Effect on myocardial perfusion of simultaneous delivery of cardioplegic solution through a single coronary artery and the coronary sinus

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Objective: This study was to determine whether simultaneous antegrade-retrograde cardioplegia through a single coronary artery and the coronary sinus provides sufficient and homogeneous perfusion to the heart.

Methods: Simultaneous antegrade-retrograde cardioplegia was conducted in 7 isolated pig hearts through the coronary sinus in conjunction with the left anterior descending artery, the left circumflex artery, and the right coronary artery, respectively. The efficacy of simultaneous antegrade-retrograde cardioplegia for myocardial perfusion was assessed by monitoring the distribution of magnetic resonance contrast agent and measuring the effluent from the venting coronary arteries.

Results: Injection of contrast agent into a perfusing artery during simultaneous antegrade-retrograde cardioplegia resulted in increased image signal intensity not only in the territory of the perfusing artery but also in the areas normally served by the other 2 venting arteries (including the right ventricular wall). The myocardium in the territories of the 2 venting arteries was lightened with contrast agent given into the coronary sinus during simultaneous antegrade-retrograde cardioplegia. Myocardium in the perfusing artery territory and right ventricular wall remained dark. Moreover, a significant amount of effluent was collected from the venting arteries during simultaneous antegrade-retrograde cardioplegia: 4.7 to 7.8 mL/min from the right coronary artery; 10.5 to 17.7 mL/min from the left anterior descending artery; and 9.7 to 15.2 mL/min from the left circumflex coronary artery.

Conclusions: Simultaneous antegrade-retrograde cardioplegia through a single coronary artery and the coronary sinus provides homogeneous perfusion to the entire heart. During simultaneous antegrade-retrograde cardioplegia, arterial flow supports its own designated myocardium, as well as adjacent myocardium normally served by the venting arteries; the arterial route also supports the right ventricular free wall when the right coronary artery is vented. Venous perfusion of simultaneous antegrade-retrograde cardioplegia mainly supports myocardium in the territories of the venting arteries and does not perfuse the right ventricular free wall. Blood flow delivered to myocardium normally supported by the venting arteries is believed to be sufficient to prevent ischemic injury.

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ntegrade and retrograde cardioplegia are often used for myocardial protection during cardiac surgery.^{1,2} In the presence of critical coronary stenosis or occlusion, antegrade cardioplegia is unable to deliver a sufficient amount of cardioplegic solution to the myocardium served by the diseased coronary arteries.^{3,4} Because atherosclerosis does not occur in the coronary venous

Figure 1. Schematic illustration of experimental protocol.

system, retrograde cardioplegia through various venous routes has gained popularity in the operating room.⁵ Because of its low flow rate, heterogeneous distribution, and poor protection of the right ventricular wall, retrograde cardioplegia has been shown to be less efficient than antegrade cardioplegia in protecting normal regions of the myocardium.^{6,7} A combination of antegrade and retrograde cardioplegia has been proposed as a better approach for protecting the diseased heart than using antegrade or retrograde cardioplegia alone.⁸⁻¹⁰

Simultaneous antegrade-retrograde cardioplegia (SARC) can be performed through the coronary sinus in conjunction with either the aorta or the ostium of a coronary artery or a completed vein graft. We have previously assessed the effica-

Figure 2. Outflow rates measured at the venting arteries during AP (upper panel) and during SARC (lower panel). Data are presented as means $\pm$ standard deviation of the mean. CF, Coronary flow.

cy of SARC through the aorta and the coronary sinus on myocardial perfusion in the jeopardized region.¹¹ In that study the left anterior descending artery (LAD) of the isolated pig hearts was occluded to create a region of jeopardized myocardium. It was found that both routes (aorta and coronary sinus) of SARC delivered cardioplegic solution to the jeopardized myocardium to sustain normal myocardial energy homeostasis. The results demonstrated that SARC through the aorta and the coronary sinus provides adequate protection to the myocardium beyond a coronary occlusion.

However, it was unclear whether SARC provides homogeneous perfusion to all regions of the heart when performed through a single coronary artery and the coronary sinus. The present study was designed to answer this question. This cardioplegic technique is often used for deairing, as well as for perfusion after completion of a coronary graft.¹²

Materials and Methods

Isolated Pig Heart Preparation

All animals used in this study received humane care in compliance with the "Guide to the Care and Use of Experimental Animals" formulated by the Canadian Council on Animal Care. The protocol for this study was approved by the Animal Care Committee of the National Research Council of Canada. The pig heart was chosen as the animal model because it shares some similarities with the human heart.^{13,14}

Seven domestic pigs weighing 45 to 50 kg were sedated by means of intramuscular injection of atropine (0.06 mg/kg body weight), diazepam (0.4 mg/kg body weight), and ketamine (20 mg/kg body weight).

Figure 3. Representative images obtained during AP through the 3 major coronary arteries with contrast agent injected into the LCX (A), the LAD (B), and the RCA (C).

Figure 4. Representative MR images. A shows an image obtained during AP with Gd-DTPA injected into the RCA. Images acquired during SARC with Gd-DTPA injected into the RCA and the coronary sinus are shown in B and C, respectively.

Anesthesia was maintained with 1.5% to 2.0% isoflurane in a mixture of oxygen and medical air. The rate and volume of positive-pressure ventilation were adjusted to keep the arterial blood gases within the normal physiologic range. The brachiocephalic artery was cannulated at the level of the common carotid artery for arterial pressure monitoring, blood sampling, and injection of cardioplegic solution.

A sternotomy was performed, and the brachiocephalic and subclavian arteries were dissected. A cannula for the infusion of cardioplegic solution was introduced into the ascending aorta from the brachiocephalic artery. The pericardium was opened longitudinally along the midline. The descending aorta was isolated at its origin for crossclamping. The animal was then heparinized by injecting 3000 IU of heparin into the right atrium. Heparinized cold (approximately 4°C) cardioplegic solution was delivered into the aortic root (10 mL/kg body weight) to arrest the heart. The heart was then excised from the animal. Blood in the chest of the pig was collected and mixed in a 1:1 ratio with Krebs-Henseleit solution. The hemoglobin concentrations in pig blood and the mixture were 9.6 ± 0.7 g/dL and 5.0 ± 0.1 g/dL, respectively. The mixture was oxygenated with 95% oxygen and 5% carbon dioxide to a final pH and PO_2 of 7.41 ± 0.02 and 545 ± 35 mm Hg, respectively.

The 3 major coronary arteries were cannulated separately at their origins by using 0.085-inch diameter polyethylene cannula for deliv-

ery and drainage of blood cardioplegic solution and for washout of contrast agent. A 15F retrograde cannula (DLP Inc, Grand Rapids, Mich) with a manually inflated balloon at the tip was positioned approximately 1 cm into the coronary sinus. The position of the catheter was adjusted such that the external edge of the balloon was at the orifice of the coronary sinus. If the anterior ascending cardiac vein drained directly into the right atrium (bypassing the coronary sinus), it was also cannulated for venous delivery during SARC. The hemiazygos vein was ligated to facilitate venous delivery of cardioplegic solution during SARC. The heart was maintained at 36°C to 37°C throughout the experiment.

Experimental Protocol

Seven pig hearts were used in this study and were perfused with a hyperkalemic (16 mmol/L KCl and 16 mmol/L $MgCl_2$) mixture of pig blood and Krebs-Henseleit solution. The hearts were first subjected to antegrade perfusion (AP) through one of the 3 coronary arteries. Two milliliters of gadolinium-diethylenetriamine penta-acetic acid (Gd-DTPA) was injected as a bolus into a coronary artery to define the artery-supported myocardium. The hearts were then subjected to SARC through one coronary artery and the coronary sinus. The coronary arteries not used to deliver cardioplegic solution during SARC were vented to zero pressure for effluent collection and

Figure 5. Representative MR images. A shows an image obtained during AP with Gd-DTPA injected into the LAD. Images acquired during SARC with Gd-DTPA injected into the LAD and the coronary sinus are shown in B and C, respectively.

Figure 6. Representative MR images. A shows an image obtained during AP with Gd-DTPA injected into the LCX. Images acquired during SARC with Gd-DTPA injected into the LCX and the coronary sinus are shown in B and C, respectively.

are referred to as the *venting arteries*. If cannulated, the anterior ascending cardiac vein was also used for venous perfusion of SARC. During SARC, 2 mL of Gd-DTPA was first injected into the arterial catheter and then into the venous catheter (including the coronary sinus). Between each injection of contrast agent, AP was carried out for approximately 5 minutes through all 3 arterial catheters to wash out the contrast agent and to resuscitate the heart. During SARC, perfusion pressures at both arterial and venous ends were maintained at 40 to 45 mm Hg. The distribution of contrast agent during AP and SARC was assessed by using T1-weighted magnetic resonance (MR) imaging. Complete washout of the contrast agent was ensured before any further injection of contrast agent by observing complete return of signal intensity to its baseline level. During SARC, the venting arterial catheters were open to the atmosphere. The experimental protocol is illustrated schematically in Figure 1.

The rate of blood flow into the arterial and venous catheters and the outflow at the venting arterial catheters were measured by using transonic flowmeters and timed collection, respectively.

MR Perfusion Imaging

The effect of SARC on myocardial perfusion was assessed by using T1-weighted MR imaging because of its high magnitude of signal enhancement and low susceptibility artifact. MR imaging was per-

formed on a 7-T, 40-cm horizontal bore magnet equipped with a Biospec console (Bruker Inc, Karlsruhe, Germany) and a Helmholtz probe surrounding the whole heart. T1-weighted MR images were acquired by using an inversion recovery Turbo-FLASH sequence with a 3.6-ms echo time and a 6.4-ms repetition time. Each image covered a $15 \times 15 \text{ cm}^2$ field of view with a 128×128 matrix, leading to a pixel size of $1.25 \times 1.25 \text{ mm}^2$. All images were acquired from a 3-mm slice parallel to the short axis of the heart.

Data Analysis

MR images were analyzed with Evident (Institute for Biodiagnostics, Winnipeg, Canada), a 2-dimensional/3-dimensional image-analysis software. Statistical analyses were performed with Statistica software (Statsoft Inc, Tulsa, Okla). Comparison of Po_2 in effluents at different venting arteries was performed by using the Student *t* test. This test was also used to compare the outflow rates from different venting arteries during SARC. All numeric results are expressed as means $\pm$ standard deviation of the mean.

Results

Figure 2 shows the efflux rates at 2 venting arteries during AP and SARC. As shown, very low efflux rates were observed at

TABLE 1. PO_2 and pH effluents at the 2 venting arteries during SARC

SARC	Route of effluent	PO_2	<i>P</i> value	pH
RCA + CS	LAD	63 ± 11	.09	7.36 ± 0.02
	LCX	48 ± 21		7.31 ± 0.08
LAD + CS	LCX	68 ± 17	.046	7.33 ± 0.03
	RCA	53 ± 6		7.36 ± 0.02
LCX + CS	LAD	105 ± 18	.003	7.32 ± 0.01
	RCA	58 ± 29		7.36 ± 0.02

Average PO_2 and pH values of oxygenated cardioplegic solution were 545 ± 35 mm Hg and 7.41, respectively.

the 2 venting arteries when the heart was perfused antegradely through a single coronary artery. Only 0.8 ± 0.2 mL/min and 0.6 ± 0.1 mL/min effluent were collected at the LAD and left circumflex artery (LCX), respectively, when AP was performed through the right coronary artery (RCA) at a flow rate of 90 ± 6.0 mL/min. With an average flow rate of 155 ± 8 mL/min during AP through the LAD, the rates of outflow at the RCA and LCX were 0.6 ± 0.2 mL/min and 0.7 ± 0.4 mL/min, respectively. When the LCX was used for AP at a flow rate of 140 ± 10 mL/min, the rates of outflow were 0.5 ± 0.2 mL/min and 0.6 ± 0.3 mL/min at the LAD and RCA, respectively. Different flow rates into the 3 arteries during AP were intended to maintain a uniform pressure load. The low rates of outflow from the venting arteries suggest that there is no significant collateral circulation between the major coronary arteries during AP. Figure 3 shows 3 representative images acquired from the same pig heart during AP, with contrast agent given into one coronary artery at a time. As the images show, each coronary artery supports its designated region of the myocardium under AP, and there is no significant overlap between each artery-supported region. This also indicates there is no significant collateral flow during AP.

During SARC, the rates of outflow from the 2 venting arteries increased significantly relative to those attainable with AP (Figure 2, lower panel). When SARC was performed through the RCA and the coronary sinus at a total flow of 170 ± 14 mL/min, the rates of outflow from the LAD and LCX were 10.5 ± 5.6 mL/min and 9.7 ± 3.6 mL/min, respectively. The difference between the outflow rates from the 2 arteries was not statistically significant ($P = .6$). When SARC was delivered through the LAD and the coronary sinus at a total flow of 195 ± 12 mL/min, the rates of outflow from the RCA and LCX were 4.7 ± 2.1 mL/min and 15.2 ± 7.0 mL/min, respectively. The difference in the outflow rates from the 2 venting arteries reaches a significant level ($P = .002$). The rates of efflux from the LAD (17.7 ± 6.4 mL/min) and RCA (7.8 ± 4.7 mL/min) were also significantly different ($P = .006$) when SARC was performed through the LCX and the coronary

sinus at a total flow of 200 ± 15 mL/min. The increased rates of outflow from the venting arteries indicate that SARC delivered through a single coronary artery and the coronary sinus helps perfuse the myocardium in the regions normally served by the venting arteries. Different total flows were used for each SARC modality to maintain perfusion pressure within the 40 to 45 mm Hg range. In addition, the efflux rate from the RCA was significantly ($P = .000$) lower than that from the LAD and LCX during SARC.

The PO_2 and the pH of the effluents collected from the 2 venting arteries during SARC are summarized in Table 1. The PO_2 in all the samples collected from the venting arteries during SARC was higher than normal (40 mm Hg) for venous blood collected at the coronary sinus under physiologic conditions. This suggests that SARC delivered through a single coronary artery and the coronary sinus provides sufficient flow to the regions served by the 2 venting arteries. The effluent rates at the venting arteries during AP were too low for reliable measurement of blood gases, and thus no data are presented.

The distributions of cardioplegic solution during AP and SARC are shown in Figures 4, 5, and 6. As mentioned above, injection of Gd-DTPA into a coronary artery during AP resulted in increases in image intensity only in the territory served by the perfusing artery (Figures 4, A, 5, A, and 6, A). Myocardium supported by the venting arteries remained dark. During SARC, injection of contrast agent into a coronary artery resulted in an increase in image intensity not only in the territory served by the perfusing artery but also in the areas normally served by the 2 venting arteries (Figures 4, B, 5, B, and 6, B). With contrast agent given into the LAD or LCX during SARC, the right ventricular free wall always brightened. The increase in signal intensity in the regions of the venting arteries was significantly less than that observed in the region supported by the perfusing artery (data not presented). The total area of brightened myocardium in the territory of the venting arteries varied from heart to heart. Nevertheless, the increase in signal intensities in the areas served by the venting arteries suggests that arterial perfusion of SARC contributes to myocardial perfusion in the areas served by the venting arteries. When contrast agent was injected into the coronary sinus during SARC, image intensity increased only in the areas normally served by the venting arteries. The region supported by the perfusing artery showed no increase in signal intensity. Moreover, the right ventricular free wall remained dark, even when the RCA was vented. The total area of contrast-enhanced myocardium in the territory of the venting arteries also varied from heart to heart. However, the sum of the brightened areas observed during SARC with contrast agent given into a coronary artery and the coronary sinus always covered the entire area of the heart viewed along its short axis. This suggests that SARC performed through a single coronary artery and coronary sinus can provide homogeneous perfusion to the heart.

Discussion

It has been demonstrated that neither antegrade nor retrograde cardioplegia provides adequate myocardial protection as a result of inhomogeneous distribution of cardioplegic solution in the presence of critical coronary stenosis. SARC through the aorta and coronary sinus has been shown to preserve normal energy metabolism and prevent ischemic injury in jeopardized areas of the myocardium. It is still unclear whether this integrated approach supports the entire heart when SARC is performed through a single coronary artery and the coronary sinus. The latter modality of SARC is used more frequently in clinical situations than that through the aorta and coronary sinus. The present study shows that (1) SARC through a single coronary artery and the coronary sinus delivers cardioplegic solution to all regions of heart; (2) the perfusing artery of SARC supports its own designated myocardium, as well as myocardium normally served by the venting arteries; and (3) the venous perfusion of SARC mainly supports myocardium in the territories served by the venting arteries, except the right ventricular free wall.

As mentioned above, the efflux rates from the 2 venting arteries during SARC ranged from 4.7 to 7.8 mL/min, 10.5 to 17.7 mL/min, and 9.7 to 15.2 mL/min in the RCA, LAD, and LCX, respectively. By using the hemoglobin concentration (5.12 ± 0.10 g/dL) and the partial pressure of oxygen (545 ± 35 mm Hg) in the delivered cardioplegic solution, it was estimated that SARC provided approximately 0.43 mL/min, 0.98 mL/min, and 0.85 mL/min oxygen to the regions served by the RCA, LAD, and LCX, respectively, when the normal supporting arteries of these regions were vented. Under normothermic arrest conditions, the oxygen consumption rate of the pig heart is around $6.7 \mu\text{L} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$.^{15,16} Tissue weights measured at the end of the experiments were 51 ± 5 g, 78 ± 6 g, and 53 ± 4 g in the regions supported by the RCA, LAD, and LCX, respectively. Using the oxygen consumption rate and tissue weight, oxygen demand was expected to be approximately 0.34 mL/min, 0.52 mL/min, and 0.35 mL/min in the RCA-supported, LAD-supported, and LCX-supported myocardium, respectively. Oxygen demand of the RCA-supported myocardium approaches the amount supplied to the region. In myocardium supported by the LAD and LCX, the supply of oxygen appears to exceed demand. This suggests that SARC can supply sufficient oxygen to the myocardium in the territories of the venting arteries. Blood flow in the region of the myocardium supported by a perfusing artery during SARC far exceeds tissue demand.

It has been suggested that myocardial capillary flow does not fully reflect effective nutrient flow or the oxygen delivery capacity of venous perfusion.¹⁷⁻²⁰ During venous perfusion, exchange or diffusion may take place in the thin-walled venous plexus, sinusoids, and thebesian system, as well as in the capillaries.^{16,21,22} Blood from the former 3 systems may drain directly into the heart chambers and not into the coro-

nary arteries.²³⁻²⁵ During SARC, myocardium normally supported by the venting arteries is believed to be perfused retrogradely because no significant arterial collateral vessels exist in the pig heart. Therefore the actual nutrient flow (flow delivering oxygen to the myocytes) in the regions of venting arteries may be much larger than the efflux rates measured at the venting arteries. In addition, the cardioplegic solution used in this study was more diluted (blood vs crystalloid in 1:1) than that (4:1) used clinically. In clinical situations, the oxygen delivery capacity of SARC in the regions served by venting arteries is expected to be greater than that attainable in this study.

Most of the venous blood from the right ventricular wall drains directly into the heart chamber through the thebesian vessels.²³⁻²⁵ This anatomic characteristic of the venous system in the right ventricular wall explains why injection of contrast agent into the coronary sinus during SARC did not increase signal intensity in the right ventricular free wall. However, when contrast agent was given into either the LAD or LCX during SARC, signal intensity increased in the right ventricle wall, as well as in myocardium supported by the perfusing artery. The increase in signal intensity was smaller in the right ventricular free wall than in the areas supported by the LAD and LCX. We believe that this observation is the result of extensive venous interconnections, which include the venovenous collaterals and thebesian pathways.

With contrast agent given into the coronary sinus during SARC, myocardium normally supported by the venting arteries was illuminated. Myocardium in the territory of the perfusing artery remained dark. At present, it is unclear why the coronary sinus route delivered cardioplegic solution only to myocardium supported by the venting arteries and not to myocardium supported by the perfusing artery under our experimental conditions. Two factors may contribute to the findings. First, during SARC, the hydraulic pressure gradient between the coronary sinus and the capillaries (or coronary arteries) is expected to be much greater in the areas supported by venting artery than in those supported by the perfusing artery because of the absence of perfusion in the former regions. Conceivably, cardioplegic solution delivered through the coronary sinus may flow more easily into the areas supported by the venting arteries than into those supported by the perfusing artery. Second, we have found that the impedance of the coronary venous system of the pig heart is approximately 5 times higher than that of the coronary artery system. If only vascular impedance is taken into consideration, the head pressure at the venous end during SARC may need to be 5 times greater than that at the arterial end to deliver cardioplegic solution to the same region of the myocardium from both routes simultaneously. This explanation is oversimplified; however, it may suggest that the perfusion pressure at the venous end should be significantly higher than that at the arterial end to deliver cardioplegic solution to the same region

of the myocardium through both routes simultaneously. In this study the head pressures at the perfusing artery and the coronary sinus were the same (40–45 mm Hg), which may explain why SARC did not deliver cardioplegic solution to myocardium supported by the perfusing arteries.

The present study was carried out on healthy young animals that had no significant arterial collateral vessels. In the hearts of human patients, extensive arterial collateral circulation usually develops after a long history of coronary disease. Thus, it is expected that SARC through a single coronary artery and the coronary sinus may provide more blood flow to the venting artery-supported myocardium in patient hearts than in normal pig hearts. In the current study the effect of SARC on tissue perfusion was assessed in a single slice of the heart. This slice was located between the apex and the atrioventricular sulcus. MR imaging results obtained from a single slice may reflect myocardial perfusion in the whole heart, but the finding should be extrapolated with caution to clinical situations. In addition, because the blood pathway in the myocardium supported by the venting arteries, particularly in the ventricular septum and right ventricular free wall, is still unclear, the nutritive efficacy of SARC in these regions of the myocardium remains to be assessed. This can readily be done by means of localized phosphorous 31 MR spectroscopy.

In summary, SARC through a single coronary artery and the coronary sinus provides homogeneous perfusion to the entire heart. During SARC, arterial perfusion supports its own designated myocardium, as well as the adjacent myocardium normally served by the venting arteries; the arterial route also supports the right ventricular free wall when the RCA is vented. Venous perfusion during SARC mainly supports myocardium in the territories of the venting arteries and not the right ventricular free wall. Blood flow delivered to myocardium supported by the venting arteries is believed to be sufficient to prevent ischemic injury.

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