The efficacy of intermittent coronary sinus occlusion in the absence of coronary artery collaterals

E. J. Toggart, M.D., S. H. Nellis, Ph.D., and A. J. Liedtke, M.D.

ABSTRACT  The purpose of this study was to evaluate the efficacy of time-controlled intermittent coronary sinus occlusion (ICSO) in preserving regional and global mechanical function during acute ischemia in an animal preparation without significant arterial collateral vessels. Seventeen (eight control, nine ICSO) swine heart preparations undergoing extracorporeal coronary perfusion in situ were subjected to ligation of the left anterior descending coronary artery (LAD) distal to the first major diagonal branch. Data were obtained before and immediately after coronary artery ligation in both animal groups. ICSO, 15 sec of occlusion alternating with 5 sec of release, was then begun in the treatment group. Additional data were obtained in both control and treatment groups at 15 min intervals for 1 hr starting immediately after coronary artery ligation. Global left ventricular function was assessed by shifts in left ventricular end-diastolic pressure and left ventricular dP/dt with left ventricular systolic pressure maintained at about 100 mm Hg. Regional mechanical function was evaluated with transmurally placed ultrasonic crystals. Pressure was also measured directly in the coronary sinus and LAD distal to the ligature. Regional myocardial blood flow was measured in the ischemic bed using 9 μm diameter radiolabeled microspheres injected before, immediately after, and 60 min after coronary artery ligation in both treated and control animals. LAD mean pressure measured distal to the ligation (less than 16 mm Hg) and ischemic bed myocardial blood flow (less than 0.01 ml/g/min) confirmed the absence of significant arterial-arterial collaterals in this preparation. Mean coronary sinus pressure increased significantly (p < .001) in treated animals during ICSO (e.g., 11.2 ± 1.6 to 66.2 ± 10.0 mm Hg at 15 min after coronary ligation). Mean LAD pressure distal to the coronary ligature also increased during ICSO (14.2 ± 1.2 to 26.8 ± 1.6 mm Hg), with a similar but delayed rate of pressure rise. No significant differences in left ventricular end-diastolic pressure or left ventricular dP/dt were noted between control or treated animals after coronary ligation. Ischemic bed systolic wall thickening, present before coronary ligation, was not present after occlusion and was not improved during intermittent coronary sinus occlusion in the treatment group. We conclude that in an animal preparation without significant collateral circulation, intermittent coronary sinus occlusion is incapable of restoring regional or global left ventricular mechanical function during conditions of acute ischemia.


SEVERAL GROUPS have reported infarct size reduction and/or preservation and return of regional mechanical function in ischemic myocardium using retrograde perfusion/infusion techniques involving the coronary venous system.1–11 The mechanism(s) of such benefits remain poorly understood. Additional controversy exists regarding optimal timing, implementation, and pressure variations associated with this approach. Synchronized diastolic retroperfusion uses active retroperfusion of arterialized blood into the coronary venous system during diastole. Its goal is to provide the ischemic zone with oxygenated perfusate. Others have used intermittent coronary sinus occlusion (ICSO), which alternates coronary sinus occlusion (lasting several cardiac cycles) with release of that occlusion. It is hypothesized that this temporary obstruction creates a pressure gradient from the venous system into the ischemic bed, inducing retroperfusion of desaturated venous blood into the ischemic zone. One proposed mechanism of myocardial salvage and preservation of mechanical function with ICSO is washout of noxious metabolites that accumulate during myocardial ischemia.9, 10

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Zalewski et al., however, was unable to demonstrate in dogs either significant salvage by selective inter-
mittent venous occlusion or active retroperfusion of unoxgenated venous blood subselectively into the
ischemic zone. These data support the notion that at
least in some species augmentation of local oxygen
levels is required for myocardial salvage and that wash-
out of ischemic metabolites alone is not adequate.

The different results within the same species, i.e.,
the negative finding of Zalewski et al. as contrasted
with the positive results of Mohl et al., may relate
to the different sites of venous occlusion and the presen-
tation of the arterial collateral flow in the ischemic zone.
Collateral flow is variable, which can be significant in
the canine preparations. Subselective venous occlusion
or retroperfusion does not produce the same effect on
outflow impedance as does ICSO. With ICSO, outflow
impedance within the coronary circulation increases in
the nonischemic as well as the ischemic bed. This could
potentially increase collateral flow into the ischemic
zone, which could then effect salvage by improving
local oxygen levels. Such a mechanism is an alterna-
tive explanation to previously reported beneficial results
with ICSO. To better sort out the roles of washout
versus augmented collateral inflow, we performed the
following experiments with ICSO in an animal prepa-
ration naturally deficient in arterial collateral cir-
culation. Our hypothesis was that in the setting of acute
regional ischemia, washout per se is sufficient to pre-
serve mechanical function.

Methods

Animal preparation. The animal preparation used in these
studies was a modification of the arterially perfused, working
swine heart in situ. Briefly, adolescent swine (40 to 60 kg
body weight) were anesthetized with pentobarbital (35 mg/kg),
dothrachally intubated, and ventilated with 70% oxygen via
a pressure controlled ventilator (Harvard Model No. 50-7400).
Arterial blood gases were monitored throughout the study and
respirator settings adjusted to maintain arterial PO2 and PCO2
within the physiologic range. An initial bolus of lidocaine (1
mg/kg) was administered intravenously before performing a
transsternotomy and bilateral thoracotomy. Thereafter, supple-
mental lidocaine was given to suppress ventricular or atrial
arrhythmias. Both phrenic nerves were transected. Both
hemiazygos veins were ligated proximally. A polyethylene can-
nula was inserted into the coronary sinus through the distal
segment of the left hemiazygos vein, which in pigs drains
directly into the coronary sinus. This catheter was connected to
a Statham P23/DB pressure transducer and was used to measure
 coronary sinus pressure directly and to obtain coronary sinus blood
 samples. A Millar catheter was inserted retrogradely into the
left ventricle through the right carotid artery. After hepa-
 rinization (10,000 U iv with hourly 5000 U doses) a coronary
perfusion circuit was established using the right femoral artery
as the source of arterial blood (figure 1). Arterial blood was
delivered to a mixing chamber and then to two low-flow roller
pumps used for independent perfusion of the right and left
 coronary arteries. The ostium of the left main coronary artery
was cannulated by a Gregg cannula inserted through the left
innominate artery. The right coronary artery was cannulated in
its proximal segment by a performed coronary cannula. Coro-
nary flow rates were adjusted to maintain perfusion equal to left
ventricular systolic pressure, after correcting for perfusion line
resistances. Left ventricular systolic pressure was maintained at
approximately 100 mm Hg by adjusting systemic volume. Vol-
ume was maintained by supplemental administration of low
molecular weight dextran.

In all animals, a cardiopulmonary bypass catheter (Sarns No.
10600, od = 7 mm, id = 4 mm) with multiple side holes
was inserted through the right atrial appendage into the coronary
sinus. This cannula was secured with an externally applied
Rommel tourniquet. The purpose of this cannula was not to
occlude sinus outflow but to divert it through a timer-controlled
solenoid valve, after which it was returned to the right atrium
(figure 1). This technique is different from those of other studies,
which have used balloon-tipped coronary sinus catheters to
perform coronary sinus occlusion. Diversion of coronary sinus
flow through this circuit did not significantly increase coronary
sinus pressure. Once established, this circuit was briefly
occluded while monitoring coronary sinus pressure. An abrupt
rise in coronary sinus pressure was used to indicate that an
effective catheter position for ICSO had been achieved (figure
2). Coronary sinus occlusion was controlled by a fixed timing
device opening and closing the solenoid valve. The cycle length
of 15 sec of occlusion alternating with 5 sec of release was based
on that initially reported by Mohl et al. This time frame allowed
for both coronary sinus and ischemic bed (pressure distal to the
ligature on the left anterior descending coronary artery [LAD])
to achieve plateau pressures. Five seconds of release was ade-
quate to allow return of coronary sinus pressure to baseline levels
(figure 2).

Ultrasonic crystal pairs were placed transmurally for the mea-
surement of normal and ischemic bed wall thickness (figure 1).
Ischemic bed crystals were placed in the perfusion bed of the
LAD distal to the site chosen for occlusion. Normal bed crystals
were placed near the base of the heart in either the proximal LAD
circuit perfusion territories.

Hemodynamic measurements, including left ventricular, cor-
onary sinus, coronary perfusion (left main, right), and LAD
pressures (distal to the ligature), the electrocardiogram, and
instantaneous normal and ischemic bed wall thicknesses were
recorded on a Gould multichannel recorder (figure 2). Data were
stored online in a Digital PDP 11/23 computer for later com-
puter-assisted data analysis. The LAD was then ligated in its
midsegment distal to the first diagonal and cannulated distally
for pressure measurement and blood sampling. ICSO, 15 sec of
occlusion (valve closed) alternating with 5 sec of release (valve
open), was then begun on the animals randomized to the treat-
ment group. The solenoid valve was continuously maintained in
the open position in the control animals.

Simultaneous blood samples obtained from the left main
coronary arterial perfusion line, coronary sinus, and ischemic
bed (sampled from the LAD cannula placed distal to the coronary
ligature) were obtained to determine percent oxygen saturation
and hemoglobin content with a Radiometer OSM2 Hemox-
imeter. Arterial blood gases were determined with a Radiometer
ABL30. Global myocardial oxygen consumption was calculated as
the product of total coronary blood flow (determined by the
 calibrated roller pumps) and the coronary arteriovenous oxygen
content (AVO2) difference. The AVO2 was calculated from the
left main coronary and coronary sinus samples. Oxygen con-
sumption was normalized for heart weight as measured at the
conclusion of each study.

Microsphere technique. Nine micrometer radiolabeled
FIGURE 1. Representation of the arterial perfused working swine heart in situ. The left main coronary artery (LCA) and right coronary artery (RCA) are perfused by separate roller pumps. The LAD is cannulated distal to the site of coronary ligation. Ultrasonic crystal pairs are placed transmurally for measurement of ischemic and nonischemic bed thickness. A mixing chamber, for the injection of radiolabeled microspheres, is present in the perfusion circuit before the roller pumps. A cardiopulmonary bypass cannula was inserted into the coronary sinus (see Methods) and secured with sutures. This directed coronary sinus flow through the solenoid valve. Blood was then returned to the right atrium (RA). LA = left atrium; CX = left circumflex coronary artery.

Microspheres (Ce, Sr, Sc; 3M) were processed, as previously reported, to ensure accurate sizing, absence of aggregation, and adequate specific activity. Energy spectra were plotted and counting windows determined on a Packard two-channel gamma counter. Based on microsphere specific activity, a dose of 0.5 ml of the adequately mixed microsphere suspension was used for all three microsphere species, thus ensuring both delivery of greater than 400 spheres/g of tissue and accurate flow determinations. The order in which the microspheres were injected was randomized for each animal to avoid bias from the effect of energy spectra and species overlap on counting efficiency. Microspheres were mixed with a magnetic stirrer for 1 min before injection. The microspheres were injected into a mixing chamber that was part of the coronary artery perfusion circuit (figure 1) and that contained a magnetic stirring bar so that the microspheres would be adequately dispersed in the coronary perfusate (see below). Tissue samples were obtained from the ischemic zone, defined at the conclusion of the study as the unstained region after methylene blue was injected into the left main and right coronary artery perfusion lines. After the animal was killed, the heart was immediately excised, atrial and valvular tissues were removed, and the left ventricle was sectioned perpendicular to the long axis in 1 cm thick slices. The entire ischemic bed was divided into endocardial and epicardial halves of approximately 0.5 g. Radiactive counts and weight data were entered into the Digital PDP 11/23 computer. Calculations for determining regional myocardial blood flow were made by means of previously developed software that compensates for counts resulting from energy spectra overlap and generates values in flow per gram wet weight tissue.

Adequacy of microsphere distribution within the coronary perfusion circuit was confirmed by simultaneous withdrawal of reference samples from both right and left coronary perfusion lines. These samples were then counted separately. Variations between total raw counts were less than 10% for all injections. This equal distribution demonstrates that the mixing chamber produced sufficient mixing, similar to injection into a cardiac chamber such as the left atrium. Selective injection into the coronary perfusion circuit allowed for a reduction in the number of labeled microspheres necessary for each study.

The purpose of microsphere injections was to measure alterations in antegrade arterial flow into the ischemic bed produced by ICSO. Because of the high venous pressures achieved during ICSO, microspheres injected into the arterial perfusion circuit might become dislodged and traverse the microcirculation, enter the coronary sinus blood pool, and from there the ischemic bed in a retrograde fashion. Microspheres from this source could not be differentiated from those arriving in an antegrade fashion. To evaluate this potential source of error in estimating antegrade flow, blood was continuously withdrawn from coronary sinus during the time of microsphere injection. Coronary sinus counts obtained in this fashion were less than 0.1% of injected counts.
for each microsphere injection in all treated and control animals.

Protocol. Hemodynamic data were recorded, blood samples obtained, and the first microsphere species injected before coronary occlusion (baseline), when the preparation had achieved hemodynamic stability after surgical manipulation and instrumentation (approximately 3 hr). Animals were considered stable after exhibiting 10 min of unchanging left ventricular pressure, heart rate, and arterial blood gases, generally less than 15 min after completion of surgery. The LAD was ligated distal to the origin of the first diagonal branch and was cannulated distally so that ischemic bed pressure and oxygen saturation could be measured. Repeat hemodynamics and blood samples were obtained immediately after coronary artery ligation (within the first 2 min) and the second microsphere species was injected.

Animals that developed ventricular fibrillation were cardioverted. If three sequential cardioversions failed to reestablish stable sinus rhythm, the animals were excluded from the study. ICSO was then begun on animals randomized to the treatment group (approximately 5 min after coronary ligation). In control animals the solenoid valve was maintained in the open position, allowing for continuous drainage of coronary sinus effluent into the right atrium. Hemodynamic recordings and samples for oxygen saturation as described above were obtained at 15, 30, 45, and 60 min after ligation in both control and treatment groups. Hemodynamics and wall motion data in the treatment groups were recorded during coronary sinus occlusion (valve closed) and release (valve open) for each time point during the treatment period. This served several purposes. First, the data confirmed that during the “valve open” or “release” phase, coronary sinus pressure returned to control levels, thus reestablishing venous drainage. Furthermore, in a preparation in vivo, autonomic reflex pathways could be stimulated because of changes in coronary sinus pressure. These reflexes might alter myocardial oxygen demand by varying ventricular loading conditions or modifying heart rate. Recording hemodynamics during occlusion and release would identify such events. Changes in wall thickness occurring from release to occlusion could also provide an index of dynamic vascular engorgement (retroperfusion). Additionally, any cycle-related effect (occluded vs release) of ICSO on regional mechanical function, positive or negative, in nonischemic or ischemic beds could also be determined.

A third microsphere species was injected 60 min after coronary artery ligation. The animals were then killed with pentobarbital overdose. Methylene blue was injected into the coronary perfusion lines to define normally perfused myocardium. The heart was immediately excised, weighed, and processed for regional myocardial blood flow determination, as described above.

Initial pilot studies attempting to extend the study to 3 hr so that tetrazolium staining for determination of infarct size could be performed were unsuccessful, primarily because of overall cardiopulmonary deterioration in both control and treated animals. This was apparent starting approximately 2 hr after coronary ligation. Because of this deterioration, in our opinion, data collected beyond 1 hr after coronary ligation would not be meaningful. Thus infarct size was not measured in this study.

Data analysis. Hemodynamic data were analyzed for the determination of heart rate, left ventricular peak-systolic and end-diastolic pressures, and positive maximal left ventricular dP/dt. Maximum, minimum, and mean coronary sinus and LAD pressures distal to the coronary ligature were also determined. End-diastolic (ED) and end-systolic (ES) and wall thickness (T) were determined with the left ventricular pressure waveform as
reference. Segmental wall thickening, an index of regional mechanical function, was defined as \((EST - EDT)/EDT \times 100\%\). Changes in EDT, EST, and absolute thickening \((EST - EDT)\) were calculated by comparing a given value to the respective baseline value before coronary artery ligation.

Comparison of control and treatment groups were performed with unpaired Student’s t test. Comparison within treatment and control groups was performed with paired Student’s t test statistics. Significance was defined as p values less than .05.

**Results**

A total of 37 surgical preparations were attempted. Seven animals died during surgical preparation due to technical problems or arrhythmias. An additional 13 animals developed refractory ventricular fibrillation immediately after coronary artery ligation. No further deaths in control or treated animals occurred after entry into the therapy segment of the protocol. Seventeen (eight control, nine ICSO) animals survived and were studied.

**Hemodynamics and regional myocardial blood flow.** Values for hemodynamic variables and myocardial oxygen consumption are listed in Table 1. As discussed in Methods, these data and regional mechanical function data are displayed for the control (continuous open valve) and treated animals during both the release (valve open) and occlusion phase (valve closed) of the ICSO cycle.

In general, there were no major differences in the left ventricular peak systolic and end-diastolic pressures and dP/dt between control and treatment groups. Heart rate tended to be higher in treatment animals and reached statistical significance immediately after ligation. Left ventricular systolic pressure was significantly higher in control as compared with treatment animals at 30, 45, and 60 min after coronary ligation. Despite these differences, myocardial oxygen consumption \((\text{MVO}_2)\) was significantly higher in the ICSO group only at 15 min after coronary ligation. No significant differences in \(\text{MVO}_2\) occurred at any other time. Overall, both groups had comparable oxygen demand and consumption during the period of ischemia.

In the ICSO group, coronary sinus and distal LAD pressures increased significantly during coronary sinus occlusion. During release (valve open), both coronary sinus and LAD pressures were similar to those in con-

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>LVSP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>LV dP/dt (mm Hg/sec)</th>
<th>MVO2 (ml/min/100 g)</th>
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</thead>
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<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>115.5 ± 8.0</td>
<td>108.5 ± 5.2</td>
<td>8.9 ± 1.2</td>
<td>26.1 ± 3.4</td>
<td>9.08 ± 0.72</td>
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<td>ICSO</td>
<td>138.5 ± 11.4</td>
<td>110.5 ± 4.1</td>
<td>7.5 ± 1.3</td>
<td>25.3 ± 4.2</td>
<td>8.88 ± 0.66</td>
</tr>
<tr>
<td><strong>PL</strong></td>
<td></td>
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</tr>
<tr>
<td>Control</td>
<td>110.0 ± 7.2</td>
<td>103.2 ± 5.0</td>
<td>14.0 ± 2.7</td>
<td>17.1 ± 1.3</td>
<td>8.13 ± 0.92</td>
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<tr>
<td>ICSO</td>
<td>129.9 ± 8.0</td>
<td>98.9 ± 4.6</td>
<td>14.2 ± 2.5</td>
<td>16.8 ± 2.1</td>
<td>9.21 ± 0.71</td>
</tr>
<tr>
<td><strong>15 min</strong></td>
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<tr>
<td>Control</td>
<td>115.0 ± 7.2</td>
<td>103.1 ± 4.8</td>
<td>12.9 ± 1.7</td>
<td>18.6 ± 1.5</td>
<td>7.76 ± 0.67</td>
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<td>ICSO-R</td>
<td>133.0 ± 8.0</td>
<td>100.9 ± 3.4</td>
<td>13.5 ± 2.6</td>
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<td>9.56 ± 0.74</td>
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<td>ICSO-O</td>
<td>133.7 ± 9.7</td>
<td>97.1 ± 4.1</td>
<td>14.3 ± 2.8</td>
<td>18.9 ± 2.1</td>
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<td><strong>30 min</strong></td>
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<tr>
<td>Control</td>
<td>118.5 ± 9.0</td>
<td>101.6 ± 3.3</td>
<td>15.0 ± 2.8</td>
<td>16.4 ± 1.4</td>
<td>8.21 ± 0.60</td>
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<td>ICSO-R</td>
<td>138.9 ± 11.7</td>
<td>96.0 ± 1.7</td>
<td>10.0 ± 1.6</td>
<td>20.2 ± 1.8</td>
<td>9.12 ± 0.74</td>
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<td>ICSO-O</td>
<td>141.1 ± 12.0</td>
<td>94.5 ± 2.4</td>
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<td>Control</td>
<td>122.3 ± 7.9</td>
<td>104.1 ± 5.9</td>
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<td>17.4 ± 1.3</td>
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<td>ICSO-R</td>
<td>142.1 ± 11.4</td>
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<td>ICSO-O</td>
<td>141.0 ± 12.1</td>
<td>93.4 ± 2.4</td>
<td>10.8 ± 1.6</td>
<td>19.2 ± 2.5</td>
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<td><strong>60 min</strong></td>
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<tr>
<td>Control</td>
<td>127.2 ± 10.7</td>
<td>105.8 ± 6.6</td>
<td>15.6 ± 1.2</td>
<td>19.6 ± 1.6</td>
<td>8.63 ± 0.87</td>
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<td>ICSO-R</td>
<td>137.8 ± 11.6</td>
<td>95.3 ± 2.6</td>
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<td>8.14 ± 0.67</td>
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<td>ICSO-O</td>
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<td>90.7 ± 3.9</td>
<td>11.7 ± 2.3</td>
<td>18.2 ± 2.6</td>
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</table>

Determinants of myocardial oxygen demand and measured myocardial oxygen consumption. Data were obtained at baseline, immediately (PL) and 15, 30, 45, and 60 min after coronary artery ligation.

ICSO-R = value obtained from treated animal with coronary sinus valve in open position; ICSO-O = value obtained from treated animal with coronary sinus valve in closed position; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; LV dP/dt = peak positive left ventricular dP/dt; MVO2 = myocardial oxygen consumption.

*<p value>.05 ICSO occluded vs control; b<p value>.05 ICSO vs control.
CONTROL GROUP

ICSO RELEASED

ICSO OCCLUDED

FIGURE 3. Coronary sinus pressure (CSP) and pressure (LADP) distal to the coronary ligature for control and treated animals (ICSO). Pressure was recorded during coronary sinus occlusion (valve closed) and release (valve open). Time points: B = baseline; PL = immediately after ligature; 15, 30, 45, and 60 min after ligation. Coronary sinus and LAD pressure increases occurring with occlusion were significant (p < .001 at all times except at 45 min [maximum LAD pressure, mean coronary sinus pressure] and at 15 min, where p < .005).

trol animals (figure 3). Tables 2 and 3 are individual data from both control and treated animals at baseline and 60 min after coronary ligation. There were no significant differences in coronary sinus and LAD pressure between control and treated animals before coronary ligation and during the release phase (valve open) at 60 min after coronary ligation, indicating adequate time for venous drainage during the release phase. The time to achieve stable pressure plateaus was also measured. The average time to plateau in the coronary sinus averaged 8.9 ± 0.3 sec after coronary sinus occlusion. The plateau in LAD pressure was achieved at 11.1 ± 0.2 sec after coronary sinus occlusion. Both coronary sinus and LAD pressure fell to control levels rapidly with release of coronary sinus occlusion in all animals, returning to basal levels before the next occlusion.

The mean LAD pressure distal to the ligature during release in the treated animals and in control animals was less than 16 mm Hg at all times (figure 3). During release, mean distal LAD pressure also exceeded mean

<table>
<thead>
<tr>
<th>TABLE 2</th>
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<tbody>
<tr>
<td>Coronary sinus and LAD pressures (mm Hg) distal to the coronary ligature before and 60 min after coronary artery ligation in control animals</td>
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</table>

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Baseline</th>
<th>60 min after ligation</th>
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<tr>
<td></td>
<td>Max</td>
<td>Min</td>
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<td>2</td>
<td>31.1</td>
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</tr>
<tr>
<td>3*</td>
<td>—</td>
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</tr>
<tr>
<td>4</td>
<td>16.0</td>
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<td>5</td>
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<td>9</td>
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<td>Mean</td>
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<tr>
<td>SEM</td>
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*Only mean pressures were recorded for animal 3.
TABLE 3
Coronary sinus and LAD pressures (mm Hg) distal to the coronary ligature before (baseline) and 60 min after coronary artery ligation in treated animals

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Baseline (valve open)</th>
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<th>60 min after ligation-release (valve open)</th>
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<tr>
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<td>Coronary sinus</td>
<td>LAD</td>
<td>LAD</td>
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<tr>
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<td>Max</td>
<td>Min</td>
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<td>11.6</td>
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<td>9</td>
<td>24.9</td>
<td>7.4</td>
<td>17.0</td>
</tr>
<tr>
<td>Mean</td>
<td>21.2</td>
<td>4.6</td>
<td>10.6</td>
</tr>
<tr>
<td>SEM</td>
<td>3.2</td>
<td>1.2</td>
<td>1.6</td>
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Coronary sinus pressure. During occlusion in the treated animals, mean coronary sinus pressure was greater than mean distal LAD pressure, thus establishing an alternating pressure gradient between the ischemic bed and the coronary sinus. This would promote average inflow into the ischemic bed during occlusion (valve closed) and washout during release (valve open).

Endocardial and epicardial blood flow in both treatment and control animals fell to near zero in the ischemic zone after coronary artery ligation (figure 4). There was no significant change in microsphere-measured regional myocardial blood flow in the ischemic zone in either group immediately and 60 min after coronary artery ligation.

Ventricular function. As shown in table 1, left ventricular end-diastolic pressure increased in both groups immediately after coronary ligation. It then tended to fall in the treatment group and to remain elevated in the control group. Left ventricular systolic pressure was maintained at nearly constant levels throughout the studies by volume adjustment. Peak positive left ventricular dP/dt fell immediately after LAD ligation in both groups, then tended to rise in the treatment group at 30 and 45 min after coronary ligation, but remained depressed in the control group. None of these differences were statistically significant.

An index of regional mechanical function, systolic wall thickening, was calculated for both the ischemic and nonischemic beds. Ischemic bed regional systolic thickening [(EST - EDT/EDT) × 100%] was markedly diminished in both treatment and control groups after coronary occlusion (figure 5). There was no sig-

FIGURE 4. Regional myocardial blood flow as measured by 9 μm diameter radiolabeled microspheres (see Methods). There was no significant difference between the control and treated groups.
significant improvement in ischemic bed wall thickening with ICSO. No consistent effect of coronary sinus occlusion on systolic wall thickening was present in treated animals during coronary sinus occlusion or release in either normal or ischemic beds.

No significant changes in nonischemic beds systolic thickening occurred in either control or treatment groups. There was consistently higher regional systolic thickening in the nonischemic myocardium in control animals as compared with the treatment group. This trend was noted throughout the study and was significant at 15, 45, and 60 min after coronary ligation.

Significant increases in end-diastolic and end-systolic wall thickness occurred in the treated animals in both ischemic and nonischemic beds at 60 min after coronary occlusion compared to those values obtained immediately after coronary occlusion (figure 6). No comparable changes occurred in control animals. Increases in thickness (end-diastolic and end-systolic) had both fixed and dynamic components (figure 6). The fixed component is represented by higher values of end-diastolic and end-systolic thickness in the treatment group 60 min after coronary ligation compared with values obtained immediately after coronary ligation. The dynamic element was noted at multiple time points in both ischemic and nonischemic beds in which there were also statistically significant differences in end-diastolic and end-systolic wall thickness during coronary sinus occlusion (valve closed) compared with release (valve open).

Because the increases in wall thicknesses alone could lower values of systolic wall thickening, absolute thickening (EST - EDT) at given times was also calculated and expressed at a fraction of absolute thickening at baseline (figure 6). The ischemic bed became and remained dyskinetic after coronary artery occlusion in both control and treatment groups. Absolute thickening did not change significantly in the normal beds throughout the course of the study.

Metabolism. Mean arterial oxygen saturation remained greater than 95% in both treatment and control animals at all times (figure 7). Immediately after coronary ligation and 45 min thereafter in the treatment group, arterial saturation was slightly (but significantly) lower than that in controls. Oxygen saturation in the coronary sinus tended to be lower in treated animals as compared with controls, with the differences reaching significance immediately after coronary ligation and at 45 min after ligation. LAD oxygen saturation (obtained distal to the ligature) in treated animals fell 15 min after coronary occlusion compared with that in control animals and remained significantly lower at 30 (p < .025), 45 (p < .005), and 60 min (p < .01) after coronary ligation. In control animals this value was similar to coronary sinus saturations, approximately 35%. In the treated animals it remained less than 20% during the treatment period.

Discussion

It has been hypothesized that ICSO salvages myocardium and improves mechanical function by washout of intermediate metabolic byproducts. These are considered noxious and inhibitory to continued function in jeopardized myocardium. Data from other preparations have indicated that washout, by removing metabolic end-products, improves cellular metabolic perfor-
performance, including accelerated glycogenolysis and glycokolysis, and allows added energy production of essential high energy phosphates.16-19

If the washout hypothesis of salvage with ICSO is correct, preservation should occur independent of arterial collateral flow. The presented data demonstrate no effective preservation of function despite early intervention and thus do not support the washout mechanism hypothesis as the sole mechanism of salvage. Changes in coronary sinus and LAD pressures, the relative magnitudes of the pressure during release and occlusion (establishing alternating pressure gradients between coronary sinus and ischemic bed), and the dynamic changes in end-diastolic and end-systolic wall thickness are all compatible with retroperfusion of the ischemic bed with the venous effluent during ICSO. Despite this, no functional improvement occurred in this preparation.

The microsphere data and low magnitude of arterial pressure in the ischemic bed confirm the absence of functionally significant arterial collaterals in this preparation. The LAD pressure distal to the coronary occlusion is lower in swine than that reported in dogs.9, 20 Additionally, despite the presence of small endocardial and intramural collaterals in porcine hearts,21-23 ICSO did not induce increased collateral flow. Because of the anatomic difference between canine and porcine collateral circulations,20-27 alterations of arterial collateral flow into the ischemic bed in the canine preparation as a mechanism of salvage by ICSO cannot be proved or excluded by this or previous studies.

Zalewski et al.11 reported only minimal salvage in a canine preparation during either intermittent venous occlusion or active retroperfusion with venous blood. However, active retroperfusion with arterial blood reduced infarct size significantly. It was thus proposed that for retroperfusion techniques to be effective, oxygen delivery to the ischemic bed must be significantly increased. Our data support this concept. Significant differences do exist, however, between this and other studies of ICSO. The present report and that of Zalewski et al.11 used timed ICSO instead of pressure-regulated occlusions. It has been suggested by others that the former may lead to longer periods of coronary sinus occlusion and pressure elevations, which have potential detrimental effects. The fixed components of increased wall thickness in the treated animals indicate the development of interstitial edema. This probably
resulted from the combination of fixed antegrade coronary perfusion and a period of coronary sinus occlusion longer than that required to achieve plateaus in coronary sinus pressure. Regional function in the nonischemic bed did not deteriorate with these changes in wall thickness, which argues against edema having masked any beneficial effect of ICSO on mechanical function in the ischemic bed. These changes, however, reinforce the concept that if ICSO is performed, control of the occlusion time may be important in preventing detrimental effects of coronary venous pressure elevation.

The essentially negative findings of this study in adolescent swine support the hypothesis that significant collateral flow into the ischemic bed is necessary for effective protection during ischemia with ICSO. The lack of salvage in the study of Zalewski et al11 may be explained by the fact that the venous occlusion was subselective, i.e., involving occlusion of venous drainage solely from the ischemic bed (great cardiac vein [GCV]). Coronary sinus occlusion, on the other hand, increases impedance in the nonischemic bed as well as the ischemic bed. This could cause increased collateral shunting to the ischemic bed, with the ischemic bed acting as a “sink” (low pressure zone). Selective venous occlusion of the ischemic bed could, in fact, have detrimental effects by reducing pressure gradients from nonischemic to ischemic myocardium. This could increase ischemic bed pressure without increasing impedance or nonischemic regions, thereby reducing inflow from collaterals or obstructed venous outflow. As demonstrated by Nakazawa et al.,28 approximately one-third of the venous drainage from the canine LAD perfusion territory occurs through venous pathways other than the GCV. Selective occlusion of the GCV may not totally impede outflow from the ischemic bed. Because distal coronary artery pressure was not measured in the study of Zalewski et al.,11 it is not known whether the pressure rise seen in the GCV was transmitted into the ischemic bed. Potentially, GCV occlusion merely diverted venous drainage through alternative venous channels without retroperfusing the ischemic bed.

High venous pressures might also cause postcapillary arterial venous mixing, increasing the oxygen of the venous retroperfusate. Our data suggest that this does not occur in the pig, since coronary sinus oxygen content did not increase during ICSO. The lower ischemic bed venous oxygen saturation also suggests that further oxygen extraction did occur in the ischemic bed in the treatment animals. This could indicate the preservation of myocardial cell viability within the ischemic bed without preservation of function (“stunned myocardium”). This could be proved only by reperfusion studies or measurements of infarct size, which were not performed in this study. Present data also do not exclude postcapillary arteriovenous mixing as a mechanism in other preparations nor as a well localized phenomenon in the peri-infarct zone in pigs.

Factors other than the presence of augmentation of collateral inflow may have produced different results seen among different preparations. The potential
importance of pressure- vs time-controlled ICSO has already been discussed. Elevations in coronary sinus pressure in intact animal preparations might also evoke autonomic reflexes that could alter heart rate or ventricular loading conditions. Changes in these variables could lower myocardial oxygen demand producing salvage independent of retroperfusion of the ischemic bed. No such changes were evident in this study. Previous studies\(^9\) have not reported hemodynamic changes during both coronary sinus occlusion and release; however, the role of such changes in other preparations remains unknown.

In conclusion, our data support the hypothesis that ICSO causes retroperfusion of the ischemic bed, but while retroperfusion may be a necessary component, it alone is not sufficient, in the absence of increased oxygen delivery, to produce effective preservation of functional mechanism. Techniques that also enhance oxygen delivery, possibly by alterations in collateral flow patterns induced by global coronary venous occlusion or by retroperfusion with a perfusate of high oxygen content appear to be more effective in salvage. This may be important in considering the potential future clinical application of these techniques and suggests that ICSO may be less effective in patients with poorly developed collateral circulation.

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