to maintain cardiac function and myocardial viability. 

Pharmacologic agents have been combined with SRP treatment and a limited experimental study has demonstrated that great cardiac vein retroperfusion with streptokinase resulted in early and reliable lysis of a thrombotic occlusion within the LAD.

HSRP may provide stabilization during threatening ischemic heart conditions and perioperative or postsurgical cardiac support. Cardiac derangements in evolving shock states or arrhythmias might also be alleviated by retrogradely supplying oxygenated blood, substrates, drugs or hypothermia into the involved ischemic segment.

Acknowledgment

The authors gratefully acknowledge the technical assistance of Myles Prevost and Xavier Escudero. We thank Valida Gaskin for her assistance with pathology studies, Barbara Voigt for secretarial assistance and Jeanne Bloom for editorial assistance.

References

20. Fishbein MC, Hare CA, Gissen SA, Spadaro J, Maclean D, Maroko PR: Identification and quantification of histochemical border zones during the evolution of myocardial infarction in


54. Meerbaum S, Povzhikov M, Haendchen RV, Broffman J, Lang TW, Corday E: Coronary artery thrombolysis by streptokinase coronary venous retroinfusion or systemic administration (abstr). Am J Cardiol. In press
Hypothermic coronary venous phased retroperfusion: a closed-chest treatment of acute regional myocardial ischemia.
S Meerbaum, R V Haendchen, E Corday, M Povzhitkov, M C Fishbein, J Y-Rit, T W Lang, T Uchiyama, N Aosaki and J Broffman

Circulation. 1982;65:1435-1445
doi: 10.1161/01.CIR.65.7.1435

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/65/7/1435