THE REGIONAL CAPILLARY DISTRIBUTION OF RETROGRADE BLOOD CARDIOPLEGIA IN EXPLANTED HUMAN HEARTS

Warm retrograde blood cardioplegia is frequently used for myocardial protection, despite experimental studies questioning the adequacy of capillary flow to the right ventricle and septum. The capillary distribution of retrograde blood cardioplegia in the human heart is unknown. Hearts from eight transplant recipients with the diagnosis of idiopathic or dilated cardiomyopathy were arrested in situ with cold blood cardioplegia and excised with the coronary sinus intact. Within 20 minutes of explantation, colored microspheres mixed in 37° C blood cardioplegia were administered through the coronary sinus at a pressure of 30 to 40 mm Hg for 2 minutes. Twelve transmural myocardial samples were taken horizontally at the level of midventricle and apex to determine regional capillary flow rates. When retrograde warm blood cardioplegia was administered at a rate of 0.42 ± 0.06 ml/gm/min, the left ventricle, the septum, the posterior wall of the right ventricle, and the apex consistently received capillary flow rates in excess of their metabolic requirements. The capillary perfusion of anterior and lateral walls of the right ventricle was marginally adequate to sustain aerobic metabolism. In explanted human hearts, retrograde blood cardioplegia provides adequate capillary flow to the left ventricle, the septum, the posterior wall of the right ventricle, and the apex; however, capillary flow to the anterior and lateral walls of the right ventricle is marginal. This study delineates the tenuous balance between supply and demand for right ventricular protection with warm continuous retrograde blood cardioplegia. (*J THORAC CARDIOVASC SURG* 1995;109:935-40)

Abbas Ardehali, MD (by invitation), Richard N. Gates, MD (by invitation), Hillel Laks, MD, Davis C. Drinkwater, Jr., MD (by invitation), Ehud Rudis, MD (by invitation), Thomas J. Sorensen, BS (by invitation), Paul Chang, BS (by invitation), and Alon Aharon, MD (by invitation),
Los Angeles, Calif.

The success of any cardioplegic formulation depends in large measure on the completeness of its delivery in terms of both distribution and flow rate. The antegrade delivery of cardioplegia into the aortic root ensures adequate distribution to both ventricles by means of unobstructed coronary arteries. Limitations of antegrade delivery include non-homogeneous distribution of the solution distal to coronary artery occlusions and the requirement for coronary ostial cannulation in procedures requiring

ascending aortotomy.¹ Retrograde administration of cardioplegia through the coronary sinus is increasingly being used as an alternative delivery method. This type of administration can be performed safely and continuously in nearly all types of cardiac surgical procedures except those involving venous system anomalies.

In the presence of coronary artery occlusion, retrograde cardioplegia has been experimentally shown to be superior to antegrade cardioplegia in the delivery of capillary flow to jeopardized myocardium.^{2,3} Several studies of retrograde coronary sinus perfusion have demonstrated poor delivery of cardioplegic solution to the right ventricle and septum, however, and the adequacy of protection is therefore questionable.⁴⁻⁶

Despite these experimental findings, multiple clinical studies attest to the efficacy of retrograde cardioplegia, even in the context of right ventricular hypertrophy.⁷⁻⁹ The discrepancy between experimental and clinical studies may be related to the

From the Division of Cardiothoracic Surgery, Department of Surgery, University of California at Los Angeles Medical Center, Los Angeles, Calif.

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Address for reprints: Hillel Laks, MD, Division of Cardiothoracic Surgery, UCLA Medical Center, CHS 62-182A, 10833 Le Conte Ave., Los Angeles, CA 90024.

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Fig. 1. Horizontal cross-sections of the explanted human heart where myocardial samples (*shaded areas*) were taken for microsphere analyses.

invalidity of inferences from canine hearts to human hearts.¹⁰ To our knowledge, there has been no published report of quantitative distribution of retrograde cardioplegia in human hearts. We therefore undertook this study to determine and quantify the capillary (nutritive) distribution of warm retrograde blood cardioplegia in explanted human hearts with idiopathic or dilated cardiomyopathy.

Methods

Cardioplegic solution. Blood cardioplegia was prepared by mixing ABO-compatible blood with crystalloid cardioplegia solution in a 4:1 ratio. The crystalloid cardioplegia solution was composed of 500 ml 5% dextrose in water, 0.2 normal saline solution, 200 ml 0.3 mol/L tris (hydroxymethyl) aminomethane (Abbott Laboratories, Abbott Park, Ill.), 50 ml citrate-phosphate-dextrose solution (Abbott), and 60 mEq potassium chloride. Heparin (2000 U/dl), calcium chloride (50 mg/dl), and sodium bicarbonate (approximately 8 mEq/dl) were then added and the cardioplegia solution was oxygenated by bubbling with 100% oxygen for approximately 5 minutes. The composition and characteristics of the final cardioplegia solution were as follows: hematocrit, 20%, oxygen tension, 150 mm Hg, carbon dioxide tension, less than 60 mm Hg; pH 7.4; sodium, 170 mEq; potassium, 40 mEq, calcium, 0.5 mEq; chloride, 95 mEq, glucose, 800 mg/dl; and osmolality, 450 mOsm/L. The blood cardioplegia solution was prepared within 1 hour of administration.

Explantation of human hearts. The explanted hearts from eight recipients undergoing heart transplantation with the diagnosis of end-stage idiopathic or dilated cardiomyopathy were the subjects of this study. These hearts were obtained from transplant recipients who (1) lacked any angiographic or pathologic evidence of coronary artery disease, (2) had no previous cardiac opera-

tions, and (3) had histologic evidence, either before or during operation, of idiopathic cardiomyopathy with interstitial fibrosis. This research protocol was in accordance with the institutional guidelines for the use of pathologic specimens.

At the time of orthotopic heart transplantation, 4° C blood cardioplegia was administered into the aortic root for 2 minutes at 80 mm Hg to cause in situ arrest. The hearts then underwent an extended subatrial explantation to ensure intact removal of coronary sinus and venous drainage systems of both ventricles. The hearts were placed in iced saline solution and immediately transferred to the laboratory for further study.

Experimental protocol. The explanted hearts were weighed, and both right and left coronary ostia were cannulated with heparin and saline-filled intravenous tubing. A silk tie was tied around the coronary arteries and tubing. A purse-string suture of 1-0 Prolene (Ethicon, Inc., Somerville, N.J.) was placed around the coronary sinus and a 16F straight aortic perfusion cannula (DLP, Inc., Grand Rapids, Mich.) was introduced into the coronary sinus. The purse-string suture was tied around the coronary sinus cannula. Both coronary ostial lines and the coronary sinus cannula were flushed. The free atrial edges were occluded with vascular clamps.

The heart was then suspended by a heavy suture placed through the aorta and pulmonary artery. Warm blood cardioplegia (37° C) was delivered at a pressure of 30 to 40 mm Hg for 2 minutes. A solution containing approximately 2,500,000 colored microspheres ($15 \pm 5 \mu\text{m}$) was then injected into the coronary sinus infusion line during the first 30 seconds of cardioplegia administration. The effluents from right coronary artery, left coronary artery, and thebesian venous system (collected in ventricular cavities) were collected.

Sample collection. The hearts were transected horizontally at the level of midventricle and apex (Fig. 1). Two horizontal slices were removed at the midventricular and

Table I. Regional capillary flow rate of retrograde blood cardioplegia in various areas of explanted human hearts

	Anterior	Lateral	Posterior	Middle	LV	RV	IVS
RV	17.6 ± 4.4	18.3 ± 6.3	29.4 ± 15.1				
LV	46.6 ± 15.4	49.3 ± 18.3	76.1 ± 25.7				
Septum	31.1 ± 10.1		22.5 ± 5.4	24.3 ± 14.0			
Apex					74.4 ± 21.9	27.1 ± 5.9	47.8 ± 10.2

Data are mean ± standard error of the mean, expressed in milliliters per 100 gm per minute. LV, Left ventricle; RV, right ventricle; IVS, interventricular septum.

apical levels. A 2.5 gm myocardial sample was excised from the following areas at the midventricular level: the anterior, posterior, and lateral walls of the right ventricle; the anterior, posterior, and lateral walls of the left ventricle; and the anterior, middle, and posterior sections of the interventricular septum. Similar myocardial samples were obtained from the lateral left ventricular free wall, the middle interventricular septum, and the lateral right ventricular free wall at the level of the apex.

Microsphere analysis. All samples were processed according to the recommendations of E-Z Trac Inc. (Los Angeles, Calif.). The manufacturer's names for the various reagents are used.¹¹ Each myocardial sample was weighed and stored with 15 ml of Tissue Digest Reagent 1. The processing included placing the sample in boiling water bath for 1 hour, vortex mixing for 1 minute, diluting to 40 ml with Tissue Digest Reagent II, and centrifuging for 30 minutes. Supernatant was poured off and the sample was resuspended in 4 ml of Tissue Microsphere Counting Reagent. The sample was washed three times with 2 ml of Tissue Microsphere Counting Reagent. The sample was again centrifuged and the supernatant was removed. Aliquots of the final solution were placed in an Improved Neubauer Hemocytometer (Hausser Scientific, Horsham, Pa.). Twelve chambers were counted for each sample and the total number of microspheres in each myocardial sample was calculated according to the following formula:

$$\begin{aligned} \text{Total microspheres} &= \frac{\text{No. counted}}{\text{No. chambers} \times 0.9 \text{ mm}^3} \\ &= \frac{1000 \text{ mm}^3}{\text{ml}} \times \text{ml suspension} \end{aligned}$$

where *No. counted* is the number of colored microspheres counted by the hemocytometer, *No. chambers* is the number of chambers counted, 0.9 mm³ is the ruled volume of each chamber, and *ml suspension* is the final dilution volume. The concentration of microspheres in effluent samples were determined by employing a similar protocol.¹¹

Flow calculations. The blood cardioplegia flow to each region was calculated from the following equation:

$$q_u = \frac{q_t \times n_u}{n_t}$$

where *q_t* is the total cardioplegia flow rate delivered by the calibrated roller pump (in milliliters per minute), *n_u* is the

number of microspheres in the specimen of interest, and *n_t* is the total number of microspheres counted in the heart as a whole (2,500,000 – number of microspheres recovered in effluents).

Statistical analyses. The capillary flow rates to the anterior and lateral walls of right ventricle were compared with the left ventricular posterior wall capillary flow rate by means of repeated-measures analysis of variance and paired *t* test.

Results

Capillary (nutritive) flow was based on the number of microspheres recovered from each region of myocardium. The regional capillary distribution of warm blood cardioplegia administered through the coronary sinus is shown in Table I. The left ventricular free walls, interventricular septum, posterior wall of the right ventricle, and apex were consistently perfused. The retrograde coronary sinus nutritive flow was consistently lower in the right ventricular anterior and lateral wall (anterior wall, 17.6 ± 4.4 ml · gm⁻¹ · min⁻¹; lateral wall, 18.3 ± 6.3 ml · gm⁻¹ · min⁻¹). The capillary flow rates to the anterior and lateral walls of the right ventricle were significantly lower than the flow rate to the posterior wall of the left ventricle (*p* ≤ 0.05). The mean retrograde blood cardioplegia flow rate in explanted human hearts was 155 ± 24 ml/min; with the range of 89 to 272 ml/min (Table II). The mean flow rate per gram of myocardium was 0.42 ± 0.06 ml/min.

Duplicate myocardial specimens of varying weights were taken from three explanted hearts and analyzed for microsphere concentrations. Results were similar, attesting to the absence of the “twinkling” phenomenon, variability in microsphere concentration caused by size of the examined specimen. Additionally, when two different batches of colored microspheres were injected simultaneously, the microsphere concentrations were again similar (data not shown). This finding confirms the adequacy of mixing during delivery. To investigate the possibility of microsphere adherence to cardioplegia tubing and cannula, after two experiments we analyzed

Table II. Retrograde blood cardioplegic flow rates in explanted human hearts

Hearts	Weight (gm)	Cardioplegic flow rate	
		Total (ml/min)	Adjusted (ml · min ⁻¹ · gm ⁻¹)
1	428	125	0.29
2	407	244	0.60
3	376	105	0.28
4	415	89	0.21
5	437	158	0.36
6	312	140	0.45
7	354	272	0.77
8	296	110	0.37
Mean ± SEM		155 ± 24	0.42 ± 0.06

SEM, Standard error of the mean.

multiple tubing samples and the coronary sinus cannula for microspheres. The proportion of adherent microspheres throughout the entire tubing was estimated at less than 6% and was therefore subsequently disregarded.

Discussion

This study provides quantitative information on the capillary flow of warm retrograde blood cardioplegia in explanted human hearts. Retrograde coronary sinus perfusion in explanted human hearts with normothermic blood cardioplegia provides substantial capillary flow to the left ventricle, the septum, and the posterior wall of the right ventricle at midventricular level, as well as at the apex. The regions that remain consistently hypoperfused (compared with the posterior wall of the left ventricle) are the anterior and lateral free walls of the right ventricle.

The objective of cardioplegic preservation is to afford the heart the maximal protection against ischemic damage. This aim is realized by minimizing myocardial oxygen consumption while maximizing capillary delivery of cardioplegia to ensure aerobic homeostasis. Diastolic cardiac arrest with either normothermia or hypothermia substantially reduces myocardial oxygen consumption.¹² Cardioplegic techniques strive to meet this reduced oxygen needs of the arrested heart. To put the regional myocardial flow rates obtained in this study into perspective, one needs to know the flow requirement of the arrested human heart under normothermic conditions. It has been conservatively estimated that at 37°C, approximately 17 ml · 100 gm⁻¹ · min⁻¹ of capillary cardioplegic flow is needed to meet the metabolic requirements of the arrested human

heart.¹³ This estimate is based on the assumption of a hemoglobin level of 8 gm/dl, an oxygen saturation of 100%, a 60% oxygen extraction, and homogeneous myocardial cardioplegic delivery.¹⁴ Despite its limitations, this theoretic estimate can be used as a crude reference point. It thus appears that retrogradely administered warm blood cardioplegia provides substantial capillary flow to all examined regions of explanted human heart except the anterior and lateral walls of the right ventricle, where the capillary flow is marginally adequate to support aerobic metabolism.

An important part in the experimental protocol of this study was the placement of a purse-string suture around the coronary sinus. This maneuver appears to maximize the retrograde coronary sinus flow to the right ventricle.¹⁵ The results of this study may therefore be an overestimation of right ventricular capillary flow. Because the clinical situation does not usually include the use of a purse-string suture, suboptimal right ventricular capillary perfusion may occur with warm continuous retrograde blood cardioplegia.

This study delineates the tenuous balance of supply and demand for right ventricular protection with warm continuous retrograde blood cardioplegia. The margin for error is quite small, and with this technique the right ventricle may have transient episodes of oxygen debt and anaerobic glycolysis. The findings of this study are in concordance with those of the experimental studies that question adequacy of the right ventricular protection with retrograde blood cardioplegia.^{4,5,16} The cardiac surgeon who uses this technique as the sole method of myocardial protection should be keenly aware of right ventricular vulnerability to warm anaerobic arrest.

An important issue facing the cardiac surgeon employing warm retrograde cardioplegia is the *flow rate*. If retrograde warm cardioplegia is administered at a rate of approximately 0.5 ml · gm⁻¹ · min⁻¹ (approximately 150 ml/min for a 300 gm heart), the capillary flow to different regions of the heart is probably similar to the distribution shown in this study, with flow to the right ventricular anterior and lateral walls marginally adequate to maintain aerobic metabolism.

The strength of this study is its use of the explanted human heart model and an experimental protocol designed to mimic the clinical situation. Explanted human hearts with angiographically and pathologically proven absence of coronary artery dis-

case were arrested under controlled circumstances; this provided a unique and valuable resource for investigation of cardioplegia distribution. The hearts were arrested with cold antegrade cardioplegia and were prepared to receive the retrograde cardioplegia dose within 20 minutes of explantation. The experimental protocol was designed to recreate the clinical scenario. Conversely, a potential limitation of this study is the appropriateness of extrapolation of data derived from human hearts with idiopathic or dilated cardiomyopathy (with interstitial fibrosis and some ventricular hypertrophy) to human hearts with congenital heart diseases, coronary artery diseases, or valvular heart diseases. The significance of this inherent shortcoming of the model remains unknown.

This study provides quantitative data on the capillary distribution of warm retrograde blood cardioplegia in explanted human hearts with idiopathic or dilated cardiomyopathy. The capillary flow rate to the left ventricle, the septum, and the posterior wall of the right ventricle at midventricular level and at the apex is sufficient to sustain aerobic homeostasis. There is limited warm blood cardioplegic flow to anterior and lateral walls of the right ventricle, barely enough to support warm aerobic metabolism. This study documents the tenuous protection of the right ventricle by warm retrograde blood cardioplegia.

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Discussion

Dr. Milton A. Meier (*Rio de Janeiro, Brazil*). For many years now, Drs. Jazbik and Kubrusly and I have done experiments with retrograde coronary perfusion in sheep and dogs. I would like to share some of our findings.

In a group of six sheep, the Beck II operation was performed. A segment of autologous vein was interposed between the descending aorta and the coronary sinus, which was then ligated proximally. Both right and left coronary arteries were then ligated at the coronary ostia. The animals survived for between 5 and 16 days. All hearts were removed and contrast medium was injected into the vein that had been anastomosed to the coronary sinus. During the injections a cinecoronariographyc study of the specimen was performed. In each heart, the first veins to show opacification were those originating from the right ventricle. Only in the subsequent stage of the injection did the left ventricle also show opacification.

When the same study was performed with a catheter introduced into the coronary sinus, results varied. The

right ventricle was still the first cavity to show opacification in most animals; in some hearts, however the distribution of contrast medium was irregular. There was less contrast medium in the right ventricle than in the left. In those hearts, coronary veins draining proximally into the coronary sinus were found.

On the basis of our experimental work and also of our good clinical results with retrograde cardioplegia through the coronary sinus and by way of the right atrium, we conclude the following: First, the right ventricle is well perfused by retrograde injection. Second, the coronary sinus cannula must be placed as far proximally as possible.

Dr. Ardehali. The findings of this study suggest that the right ventricle is protected; however, this protection is marginal. In the clinical setting, marginal protection may not be compatible with the aim of the cardiac surgeon. We therefore believe that retrograde warm blood cardioplegia may not be advisable as the sole method of protection. Furthermore, we believe that the purse-string suture placed as part of this experimental procedure caused overestimation of the degree of right ventricular capillary perfusion. Caution must therefore be exercised when retrograde warm cardioplegia is used as the only method of myocardial protection.

Dr. Robert A. Guyton (Atlanta, GA.). I have a comment and a question. First, I would like to comment that for some time we have used an external stitch around the coronary sinus. When you put the coronary sinus catheter in, it is extremely easy to lift up the catheter and, from the inferior surface of the heart, put a 3-0 Prolene stitch around the coronary sinus, use a snare on the suture, and then pull the coronary sinus catheter back. I think that it is possible to position the coronary sinus catheter near the origin of the coronary sinus without the catheter slipping out by means of this external suture.

Second, we have used light microspheres and found, as you did, large variations from sample to sample. Were there statistical differences by analysis of variance between your samples?

Dr. Ardehali. Thank you, Dr. Guyton. The placement of a purse-string suture in the clinical setting is a technique that would maximize the delivery of the retrograde cardioplegia to the right ventricle, and it may actually be recommended if technically feasible. In terms of variability, as you noted there was some variability in the number of microspheres in each myocardial specimen. Analysis of variance was not performed between groups. When we compared the right ventricular lateral and anterior wall flow rates with the left ventricular posterior wall flow rate, however, a statistically significant difference was detected.

Dr. Gordon N. Olinger (Milwaukee, Wis.). I am dis-

turbed by the data from this study because for the last 2½ or 3 years now, I have been using continuous warm retrograde blood cardioplegia exclusively for coronary operations. I have had universally excellent results and have had absolutely no problems with right ventricular protection and postoperative performance.

I think that the issue here is the rate of delivery of cardioplegia. I note that in the breakdown of the total flows you deliver to these explanted hearts, only two of the hearts received rates of flow greater than 200 ml/min. In our clinical setting, we routinely have flows greater than 200 ml/min, in large hearts often as much as 300 ml/min, and we allow the coronary sinus pressure to rise to 50 or sometimes even 60 mm Hg.

I think that this is really the single best explanation for the difference in clinical performance and results from some elegant laboratory studies, this one included, suggesting that the right ventricle may not be well protected.

Dr. Ardehali. I think that you bring up an important point, one that I tried to emphasize. The data from this study should be viewed within the context of flow. The retrograde cardioplegic solution flow rate was 0.42 ml/gm/min; for a 300 gm heart, the amount would be about 150 ml per minute. If the flow rate goes beyond that, better perfusion or improvement in the capillary flow rate would be expected, which may be an explanation for clinical success with warm retrograde blood cardioplegia. In addition, I think that one reason for the "clinical success" of warm retrograde cardioplegia is that the end points that have been used may not be sensitive indicators of right ventricular protection after operation. There also may be transient episodes of anaerobic arrest in the right ventricle.

Dr. Joseph E. Flack (Springfield, Mass.). I would just like to say that we have been using continuous warm for about the last 4 years, about 2800 cases, and we have not seen any right ventricular problems. I think that the study is interesting, and there certainly is decreased right ventricular perfusion with retrograde techniques, but this does not seem to be a clinically significant finding.

Dr. Ardehali. As I stated before, I think that the clinical significance of all our findings should be viewed within the context of the flow rate. If the flow rate is increased, perfusion of the right ventricle would obviously improve. Additionally, the end points that we have used conventionally have not been sufficiently sensitive indicators of right ventricular protection. If we used more sensitive indicators, we might be able to detect some subtle changes in right ventricular function. Right ventricular protection may be optimized by combining techniques, such as the combination of antegrade and retrograde delivery.