EXPERIMENTAL STUDIES

Effects of Pressure-Controlled Intermittent Coronary Sinus Occlusion on Regional Ischemic Myocardial Function

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Pressure-controlled intermittent coronary sinus occlusion has been reported to reduce infarct size in dogs with coronary artery occlusion, possibly because of increased ischemic zone perfusion and washout of toxic metabolites. The influence of this intervention on regional myocardial function was investigated in open and closed chest dogs. In six open chest dogs with severe stenosis of the left anterior descending coronary artery and subsequent total occlusion, a 10 minute application of intermittent coronary sinus occlusion increased ischemic myocardial segment shortening from 5.5 ± 1.2 to 8.2 ± 2.6% (NS) and from −0.1 ± 2.1 to 2.3 ± 1.2% (NS), respectively.

In eight closed chest anesthetized dogs, intermittent coronary sinus occlusion was applied for 2.5 hours between 30 minutes and 3 hours of intravascular balloon occlusion of the proximal left anterior descending coronary artery. Standardized two-dimensional echocardiographic measurements of left ventricular function were performed to derive systolic sectional and segmental fractional area changes in five short-axis cross sections of the left ventricle. Fractional area change in all the severely ischemic segments (< 5% systolic wall thickening) was −4.0 ± 4.7% at 30 minutes after occlusion,

and increased with subsequent 60 and 150 minutes of treatment to 13.1 ± 3.3 and 7.0 ± 3.3%, respectively (p < 0.05). At the most extensively involved low papillary muscle level of the ventricle, regional ischemic fractional area change was increased by intermittent coronary sinus occlusion between 30 and 180 minutes of coronary occlusion from −0.4 ± 0.1 to 14.4 ± 4% (p < 0.05), whereas a further deterioration was noted in untreated dogs with coronary occlusion.

Continuous arterial and coronary venous blood density measurements were performed in seven open chest dogs to determine the influence of pressure-controlled intermittent coronary sinus occlusion on ischemic myocardial washout. The arteriovenous density gradient was 0.16 ± 0.05 g/liter during coronary artery occlusion, and decreased to 0.05 ± 0.08 g/liter (p < 0.05) as a result of the intervention, suggesting a significant fluid washout from the myocardium. It is concluded that pressure-controlled intermittent coronary sinus occlusion provides recovery of cardiac function and that this benefit might be associated with enhanced ischemic zone washout.

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More than at any time since Beck et al. (1) reported on arterialization of the coronary sinus, scientific attention is currently focused on this alternate access route to deprived

and jeopardized ischemic myocardium. Several authors (2–4) have reported on experimental studies of differing modalities of retrograde intervention, including synchronized coronary venous retroperfusion of arterial blood (without and with supplemental hypothermia and drugs) and intermittent coronary sinus occlusion without or with pressure feedback. Both of these interventions appear promising in terms of improving ischemic zone function and reducing infarct size. Whereas synchronized coronary venous retroperfusion shunts oxygenated blood retrogradely to ischemic areas, pressure-controlled intermittent coronary sinus occlusion redistributes coronary venous blood and generates pressure as well as flow pulsations that are believed to enhance the washout of toxic metabolites from jeopardized ischemic myocardium (5).

To examine the effects of pressure-controlled intermittent coronary sinus occlusion on regional left ventricular function and fluid shifts within the ischemic microcirculation, we employed three series of experiments in dogs with coronary artery occlusion: 1) sonomicrometric measurements of local cardiac function in open chest dogs; 2) two-dimensional echocardiography in a closed chest model to map changes in contractile function; and 3) special continuous blood density determinations in the aorta and coronary sinus to evaluate fluid shifts in the myocardial microcirculation induced by the intermittent coronary sinus occlusion.

Methods

Open Chest Experiments (Fig. 1)

Experimental preparation. Adult mongrel dogs weighing 18 to 24 kg were anesthetized with intravenous sodium pentobarbital (25 mg/kg). To maintain anesthesia, piritramide (1.5 mg/kg) was continuously administered intravenously by an infusion pump. Pancuronium bromide (0.1 mg/kg) was given intravenously for muscle relaxation. The animals were artificially respired with a mixture of 1:1 oxygen and nitrous oxide. To prevent atelectasis, the end-expiratory pressure was set at 7 cm H_2O. A left thoracotomy was performed in the fifth intercostal space, and the heart was suspended in a pericardial cradle. The left anterior descending coronary artery was dissected proximal to the first diagonal branch and a snare was placed at this site for subsequent stenosis or occlusion ligation. Left anterior descending coronary artery and aortic blood flows were measured electromagnetically (SP 2202, Statham, Inc.). Left

Figure 1. Schematic illustration of the experimental preparation for open chest dogs. Coronary sinus pressure (CSP) is monitored through the coronary sinus balloon occlusion catheter, which is connected to the pumping system. The latter automatically triggers balloon inflation and deflation for pressure-controlled intermittent coronary sinus occlusion (P-ICSO). AoP = aortic pressure; COR. ART. = coronary artery; LVedP = left ventricular end-diastolic pressure; LVP = left ventricular pressure; Q Ao = aortic flow; Q cor = left anterior descending coronary artery flow.
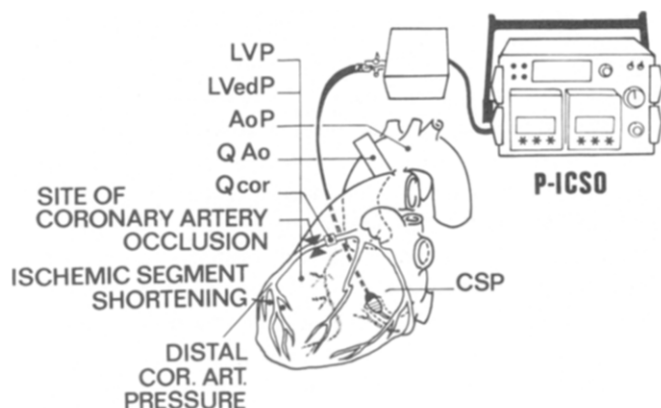

ventricular stroke volume was computed by an analog integrator (Gould Brush). A 5F catheter-tipped pressure transducer (PC 350, Millar, Inc.) was placed in the descending aorta and within the left ventricle to monitor the respective blood pressures. Maximal rate of rise in left ventricular pressure (dP/dt) was recorded on-line by left ventricular pressure differentiation. An extravascular micrometer adjustable snare was used to occlude the left anterior descending coronary artery. Distal to the site of occlusion, a 2F Teflon tube was inserted through a small coronary artery branch, the catheter tip slightly protruding into the lumen for monitoring of coronary artery pressure distal to the snare.

Myocardial dimensions and segment length measurements. To assess regional myocardial function, two miniature piezoelectric transducers (1.8 mm diameter) were implanted subendocardially and perpendicular to the long axis of the heart within the center of the distribution area of the left anterior descending coronary artery to be rendered ischemic. The ultrasound crystal technique for determining myocardial dimensions and segment lengths has been described previously (6). The position of the transducers was verified after termination of the experiment and removal of the heart, and was also visually observed to be in a mid-myocardial short-axis plane between the anterior papillary muscle and the septum. To compare actual end-diastolic lengths of different animals, baseline values were normalized to 10 mm. Systolic segment shortening was calculated from aortic valve opening to its closure, as determined from pressure recordings.

Measurements during coronary stenosis and intermittent coronary sinus occlusion. A 7F coronary sinus balloon occlusion catheter (Meditech) was inserted through the left jugular vein into the coronary sinus, with the balloon positioned under manual control at the coronary sinus orifice. The catheter was then connected to a Meditech coronary sinus pressure feedback control box, which automatically triggered intermittent balloon inflation and deflation relative to a pre-set plateau peak systolic pressure. After completion of the preparation, a single dose of 10,000 IU of heparin was administered intravenously.

Measurements were obtained in six open chest dogs. After baseline measurements had been recorded, left ventricular flow was reduced in stepwise fashion until left anterior descending coronary artery flow was less than 10% of the baseline control value (7.6 ± 7.6%) and significant dysfunction (severe hypokinesia-akinesia) was achieved. Soon after the ischemic segment was observed to exhibit stable dysfunction, pressure-controlled intermittent coronary sinus occlusion (intermittent occlusion for 25 ± 3 seconds and release periods of 4 ± 2 seconds) was started and maintained for 10 ± 3 minutes. Measurements were obtained at the end of the treatment period and were always taken toward the end of the coronary sinus balloon occlusion phase, 5 seconds before balloon deflation. These data were com-

pared with those obtained during ischemia before intermittent coronary sinus occlusion, as well as with measurements obtained 5 ± 2 minutes after the end of the treatment. The effects of pressure-controlled intermittent coronary sinus occlusion during total occlusion of the left anterior descending coronary artery were determined in a similar manner.

Blood density and plasma measurements. In a separate series of seven open chest dogs, continuous blood density and sequential plasma measurements were obtained in the aorta and coronary sinus to evaluate transcapillary fluid shifts induced by pressure-controlled intermittent coronary sinus occlusion. The mechanical oscillator principle (7) was used to continuously measure blood density with an accuracy of 0.01 g/liter, corresponding to hematocrit changes of 0.02%. This new method has been described previously (5) and appears to provide a sensitive measure of fluid shifts (filtration and reabsorption) in the microcirculation of the heart. The aorta to coronary sinus difference in blood densities essentially characterizes changes in myocardial fluid (for example, a substantial increase during edema formation or a decrease during enhanced washout).

Blood samples (8 ml³/min) were continuously withdrawn with a roller pump from the aorta and the coronary sinus, cannulated through the cartoid artery and the jugular vein, respectively. Two density meters (DMA 602 MW, Paar Austria) were employed to measure blood density (grams/liter) at a constant flow rate and temperature. Blood leaving the density meter was returned into the circulation through a cannula inserted into the left femoral vein.

To measure plasma densities, blood samples were taken from the aorta and the coronary sinus several times throughout the experiment, during coronary sinus balloon inflation as well as deflation. These samples were then centrifuged at 4,000 rpm, and the plasma density was determined.

Arteriovenous density differences were evaluated first during normal coronary artery flow and subsequently after coronary artery occlusion. Pressure-controlled intermittent coronary sinus occlusion was started 15 minutes after the coronary artery occlusion, and its effects on the aortocoronary sinus density difference were monitored during a 30 minute period.

Closed Chest Experiments

Experimental preparations. Twenty healthy mongrel dogs (weight 20 to 30 kg) were sedated with morphine sulfate (2 mg/kg intravenously) and anesthetized 30 minutes later with sodium pentobarbital (25 mg/kg intravenously). After intubation, ventilation was maintained with a Harvard respirator. Supplemental doses of the anesthetic agent were administered whenever necessary to maintain a continuous state of anesthesia. An initial heparin sulfate dose (10,000 IU intravenously) was given and supplemented every 2 hours.

Ascending aortic and left ventricular blood pressures

were monitored through catheters inserted into femoral arteries and using Statham P23Db pressure transducers. A triple lumen Swan-Ganz catheter (American Edwards Laboratories) was positioned in the pulmonary artery through the femoral vein. Cardiac output was determined by thermodilution (cardiac output computer 8520, American Edwards Laboratories. *Systemic vascular resistance was calculated* according to:

$$\frac{AoPm}{CO} \times 80 \text{ dynes·s·cm}^{-5},$$

where AoPm = mean aortic pressure and CO = cardiac output.

Coronary artery and coronary sinus occlusion. The left anterior descending coronary artery was catheterized with a 9F Judkins catheter, which served as a guide for insertion of a 4F double lumen balloon catheter (American Edwards Laboratories). Selective coronary angiography was used to verify the balloon site in the proximal left anterior descending coronary artery immediately beyond the first diagonal branch. Coronary artery pressure distal to the intracoronary balloon occlusion was monitored through the center lumen of the 4F catheter, and served as a check for maintained balloon occlusion.

Pressure-controlled coronary sinus occlusion was performed with a 7F double lumen catheter (Meditech) inserted through the jugular vein. The balloon is located 5 mm from the catheter tip and inflates up to a 10 mm diameter. The catheter was passed through the right atrium and positioned under fluoroscopic guidance in the coronary sinus as close as possible to its ostium. From experience gained in the open chest dog series, the pressure-controlled intermittent coronary sinus occlusion cycle was adjusted to allow the coronary sinus pressure to reach a peak, at which time the occlusion was released for a short period until coronary sinus pressures decreased to baseline values (9.9 ± 1.5 seconds occlusion versus 1.8 ± 0.3 seconds release). Regional left ventricular wall motion studies were obtained without special classification in the pressure-controlled intermittent coronary sinus occlusion cycle.

Regional left ventricular wall motion studies (echocardiography). Two-dimensional echocardiography with a mechanical sector scanner (ATL, Mark 300) was used for sequential quantitative assessment of regional left ventricular function. Imaging of the left ventricle was performed with the dog lying in a right lateral position and the 3 MHz transducer placed underneath the chest wall (8). Five short-axis left ventricular cross-sectional images were obtained in each dog. Images were recorded onto videotape (Panasonic NV 8200), and wall motion analysis was initiated by outlining epicardial and endocardial interfaces in end-diastolic and end-systolic stop frames using a videodisc system. The end-diastolic frame was chosen as the largest and most circular short-axis cross section, and the end-systolic frame as

the smallest cross section. The endocardial and epicardial interface delineation was checked in the dynamic state by repeat playback of the tape at slow or fast speed. Images were traced from a video screen using transparent overlays, and were then digitized into a computer (PDP 11/34) for calculation of areas and perimeters. A leading edge methodology was employed for tracing interfaces in all images. Computer-aided subdivision of short-axis cross sections into eight segments and analysis of segmental endocardial wall motion were standardized on the basis of a fixed referencing system by drawing an indexing line from the diastolic endocardial geometric center to the anterior junction of the right ventricular free wall and septum (9).

Sectional as well as segmental systolic fractional area changes were employed as indexes of contractile function. Segments showing less than 5% systolic wall thickening 30 minutes after left anterior descending coronary artery occlusion were defined as representing profoundly dysfunctioning segments in the center of the ischemic zone. The octant located 180° from the most dyskinetic segment was used to characterize contraction in the nonischemic zone.

Experimental protocol. After the animal preparation was stabilized, control hemodynamic measurements were obtained and the baseline two-dimensional echographic study was performed. The left anterior descending coronary artery was then occluded by inflation of the intracoronary balloon. Coronary occlusion was maintained in all experiments for 3 hours, and measurements were obtained at 30, 90 and 180 minutes after occlusion. The dogs surviving for 30 minutes after coronary occlusion were randomized immediately after the postocclusion measurements into 1) untreated control dogs subjected to 3 hours of occlusion, and 2) dogs treated with pressure-controlled intermittent coronary sinus occlusion. The treatment was continued during maintained coronary occlusion until the end of the experiment.

Statistics. All data were averaged and expressed as mean values ± SEM. Statistical evaluation was by paired and unpaired *t* tests.

Results

Intermittent Coronary Sinus Occlusion in the Open Chest Model

Coronary sinus pressure dynamics. Occlusion of the coronary sinus caused a beat to beat increase in systolic and diastolic coronary sinus blood pressure (Fig. 2). The increase in systolic pressure followed a monoexponential pattern up to a plateau.

In the normally contracting heart with unobstructed coronary arteries, systolic coronary sinus pressure increased as a result of balloon occlusion from 16.6 ± 2.5 to a maximum of 58.2 ± 5.8 mm Hg (corresponding to 53 ± 0.4% of the left ventricular pressure) and end-diastolic coronary si-
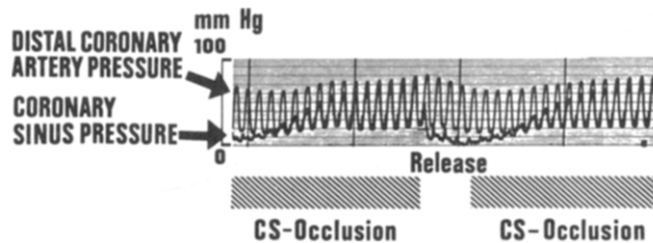

Figure 2. Typical pressure tracing during intermittent coronary sinus (CS) occlusion; time lines are at 5 second intervals.

nus pressure increased from 16.4 ± 8.7 to 28.0 ± 5.0 mm Hg. The time for coronary sinus systolic pressures to reach a stable peak value (three adjoining beats exhibiting <5% change) was 10.5 ± 1.6 seconds).

After left anterior descending coronary artery occlusion, the time to peak pressure increased to 13.3 ± 5.8 seconds (p < 0.01) while the plateau systolic coronary sinus pressure level decreased significantly (p < 0.05) as compared with that before occlusion (37.3 ± 4.8 mm Hg, that is, 44 ± 0.18% of the left ventricular pressure).

Effects of brief intermittent coronary sinus occlusion. *Hemodynamics.* During severe coronary stenosis with flow reduction to 7.6 ± 7.6% of the control valve, heart rate and left ventricular end-diastolic pressure increased while left ventricular pressure, dP/dt$_{max}$, cardiac output and stroke volume decreased (Table 1). These measurements were not significantly altered during a 10 minute application of pressure-controlled intermittent coronary sinus occlusion. Similarly, brief pressure-controlled intermittent coronary sinus occlusion did not significantly alter hemodynamics in the presence of a total left anterior descending coronary artery occlusion.

Ischemic segment shortening. After severe stenotic reduction of left anterior descending coronary flow, ischemic myocardial segment shortening (Fig. 3) was depressed from a pre-stenotic baseline level of 14.0 ± 2.4 to 5.5 ± 1.2%. Ischemic segment shortening improved slightly during a 10 minute application of pressure-controlled intermittent coronary sinus occlusion (to 8.9 ± 2.6%, NS). Untreated complete left anterior descending coronary artery occlusion resulted in a more profound deterioration in ischemic segment shortening (to −0.1 ± 2.1%). In this setting, 10 minutes of pressure-controlled intermittent coronary sinus occlusion resulted in a slight improvement of ischemic segment shortening (to 2.3 ± 1.2%, NS). Significance may not have been reached because of the limited number of studies performed. Pooling all the available ischemic zone data (that is, 20 measurements after either severe stenosis or total occlusion of the left anterior descending coronary artery) resulted in a moderate but significant (p < 0.02) increase in function with 10 minute pressure-controlled intermittent coronary sinus occlusion compared with that before treatment. This

Table 1. Effects of Pressure-Controlled Intermittent Coronary Sinus Occlusion on Hemodynamics in Open Chest Dogs During Severe Coronary Artery Stenosis and Occlusion

	Control	Coronary Stenosis	PICSO	Coronary Occlusion	PICSO
LVedP (mm Hg)	3.3 ± 1.0	4.3 ± 0.5	3.9 ± 0.8	3.5 ± 0.3	3.6 ± 0.5
LVP (mm Hg)	113 ± 6.1	101 ± 7.6	97 ± 8.1	94 ± 8.7	93 ± 8.2
dP/dt$_{max}$ (mm Hg/s)	1,767 ± 300	1,488 ± 130	1,524 ± 157	1,445 ± 157	1,522 ± 160
dP/dt$_{min}$ (mm Hg/s)	−2,127 ± 267	−1,614 ± 167	−1,530 ± 184	−1,511 ± 215	−1,562 ± 170
AoPm (mm Hg)	102 ± 5.6	91 ± 7.5	87 ± 8.3	83 ± 8.3	83 ± 7.6
HR (beats/min)	105 ± 11	110 ± 9.0	111 ± 10	106 ± 9.0	110 ± 9.0
SV (ml)	14.4 ± 3.7	11.4 ± 2.5	11.6 ± 2.2	10.5 ± 2.3	10.1 ± 2.1
CO (liters/min)	1.4 ± 0.3	1.1 ± 0.1	1.2 ± 0.1	1.0 ± 0.1	1.0 ± 0.1

AoPm = mean aortic pressure; CO = cardiac output; dP/dt = derivative of left ventricular pressure, maximal (max) and minimal (min); HR = heart rate; LVedP = end-diastolic left ventricular pressure; LVP = left ventricular pressure; PICSO = pressure-controlled intermittent coronary sinus occlusion; SV = stroke volume.

improvement persisted during measurements 5 minutes after termination of pressure-controlled intermittent coronary sinus occlusion.

Detailed analysis of the ischemic segment shortening data in relation to the coronary sinus pressure buildup (in individual pressure-controlled intermittent coronary sinus occlusion cycles) revealed that a maximal improvement had already been achieved at a time when the coronary sinus

Figure 3. Ischemic segment shortening (ΔL%) measured by sonomicrometry in open chest dogs during reduction of left anterior descending coronary artery flow to 7.6 ± 7.6% of baseline flow (severe stenosis), and subsequently during complete coronary artery occlusion, both before and 10 minutes after pressure-controlled intermittent coronary sinus occlusion (P-ICSO).

pressure approached its peak value. Thus, there was indication that further protraction of the coronary sinus occlusion plateau may be counterproductive.

Continuous blood density measurements. As a result of lymphatic flow, blood density in the coronary sinus is normally slightly higher than that in the aorta (aortocoronary sinus blood density difference measured 0.05 ± 0.07 g/liter). After coronary artery occlusion, the aortocoronary sinus blood density difference increased to 0.16 ± 0.05 suggesting fluid leakage into the interstitial space. During pressure-controlled intermittent coronary sinus occlusion (Fig. 4) coronary sinus balloon inflation was associated with a synchronous increase in both the coronary sinus pressure and coronary sinus blood density. Coronary sinus balloon deflation resulted in a converse pressure decrease and a marked reduction in blood density. Mean coronary sinus blood density during the intermittent coronary sinus occlusion treatment was determined by averaging the mean values of cyclic amplitudes of coronary sinus blood density. Aortocoronary sinus density difference decreased significantly during the treatment (0.05 ± 0.08 g/liter, p < 0.05 versus postocclusion). Throughout the experiment, periodic plasma density measurements showed a constancy in the aortocoronary sinus gradient, during both coronary sinus occlusion and the release phase.
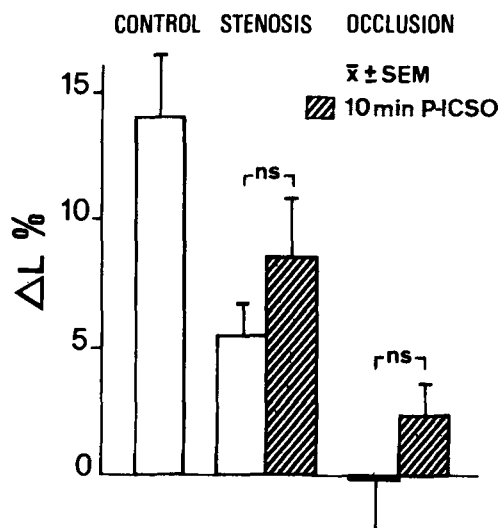
Intermittent Coronary Sinus Occlusion in the Closed Chest Model

Based on these open chest experiments with intermittent coronary sinus occlusion, the pressure-controlled cycle of coronary sinus occlusion in the closed chest study was intermittently released after systolic coronary sinus pressures
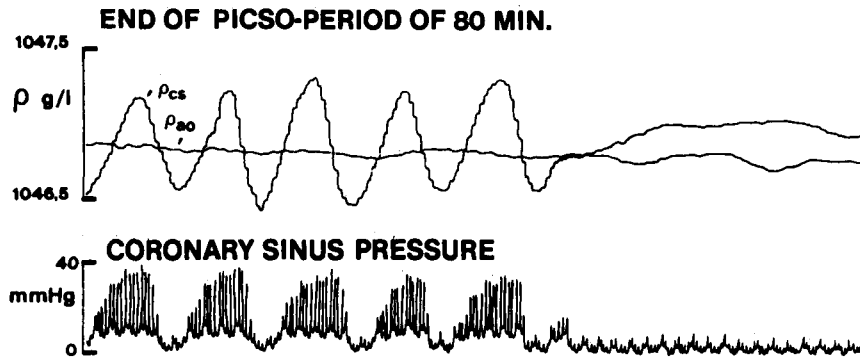
END OF PICSO-PERIOD OF 80 MIN.

Figure 4. Typical recording of coronary sinus blood density oscillations in relation to coronary sinus pressure changes, at the end of a pressure-controlled intermittent coronary sinus occlusion (PICSO) treatment period in the presence of left anterior descending coronary artery occlusion. ρao and ρcs = blood density in aorta and coronary sinus, respectively.

approached their peak values; that is, a period of 9.9 ± 1.5 seconds of coronary sinus occlusion was followed by a balloon deflation period of 1.8 ± 0.3 seconds, the latter permitting the coronary sinus blood pressure to return to baseline.

Of 20 dogs entering the closed chest study, 4 died before randomization to pressure-controlled intermittent coronary sinus occlusion and control, that is, within 30 minutes of coronary artery occlusion. Two dogs exhibited ventricular fibrillation within the first two cycles of pressure-controlled intermittent coronary sinus occlusion, and although one of the dogs could be defibrillated during maintained treatment and completed 3 hours of coronary artery occlusion, this animal was excluded from analysis. The analysis was, therefore, performed on 14 dogs, with Group A consisting of 6 dogs treated with pressure-controlled intermittent coronary sinus occlusion, and Group B consisting of 8 control dogs.

Hemodynamics (Tables 2 and 3). Pre-occlusion heart rate, systolic aortic pressure, left ventricular end-diastolic pressure, cardiac index and systemic vascular resistance did not differ significantly in the control and treated groups. Coronary artery occlusion caused an increase in heart rate, left ventricular end-diastolic pressure and systolic vascular resistance, while cardiac index decreased. Systolic aortic pressure showed only a minor change. In the treated group, there was a slight but nonsignificant decrease in heart rate and a significant (p < 0.05) decrease in left ventricular end-diastolic pressure at 90 minutes post-coronary artery occlusion (60 minutes of treatment), while other hemodynamic variables showed no differences relative to the untreated control group. Intermittent occlusions of the coronary sinus were reflected in concordant cyclic oscillations of coronary sinus and left anterior descending artery pressures, with statistically significant differences between pressures occurring during coronary sinus balloon inflation and deflation (Table 3).

Two-dimensional echocardiographic data. Figure 5 illustrates the time course of segmental systolic fractional area changes of all those ischemic segments (n = 35) that exhibited less than 5% wall thickening in all cross sections 30 minutes after coronary artery occlusion. Fractional area

change decreased from 56.1 ± 3.8% in the preocclusion control study to −4.0 ± 4.7% at 30 minutes after occlusion. Subsequently, in the treated series, 1 hour of pressure-controlled intermittent coronary sinus occlusion resulted in a significant increase in fractional area change to 13.1 ± 3.3% (p < 0.01). At 180 minutes postocclusion (2.5 hours of treatment), fractional area change was 7.0 ± 3.3%, significantly (p < 0.05) improved compared with 30 minutes postocclusion, but still significantly depressed when compared with the preocclusion state.

Segmental systolic fractional area changes. Table 4 compares global sectional and segmental systolic fractional

Figure 5. Two-dimensional echocardiographic measurements in closed chest dogs. Effects of pressure-controlled intermittent coronary sinus occlusion (PICSO) on segmental systolic fractional area change (%FAC) in all ischemic left ventricular segments showing less than 5% wall thickening 30 minutes after left anterior descending coronary artery occlusion (Occ).
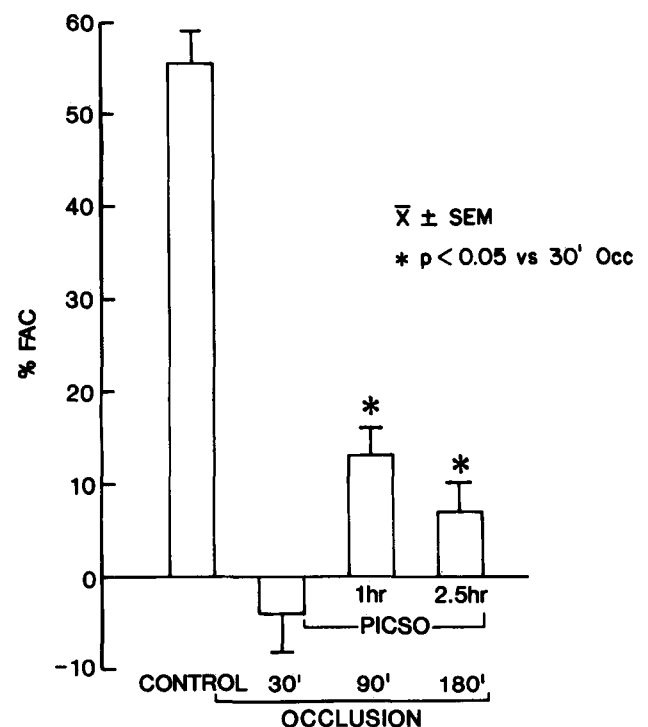
Table 2. Closed Chest Comparison of Pressure-Controlled Intermittent Coronary Sinus Occlusion in Treated (Group A) and Untreated (Group B) Dogs: Hemodynamics During 3 Hours of Left Anterior Descending Coronary Artery Occlusion

	Group	HR (beats/min)	Systolic Pressure (mm Hg)	LVEDP (mm Hg)	Cardiac Index (liters/min per m²)	SVR (dynes·s·cm⁻⁵)
Preocclusion	A	96 ± 8	126 ± 6	4.6 ± 1.4	2.35 ± 0.27	3,738 ± 533
	B	102 ± 8	112 ± 8	8.6 ± 0.8	2.79 ± 0.47	2,667 ± 290
30 minutes of occlusion	A	127 ± 11*	125 ± 6	12.4 ± 2.6*	2.22 ± 0.18	3,948 ± 509
	B	109 ± 7	114 ± 5	14.6 ± 1.6*	2.35 ± 0.23	3,203 ± 337
90 minutes of occlusion	A	106 ± 3	127 ± 8	8.0 ± 2.6*†	1.76 ± 0.18*†	5,476 ± 884*†
180 minutes of occlusion	A	122 ± 8*	124.5 ± 6	11.1 ± 3.1*	1.43 ± 0.11*†	5,801 ± 545*†
	B	125 ± 9*†	118 ± 3	15.3 ± 2.1*	1.78 ± 0.09*†	4,226 ± 346*†

*$p < 0.05$ versus preocclusion; †$p < 0.05$ versus 30 minutes of occlusion. Data are reported as mean ± SEM. SVR = systemic vascular resistance; other abbreviations as in Table 1.

area changes at the low papillary level of the left ventricle for pressure-controlled intermittent coronary sinus occlusion and control series (Groups A and B). In all cases, coronary artery occlusion led to a marked decrease in global sectional function, which subsequently deteriorated significantly further in the control animals, whereas in the treated dogs this global sectional fractional area change remained unaltered up to the end of the experiment. Ischemic segments exhibited a fractional area change of −0.4 ± 10.1% at 30 minutes after coronary artery occlusion, but improved significantly ($p < 0.025$) to 17.0 ± 5.9% at 90 minutes postocclusion with 60 minutes of pressure-controlled intermittent coronary sinus occlusion. After 180 minutes of left anterior descending artery occlusion (with 2.5 hours of treatment), fractional area change was 14.4 ± 4.4% ($p < 0.05$ versus 30 minutes postocclusion). Contraction of remote segments decreased moderately after coronary artery occlusion in both series of dogs but did not change significantly throughout the remainder of the experiment, although a slight decrease was noted in the animals treated with pressure-controlled intermittent coronary sinus occlusion.

Discussion

Effects of intermittent coronary sinus occlusion. Pressure-controlled intermittent coronary sinus occlusion represents a relatively simple methodology, and the current study indicates its ability to improve ischemic myocardial function during acute coronary occlusion. After a 10 minute application of pressure-controlled coronary sinus occlusion in open chest dogs, acutely ischemic myocardial segment shortening seemed to improve, but this change did not reach statistical significance. Prolonged 2.5 hour administration of intermittent coronary sinus occlusion in closed chest dogs during a 3 hour period of maintained left anterior descending coronary artery occlusion resulted in a moderate yet significant enhancement of regional ischemic myocardial function.

Proposed mechanism. During acute myocardial ischemia, progressive events leading to cell death are a function of various factors, including the duration and degree of the insult (10). Thus, subcellular ischemic derangements and loss of fluid control result in myocardial edema and leakage

Table 3. Coronary Artery and Venous Pressure Changes (mm Hg) Induced by Pressure-Controlled Intermittent Coronary Sinus Occlusion

Pressure	Pre-Occl.	30 Minutes of Occl.	90 Minutes of Occl. CS Balloon Inflation	90 Minutes of Occl. CS Balloon Deflation	180 Minutes of Occl. CS Balloon Inflation	180 Minutes of Occl. CS Balloon Deflation
LV	124 ± 7	123 ± 7	126 ± 7	126 ± 7	121 ± 6	121 ± 6
LAD						
Syst	116 ± 7	41 ± 7	51.4 ± 6.7*	39.7 ± 7.0	51.0 ± 4.9*	37.1 ± 5.0
Diast	82 ± 7	16.6 ± 3.8	14.9 ± 8.3*	10.2 ± 2.2	15.6 ± 2.5*	10.0 ± 1.8
CS						
Syst	2.7 ± 1.0	3.6 ± 0.7	62.9 ± 4.2*	4.4 ± 2.3	58.9 ± 6.6*	5.7 ± 1.8
Diast	4.7 ± 1.8	6.8 ± 1.3	14.3 ± 2.3*	6.3 ± 3.0	15.4 ± 3.2*	9.0 ± 1.8

*$p < 0.05$ inflation versus deflation. Data are reported as mean ± SEM. CS = coronary sinus; Diast = diastolic; LAD = left anterior descending coronary artery; LV = left ventricular; Occl. = left anterior descending coronary artery occlusion; Syst = systolic.

Table 4. Comparison of Pressure-Controlled Intermittent Coronary Sinus Occlusion in Treated (Group A) and Untreated (Group B) Closed Chest Dogs: Two-Dimensional Echocardiographic Systolic Fractional Area Changes in Low Papillary Left Ventricular Short-Axis Cross Section

| | Group | Sectional FAC (%) | Segmental FAC (%) | |
			Ischemic Segment	Remote Segment
Preocclusion	A	58.0 ± 5.3	59.8 ± 9.9	67.9 ± 6.6
	B	55.4 ± 1.1	54.3 ± 2.3	52.3 ± 4.1
30 minutes	A	27.5 ± 0.6*	−0.4 ± 10.1*	51.2 ± 6.2*
of occlusion	B	16.3 ± 2.7*	12.6 ± 6.1*	41.3 ± 3.9*
90 minutes	A	26.9 ± 4.1*	17.0 ± 9.8*†	36.7 ± 10.3*
of occlusion				
180 minutes	A	24.5 ± 1.8*	14.4 ± 4.4*†	46.3 ± 3.7*
of occlusion	B	10.0 ± 3.3*†	4.1 ± 6.9*	52.7 ± 3.5

*$p < 0.05$ versus control; †$p < 0.05$ versus 30 minutes of occlusion. Data are reported as mean ± SEM. FAC = systolic fractional area change.

into the interstitium of intracellular contents through dysfunctioning membranes (11). In the absence of adequate ischemic zone circulation, toxic metabolites tend to accumulate (reflected by a reduction of myocardial tissue pH), and this may precipitate viscous metabolite cycles leading to further deterioration and expansion of the ischemic injury (12). Experimental data (13) show that the contractile force of an in situ papillary muscle decreases much more gradually during anoxia alone (with preserved flow) than during ischemia with severe reduction in perfusion, indicating that flow itself might be a significant correlate of myocardial contractile force.

Retrograde coronary flow. During intermittent coronary sinus occlusion, pressures in the coronary sinus and those distal to the occlusion of the left anterior descending artery appear to be closely related (Fig. 2, Table 2). This could be due to intermittent blockage and high resistance of the coronary sinus occlusion into the low pressure and underperfused ischemic zone microvasculature (presumably retrograde flow through small venules that are "squeezed," particularly in systole, by action of the nonischemic myocardium). This is followed by efflux during the coronary sinus release phase.

Myocardial fluid "washout." Using a new method for continuous measurement of blood densities, our preliminary experiments indicate that the periodic changes in pressure and flow in the coronary venous system induced by intermittent coronary sinus occlusion result in a net reduction of the aortocoronary sinus density difference, suggesting a myocardial fluid washout. Since supplemental sampling and measurements revealed that plasma densities remained constant throughout the experiments, it would appear that a plasma-like high molecular weight fluid is shifted out during the periodic "loading" and "unloading" of the underperfused myocardial microvasculature. We hypothesize that this "washout" induced by intermittent coronary sinus occlusion reverses some of the ischemic derangements of the

myocardial interstitium, allowing partial restoration of reversibly injured cell function and thus enhancing both myocardial performance and viability.

Previous studies using intermittent coronary sinus occlusion. Arealis et al. (14) were the first to use intermittent coronary sinus occlusion synchronized to the cardiac cycle and they observed some improvement in survival time after left anterior descending coronary artery occlusion in dogs. Tziroglou et al. (15), after occluding branches of the left coronary artery, reported some hemodynamic improvement when the coronary sinus was intermittently occluded at a fixed rate of 60/min. The concept of using the pressure built up in the coronary sinus as a feedback variable for intermittent coronary sinus occlusion was developed by our group. In open chest dogs, a marked reduction in infarct size was reported after 6 hours of left anterior descending coronary artery occlusion (16). These findings were recently corroborated by another group (17), which demonstrated significant infarct reduction after a 3 hour left anterior descending coronary artery occlusion with 2.5 hours of intermittent coronary sinus occlusion treatment.

Limitations of the study. *Interference with perfusion of normal myocardium.* Despite the significantly enhanced regional ischemic zone function, hemodynamic variables reflecting global left ventricular performance (left ventricular end-diastolic pressure, cardiac index) were not improved by pressure-controlled intermittent coronary sinus occlusion in the closed chest dog experiments. This could be a consequence of the slight reduction in normal or remote zone function observed in the treated group. Pressure-controlled intermittent coronary sinus occlusion might interfere with perfusion of myocardium subserved by the nonoccluded coronary artery. Therefore, optimization of the intermittent occlusion-release cycle merits further studies to overcome this limitation. Thus, it might be undesirable to prolong the coronary sinus occlusion beyond the initial approach to the coronary sinus pressure plateau because of a

potentially counterproductive reduction in arterial inflow in the nonischemic zone and also retardation of the necessary coronary venous drainage. Conversely, the coronary sinus balloon deflation period may have to be specifically tailored so as to allow sufficient washout without infringing on the beneficial redistribution of coronary venous circulation toward the ischemic regions induced by pressure-controlled intermittent coronary sinus occlusion.

Ventricular fibrillation. Although ventricular fibrillation occurred in two dogs in this series shortly after application of pressure-controlled intermittent coronary sinus occlusion, we believe that these were unusual incidents since more than 50 animals treated with this method in various series of experiments showed no such adverse effects. However, pressure-controlled intermittent coronary sinus occlusion might theoretically precipitate ventricular fibrillation, either because a sudden increase in coronary sinus pressure may cause reflexive reduction in systemic pressure (18), thereby decreasing coronary artery perfusion and lowering the threshold of fibrillation, or because sudden retrograde inflow of blood in the ischemic zone might precipitate arrhythmias similar to those caused by reperfusion. A gradual and controlled start of pressure-controlled intermittent coronary sinus occlusion might mitigate the influence of those two factors and circumvent the potential hazards.

Postocclusion time of treatment. The maximal period of untreated occlusion in our experiments was 30 minutes, a period not applicable to most clinical situations. Preliminary data from our laboratory indicate that pressure-controlled intermittent coronary sinus occlusion could be effective even when started 2 hours after left anterior descending artery occlusion (resulting in a reduction in infarct size).

Method of blood density measurements. To explore the mechanisms of pressure-controlled intermittent coronary sinus occlusion, we employed a new method of continuous blood density measurements. Although this method has been reported to be highly accurate, and repeated density measurements were reproducible within 0.01 g/liter, these data represent only preliminary and indirect indications of changes induced by pressure-controlled intermittent coronary sinus occlusion in the microvascular bed. Further studies using alternate techniques were needed to corroborate our findings and prove our hypothesis that a "washout" effect is induced by pressure-controlled intermittent coronary sinus occlusion.

Clinical implications. Pressure-controlled intermittent coronary sinus occlusion represents a relatively simple technique requiring coronary sinus catheterization, which can be readily accomplished in the catheterization laboratory and even in a cardiac intensive care unit. During acute myocardial infarction, pressure-controlled intermittent coronary sinus occlusion might help to improve cardiac function and preserve tissue viability until a definitive procedure such as thrombolysis or angioplasty can be instituted. The proposed mechanism of pressure-controlled intermittent coronary sinus occlusion (that is, enhanced washout) makes its use especially attractive as a treatment for reperfusion derangements ("no reflow" phenomenon). However, further studies are clearly needed to establish a beneficial effect of pressure-controlled intermittent coronary sinus occlusion during reperfusion. Alternatively, this technique might be applied in the perioperative period during coronary bypass surgery. Further studies are needed to optimize the technique and establish the proposed mechanism.

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