THE EFFECTS OF RETROGRADE CARDIOPLEGIA TECHNIQUE ON MYOCARDIAL PERFUSION AND ENERGY METABOLISM: A MAGNETIC RESONANCE IMAGING AND LOCALIZED PHOSPHORUS 31 SPECTROSCOPY STUDY IN ISOLATED PIG HEARTS

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Objective: The present work was designed to study the myocardial perfusion and energy metabolism during retrograde cardioplegia performed with different methods, including deep coronary sinus cardioplegia, coronary sinus orifice cardioplegia, and right atrial cardioplegia.

Methods: Isolated pig hearts were subjected to antegrade cardioplegia, right atrial cardioplegia, deep coronary sinus cardioplegia, and coronary sinus orifice cardioplegia in a random order. Cardioplegic distribution was assessed by T1-weighted magnetic resonance imaging in 1 group of hearts ($n = 8$). The flow dynamics of cardioplegia were assessed by T2*-weighted imaging in a second group of hearts ($n = 8$).

Results: T1-weighted images revealed an apparent perfusion defect in the posterior wall of the left ventricle, the posterior portion of the interventricular septum, and the right ventricular free wall during deep coronary sinus cardioplegia. The perfusion defect observed in the first 2 regions with deep coronary sinus cardioplegia resolved with coronary sinus orifice cardioplegia. Right atrial cardioplegia provided the most homogeneous perfusion to all regions of the myocardium relative to the other 2 retrograde cardioplegia modalities. T2*-weighted images showed that the 3 retrograde cardioplegia modalities provided similar cardioplegic flow velocities. Localized phosphorus 31 spectroscopy showed that the levels of adenosine triphosphate and phosphocreatine were significantly lower in the posterior wall (adenosine triphosphate, $42.86\% \pm 5.91\%$ of its initial value; phosphocreatine, $11.43\% \pm 11.3\%$) than the anterior wall (adenosine triphosphate, $89.19\% \pm 8.83\%$; phosphocreatine, $59.54\% \pm 12.58\%$) of the left ventricle during 70 minutes of normothermic deep coronary sinus cardioplegia.

Conclusions: Deep coronary sinus cardioplegia results in myocardial ischemia in the posterior wall of the left ventricle and the posterior portion of the interventricular septum, as well as in the right ventricular free wall. Coronary sinus orifice cardioplegia improves cardioplegic distribution in these regions. Relative to deep coronary sinus cardioplegia and coronary sinus orifice cardioplegia, right atrial cardioplegia provides the most homogeneous perfusion. (J Thorac Cardiovasc Surg 2000;120:544-51)

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Retrograde cardioplegia has been accepted as an alternative technique for myocardial protection during cardiac surgery in a variety of cardiac surgical procedures, particularly in valve and coronary bypass surgery.¹⁻³ The rapid gain in its popularity is probably due to the finding that nutritional flow of retrograde cardioplegic solution is sufficient to sustain the reduced energy demands of the arrested heart.^{4,5} In addition, use of retrograde cardioplegia provides a less cluttered operative field than does antegrade cardioplegia. Inasmuch as the coronary venous system is not affected by atherosclerosis, retrograde cardioplegia may be better than antegrade cardioplegia in protecting the jeopardized myocardium supplied by occluded coronary arteries.⁶⁻⁸

Retrograde cardioplegia can be carried out through various means. Some surgeons deliver cardioplegic solution through a retrograde catheter placed far into the coronary sinus with a balloon fully inflated to ensure proper wedging of the catheter in the coronary lumen (we refer to this technique as *deep coronary sinus cardioplegia* [DCSC]).^{7,9-11} Others prefer to tighten up the orifice of the coronary sinus using a purse-string suture with minimum balloon inflation during retrograde cardioplegia (we named this method *coronary sinus orifice cardioplegia* [CSOC]).^{12,13} The right atrium has also been used as a site for delivering cardioplegic solution (right atrial cardioplegia [RAC]).¹⁴⁻¹⁶ The 3 modalities have all been used in cardiac surgery. Each technique has its advantages and disadvantages in terms of operation placement, myocardial cooling efficacy, and the possibility of complications. It has not been demonstrated whether there are any significant differences between these techniques in terms of myocardial perfusion.

The present study was to assess the effects of the 3 retrograde cardioplegia modalities on myocardial perfusion and energy metabolism under normothermic conditions. Perfusion magnetic resonance imaging (MRI) was used to assess distribution and flow dynamics of cardioplegic solutions. Localized phosphorus 31 (³¹P) MRI spectroscopy was used to assess regional myocardial energy metabolism during DCSC.

Methods

Isolated pig heart preparation. All animals received humane care in compliance with the "Guide for the Care and Use of Experimental Animals" formulated by the Canadian Council on Animal Care, and the protocols used in this study were approved by the Animal Care Committee of National Research Council of Canada.

Standard procedures for the isolated heart preparation have been previously described.⁵ The following is the outline of a

few key procedures used in this study. Domestic pigs weighing 45 to 50 kg were sedated with an intramuscular injection of atropine (0.05 mg/kg body weight), diazepam (0.4 mg/kg body weight), and ketamine (20 mg/kg body weight). Anesthesia was maintained with 1.5% to 2.0% isoflurane in a mixture of oxygen and medical air. A sternotomy was performed, and the great arteries and veins were dissected and clamped. Heparinized cold (~4°C) cardioplegic solution was delivered into the aortic root to arrest the hearts. After removal, the isolated hearts were mounted on a Langendorff perfusion apparatus.

Perfusion medium. The isolated pig hearts were perfused with a mixture of pig blood and modified Krebs-Henseleit solution in a 1:1 ratio, leading to an average hematocrit level of 13.1% ± 3.5%. Krebs-Henseleit solution contained the following components: NaCl, 118 mmol/L; KCl, 16 mmol/L; MgCl₂, 16 mmol/L; glucose, 11 mmol/L; NaHCO₃, 25 mmol/L; CaCl₂, 1.75 mmol/L; ethylenediaminetetraacetic acid, 0.5 mmol/L; KH₂PO₄, 1.2 mmol/L; and bovine serum albumin, 0.5%. The mixture was oxygenated with a 95% oxygen/5% carbon dioxide gas, and the pH of the mixture was maintained at 7.35 to 7.45. The final concentration of K⁺ and Mg⁺⁺ in the mixture was adjusted to 16 mmol/L to keep the heart arrested throughout the protocol. There were no differences in composition of the cardioplegic solutions between groups.

Retrograde cardioplegia. In this study retrograde cardioplegia was performed with the use of a 15F retrograde cannula (DLP Inc, Grand Rapids, Mich) with a manually inflated balloon at the tip. The perfusion pressures for retrograde and antegrade cardioplegia were controlled in the same pressure ranges (30-40 mm Hg). This pressure range of antegrade cardioplegia is sufficient to maintain normal myocardial energy homeostasis and to prevent myocardial ischemia.^{5,17} Heart temperature was maintained at 36.5°C ± 0.5°C throughout the protocol.

RAC was conducted by inserting a retrograde cannula into the right atrium through the right atrial appendage and then ligating both venae cavae and the pulmonary artery. Retrograde cardioplegia through the coronary sinus was conducted by means of 2 different modalities. One involved placing a retrograde cannula far into the coronary sinus with the balloon fully inflated. This technique was termed DCSC. With the second technique, retrograde cardioplegia was performed through a retrograde cannula positioned approximately 1 cm into the coronary sinus. The orifice of the coronary sinus was tightened by means of a purse-string suture. The balloon was not inflated to avoid blocking the ostia of the posterior interventricular vein and the posterior veins of the left ventricle (LV). This retrograde cardioplegia method was referred to as CSOC.

Group and protocols. The hearts in groups 1 (n = 8) and 2 (n = 8) were subjected to the same protocol, which consisted of 10 minutes of antegrade cardioplegia, 10 minutes of RAC, 10 minutes of DCSC, and 10 minutes of CSOC in random order. In group 1, 3 mL of an extracellular MRI contrast reagent (gadolinium-diethylenetriamine pentaacetic acid [Gd-DTPA]; Berlex, Montreal, Canada) was injected as a

bolus into the cardioplegia line during each period of the protocol. The distribution of the contrast reagent (representative of cardioplegic distribution) was determined by using T1-weighted MRI. Five milliliters of an intravascular MRI contrast reagent (Gd-DTPA-polylysine; Schering AG, Berlin, Germany) was injected into the cardioplegia line during each period of the protocol in group 2 hearts to assess cardioplegic intracapillary flow velocity by using T2*-weighted MRI. Both T1- and T2*-weighted images covered a $15 \times 15\text{-cm}^2$ field of view with a 128×128 matrix, leading to a pixel size of $1.17 \times 1.17\text{ mm}^2$. During the intervals between each period of the protocol, the hearts in both groups were subjected to approximately 2 minutes of antegrade perfusion to ensure a complete washout of the contrast reagent injected previously to preclude its potential interference with the subsequent MRI assessment. Eight T1-weighted images were usually acquired near the end of the 2-minute antegrade interval to determine whether the contrast agent had been completely washed out. Complete washout of contrast agent must be achieved before starting the next retrograde perfusion.

To determine whether DCSC results in regional myocardial ischemia, we subjected the hearts in group 3 ($n = 6$) to a protocol consisting of 10 minutes of antegrade cardioplegia, 70 minutes of DCSC, and 10 minutes of antegrade cardioplegia. The temperature of the hearts was kept at $36.5^\circ\text{C} \pm 0.5^\circ\text{C}$. An MRI surface coil was placed on the anterior and posterior walls of the LV, respectively, to monitor the changes in energy metabolites in the 2 regions of the myocardium on a continuous basis. Each ^{31}P spectrum was acquired over a 4-minute period.

MRI and spectroscopy were performed in a 7-T, 40-cm horizontal bore magnet equipped with a Biospec spectrometer (Bruker Inc, Karlsruhe, Germany).

Image processing and data analysis. Image data were processed by using EvIdent (a 2D/3D image analysis software; Institute for Biodiagnostics, NRC, Winnipeg, Canada). Because Gd-DTPA increases the signal intensity in the myocardium, bright areas in T1-weighted images indicate the regions of perfused myocardium, and dark areas reveal nonperfused myocardium. The effect of the retrograde cardioplegia modalities on flow dynamics was assessed by measuring the mean transit time of Gd-DTPA-polylysine. This parameter implies average time required for the contrast reagent to travel along blood flow from the injection site to the imaging slice.

Statistical analyses were performed by STATISTICA software (Statsoft Inc, Tulsa, Okla). All numeric results are expressed as means $\pm$ SE. The comparison of phosphorus metabolites (adenosine triphosphate, phosphocreatine, and inorganic phosphate) observed in the anterior and posterior walls of the LV during DCSC were carried out by 1-way analysis of variance with repeated measures. The same test was used to compare the mean transit times obtained with the 4 different perfusion modalities.

Results

Representative T1-weighted images obtained from group 1 during each period of the protocol are shown in

Fig 1. All regions of the myocardium brightened equally during antegrade perfusion (Fig 1, *left top panel*), indicating that antegrade cardioplegia, even at a relatively low perfusion pressure, provided homogeneous distribution of cardioplegic solution to all regions of the myocardium. This perfusion characteristic of antegrade cardioplegia was observed in all hearts (8/8). When the hearts were subjected to DCSC, no contrast agent was detected in the posterior portion of the interventricular septum, the posterior wall of the LV, or in the right ventricular free wall (Fig 1, *left bottom panel*). Although the relative sizes of the nonperfused regions varied from heart to heart, all hearts showed similar perfusion defects in these regions during DCSC. Even within the DCSC-supplied regions (the anterior and lateral walls of the LV), the distribution of Gd-DTPA was heterogeneous, suggesting that patches of myocardium could become ischemic. During CSOC, the posterior portion of the interventricular septum and the posterior wall of the LV were as bright as the anterior and lateral walls of the LV, suggesting that CSOC improved myocardial perfusion in these regions relative to DCSC (Fig 1, *right bottom panel*). The size of the unperfused region in the right ventricular wall was also reduced. Two hearts (2/8) did not show any apparent perfusion defect in the right ventricular wall. The images obtained during RAC showed uniform cardioplegic distribution in both ventricular free wall and the interventricular septum (Fig 1, *top right panel*).

Under similar perfusion pressure, the cardioplegia flow rate of RAC ($101 \pm 59\text{ mL/min}$) was significantly higher than those obtained with DCSC ($42.6 \pm 11.6\text{ mL/min}$, $P = .01$) and CSOC ($52.4 \pm 20.5\text{ mL/min}$, $P = .02$). The difference in cardioplegia flow obtained during DCSC and CSOC was not statistically significant ($P = .69$).

T2*-weighted images showed that the mean transit times of Gd-DTPA-polylysine were significantly ($P = .001$) longer with retrograde perfusion (608 ± 64 seconds) than with antegrade perfusion (54.8 ± 4.4 seconds). This approximately 10 times longer mean transit time indicates that the flow velocity of retrograde cardioplegia was about 10 times slower than that of antegrade cardioplegia. If the vascular volumes were comparable under the conditions of antegrade and retrograde cardioplegia, this difference in mean transit time could suggest that the nutritional flow of retrograde cardioplegia was approximately one tenth of that obtained with antegrade cardioplegia. In addition, among the 3 retrograde cardioplegia modalities, mean transit time was not significantly different (RAC, 585 ± 62 seconds; DCSC, 621 ± 59 seconds; CSOC, 620 ± 66

Fig 1. Representative T1-weighted images obtained during antegrade cardioplegia (AC), right atrial cardioplegia (RAC), deep coronary sinus cardioplegia (DCSC), and coronary sinus orifice cardioplegia (CSOC). LV, Left ventricle; RV, right ventricle.

seconds), suggesting that they provided similar nutrient flow per unit of tissue in the perfused areas.

Comparisons of the myocardial energy metabolites measured at the anterior and posterior walls of the LV during DCSC are shown in Figs 2, 3, and 4. During 70 minutes of DCSC, the posterior wall of the LV showed a rapid decrease in phosphocreatine level and an increase in inorganic phosphate level (Figs 2 and 3). At the end of 70 minutes of DCSC, the phosphocreatine level was significantly ($P = .02$) lower in the posterior ($11.4\% \pm 11.3\%$ of its control level) than in the anterior ($59.5\% \pm 12.5\%$ of its control level) wall of the LV (Fig 2). After the switch to antegrade cardioplegia (reperfusion), the anterior myocardium showed a complete recovery of phosphocreatine ($105\% \pm 25\%$ of its control value), whereas the recovery of phosphocre-

atine level in the posterior wall of the LV was very limited ($41.7\% \pm 16.6\%$ of its control value, Fig 2). In synchrony with the changes in phosphocreatine, the inorganic phosphate level was significantly higher in the posterior ($702\% \pm 153\%$ of its initial value) than the anterior wall ($267\% \pm 16\%$ of its initial value) of the LV at the end of 70 minutes of DCSC (Fig 3). Intracellular pH in the posterior wall of the LV (6.3 ± 0.05 pH unit) was also significantly ($P = .02$) lower than that of the anterior wall of the LV (6.7 ± 0.1 pH unit) at the end of DCSC. Furthermore, the posterior wall of the LV showed a significantly ($P = .001$) lower level of adenosine triphosphate ($42.8\% \pm 5.9\%$ of its initial value) at the end of 70 minutes of DCSC than that ($89.1\% \pm 8.8\%$) observed in the anterior wall of the LV (Fig 4). Switching to antegrade cardioplegia

Fig 2. The changes in phosphocreatine (*PCr*) levels in the anterior and posterior walls of the LV observed during 70 minutes of normothermic DCSC. Asterisks indicate a significant difference.

Fig 3. Changes in inorganic phosphate (*Pi*) levels in the anterior and posterior walls of the LV during DCSC. Asterisks indicate a significant difference.

(reperfusion) did not lead to any recovery in the adenosine triphosphate level in the posterior part of the LV wall (Fig 4).

Discussion

Uniform distribution of cardioplegic solution to all regions of the myocardium is a prerequisite for achieving optimal myocardial protection. Coronary arterial disease, aortic stenosis, or aortic insufficiency may compromise the delivery of cardioplegic solution, leading to regional myocardial ischemic injury. It has been

demonstrated that the coronary venous system is not affected by atherosclerosis and that the nutritional flow of retrograde perfusion may be sufficient to sustain myocardial energy demands of the arrested heart.^{4-6,18} This fact, along with the absence of instruments in the operative field, has made retrograde cardioplegia an alternative for myocardial protection. As mentioned above, retrograde cardioplegia can be administered in various modalities. It is therefore important to determine whether there is any significant difference among these techniques in terms of cardioplegic distribution

Fig 4. Changes in the levels of adenosine triphosphate (ATP) in the anterior and posterior walls of the LV during 70 minutes of normothermic DCSC. Asterisks indicate a significant difference.

and efficacy of myocardial protection. The present study was designed to evaluate the efficacy of the 3 retrograde delivery models by using MRI and spectroscopy.

The coronary veins may connect each other through superficial venous anastomoses and intramural venous networks.¹⁹⁻²¹ As a consequence of the presence of the numerous venous anastomoses, the delivery of cardioplegic solution through some cardiac veins may result in the irrigation of other cardiac veins through these interconnecting vessels. However, we found in this study that when the ostia of the posterior interventricular vein and the posterior veins of the LV were blocked by the retrograde balloon (during DCSC), apparent perfusion defects were noted in the regions of myocardium supported by the veins. The localized ³¹P MRI spectra obtained during DCSC also demonstrated severe ischemic changes in the posterior walls of the LV. Tightening the orifice of the coronary sinus by means of a purse-string suture may help open the coronary veins that directly drain into the lumen of the coronary sinus. We believe that this is the mechanism underlying the improved perfusion observed in the posterior portion of the interventricular septum and the posterior wall of the LV during CSOC. Our results suggest that DCSC does not provide adequate cardioplegic perfusion to the posterior wall of the LV, the posterior portion of the interventricular septum, or the right ventricular free wall. Keeping the coronary venous ostia open during retrograde cardioplegia is helpful, but not ideal,

for achieving homogeneous myocardial perfusion in these regions. Our results also suggest that the superficial venous anastomoses and the intramural venous networks may not be sufficient to irrigate the adjacent coronary veins adequately. This apparent failure of the venous anastomoses to provide adequate myocardial perfusion in adjacent regions may be related to the sporadic valves present in the coronary veins.^{20,22} On the other hand, it must also be mentioned that the development of the venous collateral flow may be significantly different between pigs and human subjects. It is expected that venous anastomoses in elderly patients may be much more developed than those in the young healthy pigs used in this study. It has been demonstrated that coronary arterial disease stimulates the development of the venous anastomoses.⁶ Therefore, it is possible that the actual distribution of retrograde cardioplegic solution with DCSC in diseased human hearts may be better than that observed in this study. Therefore, extrapolating the data of this study to clinical situations must be done with caution. In addition, it has been demonstrated that the degree of superficial venous anastomoses may vary significantly from heart to heart. Because myocardial protection during cardiac arrest is highly dependent on the homogeneity of cardioplegic distribution, efficacy of retrograde cardioplegia, in particular for the protection of the right ventricle, may vary between individual hearts.

During RAC, all cardiac veins were adequately perfused, resulting in no apparent perfusion defect, even in

the right ventricular free wall. The potential adverse effect of the sustained elevation of intraventricular pressure during RAC remains to be determined. In addition, it has been demonstrated that the thebesian vessels, a continuation of the intramuscular venous plexuses channeling directly to the ventricular chambers, drain approximately 45% of venous blood of the myocardium.^{21,23-24} Under physiologic conditions, thebesian veins play an important role in coronary venous drainage during the systolic phase of a cardiac cycle.¹⁸ During retrograde perfusion, thebesian vessels may divert a large portion of retrograde solution delivered through the coronary sinus from reaching the intramuscular venous plexus and the capillaries.¹⁸ As a consequence of the heterogeneous distribution of the open and closed thebesian vessels, retrograde cardioplegia cannot provide homogeneous perfusion.²¹ It is consistent with our observations in T1-weighted images that some areas of the myocardium in the anterior and lateral walls of the LV were not perfused during DCSC and CSOC. The elevated right ventricular pressure during RAC may help nourish the myocardium by delivering cardioplegic solution through the thebesian vessels. This may be one of the reasons underlying the improved distribution of retrograde cardioplegia with RAC relative to that observed with DCSC and CSOC.

The results of the present study do not necessarily suggest that CSOC and RAC are superior to DCSC because cardioplegic distribution is not the only factor determining the efficacy of myocardial protection. Surgical occlusion of the coronary sinus orifice during retrograde cardioplegia may be associated with some unwanted effects. Additionally, it is not clear whether prolonged right ventricular distension will damage myocardium in the interventricular septum and the right ventricular wall. Therefore, it must be with caution that we extrapolate the results of the present study to clinical situations.

In summary, DCSC does not deliver cardioplegic solution to the posterior portion of the interventricular septum, the posterior wall of the LV, or the right ventricular free wall, resulting in severe ischemic changes in these regions. CSOC improves myocardial perfusion in the posterior portion of the interventricular septum and the posterior wall of the LV. RAC delivers cardioplegic solution to all regions of the myocardium. Moreover, with retrograde cardioplegia alone, flow to various regions of the myocardium may vary significantly from one region to another, suggesting that retrograde cardioplegia should be combined with antegrade cardioplegia to achieve adequate myocardial protection.

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