# CORONARY SINUS OSTIAL OCCLUSION DURING RETROGRADE DELIVERY OF CARDIOPLEGIC SOLUTION SIGNIFICANTLY IMPROVES CARDIOPLEGIC DISTRIBUTION AND EFFICACY

**This study documents the gross flow characteristics and capillary distribution of cardioplegic solution delivered retrogradely with the coronary sinus open versus closed.** ***Methods:*** **Five explanted human hearts from transplant recipients were used as experimental models. Hearts served as their own controls and received two doses of warm blood cardioplegic solution, each containing colored microspheres. The first dose was delivered through a retroperfusion catheter with the coronary sinus open and the second dose was delivered with the sinus occluded. Capillary flow was measured at twelve ventricular sites and gross flow was measured by examining coronary sinus regurgitation, thebesian vein drainage, and aortic effluent (nutrient flow).** ***Results:*** **Coronary sinus ostial occlusion allowed for a significant decrease in total cardioplegic flow (1.74 ± 0.40 ml/gm versus 1.06 ± 0.32 ml/gm; $p < 0.05$) to occur while maintaining an identical intracoronary sinus pressure. Ostial occlusion also resulted in an increase in the ratio of nutrient flow/total cardioplegic flow from 32.3% ± 15.1% to 61.3% ± 7.9% ($p < 0.05$). A statistically significant improvement in capillary flow was found at the midventricular level in the posterior intraventricular septum and posterolateral right ventricular free wall. This improvement was also documented for the intraventricular septum and right ventricle at the level of the apex.** ***Conclusion:*** **Coronary sinus occlusion during retrograde cardioplegia significantly improves cardioplegic delivery to the right ventricle and posterior intraventricular septum. Furthermore, the technique affords a significant improvement in nutrient cardioplegic flow while reducing the overall volume of cardioplegic solution administered. (J THORAC CARDIOVASC SURG 1995;109:941-7)**

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Retrograde techniques for delivery of cardioplegic solution have greatly advanced the field of myocardial protection. The retrograde approach has been shown to provide superior cardioplegic delivery to myocardium distal to acute coronary occlusions when compared with the antegrade approach.[1-5] Retrograde techniques greatly simplify and expedite the conduct of many procedures, particularly those in which the aortic root is opened or the heart is positioned such that the aortic valve is rendered incompetent. Multiple reports attest to the clinical efficacy of both cold and warm cardioplegic solutions delivered retrogradely.[6-11] As a result, the use of retrograde delivery techniques has become widespread.

Despite this, relatively little information is available regarding the optimal clinical approach to retrograde delivery and distribution of cardioplegic solution, particularly in the human heart. During our group's early clinical experience using retrograde delivery of blood cardioplegic solutions, we noted the following clinical observations:

1. In procedures in which the right atrium was opened and cardioplegic solution was being delivered retrogradely by a nonocclusive catheter placed into the coronary sinus, a significant volume of cardioplegic solution was noted to regurgitate back out the coronary sinus ostium.

2. In nearly all cases in which cardioplegic solution was being delivered retrogradely by a nonocclusive catheter placed into the coronary sinus, the *posterior intraventricular* vein was less tensely filled than other veins on the left ventricular free wall.

3. In procedures in which the right atrium was opened and cardioplegic solution was being delivered retrogradely into the coronary sinus, if a purse-

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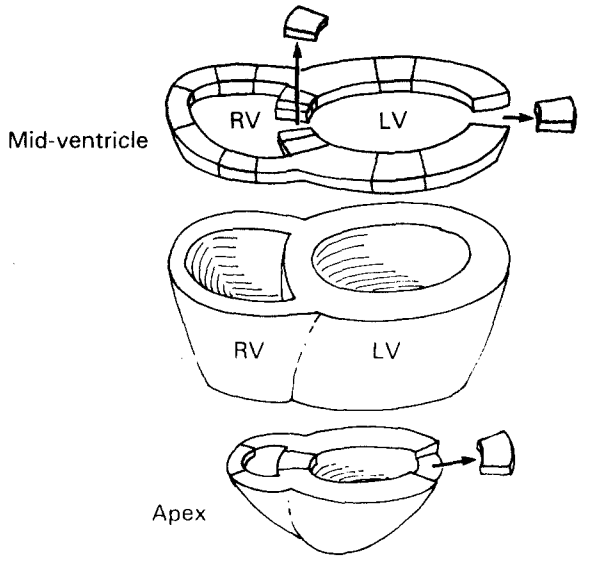


**Fig. 1.** Samples taken from the ventricles for microvascular flow analysis. *RV,* Right ventricle; *LV,* left ventricle. (From Gates RN, Laks H, Drinkwater DC, et al. Gross and Microvascular Distribution of Retrograde Cardioplegia in Explanted Human Hearts. Ann Thorac Surg 1993; 56:410-7. Published with permission.)

string suture was placed about the coronary sinus ostium several changes occurred. First, a significantly lower volume of cardioplegic solution per gram heart weight could be delivered to achieve an identical coronary sinus pressure. Second, the posterior intraventricular vein filled similarly to other left ventricular free wall veins. Third, the amount of cardioplegic solution vented out the coronary artery ostia per volume delivered was far greater.

These observations led us to the hypothesis that coronary sinus ostial occlusion during retrograde delivery of cardioplegic solution alters cardioplegic distribution. The experiments presented within this article were designed to test this hypothesis in our previously described model of the explanted human heart.[12]

## Materials and methods

Five explanted human hearts were used for this study. These hearts were obtained from heart transplant recipients with both a preoperative and postoperative histologic diagnosis of idiopathic cardiomyopathy with interstitial fibrosis. These patients had no history of cardiac or thoracic operations and had normal coronary artery anatomy with no angiographic or pathologic evidence of atherosclerotic coronary artery disease. Use of explanted hearts was in accordance with the hospital autopsy research guidelines and was approved by the Department of Pathology, University of California at Los Angeles School of Medicine.

At the time of orthotopic heart transplantation, explanted hearts were arrested in situ with 4° C blood cardioplegic solution delivered antegradely at 80 mm Hg for 2 minutes. The composition of the arresting solution was as previously described.[12] Hearts were then excised in the standard bicaval cardiectomy fashion, leaving a slightly shorter inferior vena cava–atrial cuff. This ensured that the coronary sinus and the venous drainage system of both the left and right ventricles was intact. Hearts were then placed in an iced saline solution and immediately transferred to the laboratory for investigation.

Hearts were weighed and prepared for retrograde perfusion. The left and right coronary ostia were identified and cannulated with intravenous tubing filled with heparin and saline solution. A 10 mm polytetrafluoroethylene (PTFE) tube graft* was sutured end to end to the coronary sinus ostium with 6-0 Prolene sutures (Ethicon, Inc., Somerville, N.J.). The free atrial resection line was occluded with vascular clamps. The heart was emptied of any fluid and suspended in air by a heavy suture placed through the aorta and pulmonary artery. A coronary sinus retroperfusion catheter (NPC-014 Research Medical Inc., Midvale, Utah) with a self-inflating (but nonocclusive) tip was introduced through the PTFE tube into the coronary sinus.

Warm blood cardioplegic solution (37° C) was prepared as previously described.[12] Additionally, 2,500,000 colored microspheres (15 ± 5 $\mu$m) were added to the cardioplegic solution. The microsphere-containing solution was continuously agitated and delivered as previously outlined[12] for 2 minutes at a pressure of 30 to 40 mm Hg. Pressure was monitored at the tip of the catheter by a dedicated pressure-monitoring line designed into the retroperfusion catheter. Effluents from the right and left coronary arteries, the thebesian system (collected in the dependent body of the ventricles), and regurgitating about the PTFE tube were then collected and measured. A 0-0 silk suture was tied around the PTFE tube taut on the retroperfusion catheter (to prevent regurgitation and to mimic coronary sinus ostial occlusion). A second dose of warm blood cardioplegic solution with different colored microspheres was then given in the same fashion as just described. Thus each heart acted as its own control. Approximately 20 to 30 seconds was required between injections to reprepare the model. This short period of time was not thought to be significant enough to induce a change in distribution of the second infusion related to interval ischemia.

Thin slices of the heart were taken at the midventricular and apex level. For the midventricular slice, a 2.5 gm myocardial specimen was taken from the anterior, lateral, and posterior free walls of the left and right ventricles. An anterior, middle, and posterior specimen was taken from the intraventricular septum. At the level of the apex, a specimen was taken from the lateral left ventricle, midintraventricular septum, and the lateral right ventricle (Fig. 1).

All tissue specimens were processed according to the

*Gore-Tex graft, registered trademark of W. L. Gore & Associates, Inc., Elkton, Md.

**Table I.** *Effluent data*

| | *Open* | *Closed* | *p Value* |
|---|---|---|---|
| Total CPG volume (ml/gm) | 1.74 ± 0.40 | 1.06 ± 0.32 | <0.05 |
| CS regurgitation volume/total CPG volume (%) | 46.1 ± 9.2 | 0.9 ± 0.9 | <0.05 |
| Thebesian vein volume/total CPG volume (%) | 22.1 ± 3.8 | 34.5 ± 4.6 | <0.05 |
| Nutrient flow volume/total CPG volume (%) | 32.3 ± 15.1 | 61.3 ± 7.9 | <0.05 |

*CPG,* Cardioplegia; *CS,* coronary sinus; *Nutrient,* aortic root effluent.

procedures outlined by EZ-Trac Inc. (Los Angeles, Calif.), and the manufacture's names for the various reagents will be used hereafter.[13] Each specimen was weighed and processed with 15 ml of Tissue Digesting Reagent 1. This involved placing the specimen in a boiling water bath for 1 hour, vortex mixing for 1 minute, diluting to 40 ml with Tissue Digesting Reagent 2, and centrifuging for 30 minutes. Supernatant was removed and resuspended in 4 ml of Tissue Microsphere Counting Reagent. The specimen was then washed on three occasions with 2 ml of Tissue Counting Reagent. The sample was again centrifuged and the supernatant removed. Aliquots of this final specimen were then placed in an improved Neubauer hemocytometer (Hausser Scientific, Horsham, Pa.). Twelve chambers were counted for each specimen. The total number of microspheres recovered in each specimen was calculated as follows:

$$\text{Total microspheres} = \text{number counted/number of chambers} \times (0.9\ \text{mm})^3 \times (1000\ \text{mm})^3/\text{ml} \times \text{ml suspension}$$

where number counted is the number of colored microspheres counted, number of chambers is the number of chambers counted, $(0.9\ \text{mm})^3$ is the ruled volume of the chamber, and ml suspension is the final dilution volume. The number of microspheres in effluent samples was determined by means of a similar protocol.[13]

Flow of blood cardioplegic solution to a given region was calculated from the equation:

$$Qu = Qt \times Nu/Nt$$

where Qt is the total cardioplegia flow rate delivered by the calibrated roller pump $[ml \cdot (min)^{-1}]$, Nu is the number of microspheres in the specimen of interest, and Nt is the total number of microspheres counted in the total heart (2,500,000 − number of microspheres recovered in the effluents). Gross effluents and microvascular flow rates were compared by the paired two-tailed Student's *t* test.

## Results

**Effluent data.** Table I shows data regarding flow rates. This compares the mean and standard deviations of the five hearts for the open versus closed coronary sinus. Aortic root effluent was defined as nutrient flow because this indicates that the cardioplegic solution has traversed the microvasculature and exited either the left or right coronary artery.

**Table II.** *Microvascular data (coronary sinus open versus closed)*

| | *Anterior* | *Lateral/mid* | *Posterior* |
|---|---|---|---|
| LV | 0.34 ± 0.32 | 0.20 ± 0.26 | 0.11 ± 0.13 |
| | vs. | vs. | vs. |
| | 0.25 ± 0.30* | 0.10 ± 0.07* | 0.26 ± 0.28* |
| RV | 0.20 ± 0.21 | 0.05 ± 0.03 | 0.04 ± 0.03 |
| | vs. | vs. | vs. |
| | 0.21 ± 0.19* | 0.17 ± 0.13† | 0.18 ± 0.13† |
| IVS | 0.12 ± 0.31 | 0.11 ± 0.08 | 0.02 ± 0.01 |
| | vs. | vs. | vs. |
| | 0.26 ± 0.20* | 0.24 ± 0.17* | 0.19 ± 0.10† |
| | RV | IVS | LV |
| Apex | 0.11 ± 0.07 | 0.14 ± 0.12 | 0.12 ± 0.18 |
| | vs. | vs. | vs. |
| | 0.23 ± 0.12† | 0.35 ± 0.23† | 0.30 ± 0.29* |

*LV,* Left ventricle; *RV,* right ventricle; *IVS,* intraventricular septum. All flows are expressed in milliliters per gram myocardium.
*$p > 0.05$.
†$p < 0.05$.

**Microvascular data.** In Table II, flow is expressed in milliliters per gram myocardium. Values are presented as the mean and standard deviation of the five hearts for the open versus closed coronary sinus.

## Discussion

Achieving complete distribution of cardioplegic solution to all areas of the myocardium is considered optimal when planning strategies for myocardial protection.[14] As the clinical use of the retrograde delivery technique for cardioplegic administration has increased, so too has interest in documenting the distribution of the solution. Multiple animal studies in pigs or dogs have uniformly suggested that capillary flow to the posterior intraventricular septum and posterolateral free wall of the right ventricle is minimal or nonexistent when compared with the excellent flow noted for the left ventricle.[2, 15-18]

In human beings, however, less information is present. Using an intracapillary marker and explanted human hearts, our group has previously demonstrated that the microvasculature of the right ventricle is indeed perfused by retrograde techniques.[12] Nonetheless, further studies with explanted human hearts and colored microspheres have suggested that, per gram myocardium, the left ventricle receives threefold to fourfold more capillary flow than the right ventricle.[19] Using intraoperative contrast echocardiography, Allen,[20] Aronson,[21] and their associates have confirmed human right ventricular perfusion by retrograde delivery of cardioplegic solution. In Allen's study, cardioplegic distribution was four times higher to the left ventricle than to the right ventricle.

These differences between animals and human beings with regard to the degree of right ventricular capillary perfusion can probably be explained on an anatomic basis. In human beings, the posterior intraventricular vein, which parallels the posterior descending coronary artery, most frequently empties into the coronary sinus a few centimeters beyond the coronary sinus ostium. In piglets, this vessel enters just at the coronary sinus ostium, or more frequently as a separate vein near the coronary sinus ostium. Despite this, the posterior intraventricular vein of the piglets receives some retrograde coronary sinus perfusion through the rich venovenous and venothebesian connections present throughout the myocardium. We believe the observed differences between animals and human beings with regard to retrograde cardioplegic distribution is a result of the anatomic differences in the posterior intraventricular vein and venovenous/venothebesian systems.

During our group's early experience using retrograde delivery of blood cardioplegic solution for procedures in which the right atrium was opened, we noted that a significant amount of infused cardioplegic solution simply regurgitated about the coronary sinus ostium. By placing a pursestring suture about the ostium, we eliminated this regurgitation and noted several changes. First, a significantly lower volume of cardioplegic solution per gram heart weight could be delivered to achieve an identical coronary sinus pressure. Second, the posterior intraventricular vein appeared to be more tensely distended and filled more like left ventricular free wall veins. Finally, the volume of cardioplegic solution vented out the coronary artery ostia per volume delivered was far greater.

Because of these observations, we sought to document the change in cardioplegic distribution achieved by coronary sinus ostial occlusion during retrograde delivery of cardioplegic solution. The results of this study indicate that coronary sinus ostial occlusion has several profound effects on retrograde cardioplegic flow and distribution. Indeed, with routine retrograde administration 46.1% ± 9.2% of the cardioplegic dose was found to regurgitate around the nonocclusive self-inflating distal cannula balloon and out the coronary sinus. By coronary sinus ostial occlusion, a statistically significant decrease in cardioplegic volume administered (1.74 ± 0.40 ml/gm versus 1.06 ± 0.32 ml/gm) could be achieved while maintaining identical intracoronary sinus pressure. The percentage of the total cardioplegic dose delivered that exited the coronary artery ostia also significantly increased from 32.3% ± 15.1% to 61.3% ± 7.9%. We consider flow returned through the coronary artery ostia to represent nutrient flow because this cardioplegic solution has traversed the capillaries to exit through the coronary arteries. Thus coronary sinus occlusion during retrograde cardioplegic administration significantly improves its efficacy. The clinical benefits of this are relatively straightforward and primarily include a reduced potassium and crystalloid volume load.

Coronary sinus ostial occlusion also had an effect on relative capillary flow through the myocardium. At the midventricular level, flow was decreased to the anterior and lateral left ventricle, although this was not a statistically significant difference. Flow was increased in all sections of the intraventricular septum, and this difference reached statistical significance at the midventricular–posterior intraventricular septum and at the apex-intraventricular septum. Of greatest interest was that capillary flow greatly increased to all regions of the right ventricle. This increase was highly significant in the lateral and posterior regions of the right ventricle at the midventricular level. These flow rates then approach an even to one-half level when compared with all other regions of the heart examined. We believe that these findings were the direct result of the equivalent pressure perfusion in the posterior intraventricular vein when compared with the distal coronary sinus.

Of further interest was the significant variability between hearts with regard to regional microvascular flow despite nearly identical perfusion pressures (see Table II). Such variability has also been documented by Aldea and associates.[22] In their excellent

study the coefficient of variation for retrograde cardioplegia was found to be 106% ± 16%. The data presented within our paper support their findings and also their suggestion of a complementary role for combined or sequential antegrade/retrograde cardioplegia to maximize cardioplegic distribution.

In conclusion, the data presented herein suggest that coronary sinus occlusion during retrograde administration of cardioplegic solution favorably affects cardioplegic distribution and improves overall efficacy. In procedures in which the right atrium is open, retrograde perfusion is most easily achieved by placing a pursestring suture about the coronary sinus ostium. In procedures in which transatrial coronary sinus intubation is performed, the use of catheters that occlude or partially occlude the coronary sinus would be preferred. Continuous coronary sinus ostial occlusion results in antegrade flow being vented through thebesian veins and not the coronary sinus. We and others have not found this to be injurious to the heart.[23] Although transatrial catheters that occlude the coronary sinus will eliminate needless coronary ostial regurgitation and improve cardioplegic efficacy, they probably will not result in any significant positive change in right ventricular capillary flow unless they are positioned properly with respect to the orifice of the posterior intraventricular vein.

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## Discussion

**Dr. Steven R. Gundry** *(Loma Linda, Calif.).* Throughout the manuscript the authors take pain to point out that their experiment uses a nonocclusive coronary sinus balloon catheter. This is what is commonly referred to as an autoinflating coronary sinus catheter. In the 1950s Dr. Lillehei and his colleagues working at the University of Minnesota introduced the concept of continuous retroperfusion of the heart with arterialized blood. In those days they achieved their retroperfusion by suturing into the coronary sinus their retroperfusion catheter and occluding the coronary sinus with their pursestring suture. Interestingly enough, during this period was also the start of the Medtronics Corporation and their pacemaker technology because of the number of injuries to the conduction system that were caused by suturing around the coronary sinus. As you know, this technique gradually fell into disfavor. It was not until the mid-1980s when we introduced the concept of transatrial intubation of the coronary sinus that retrograde cardioplegia regained favor. I am therefore most interested in your study and several questions arise.

First, where within the coronary sinus was your balloon catheter placed?

**Dr. Rudis.** In all cases a PTFE tube was sutured to the opening of the coronary sinus. During nonocclusive perfusion the self-inflating retroperfusion catheter was placed through the PTFE tube to lie approximately 1 to 1½ inches from the coronary sinus ostium. During occlusive perfusion the retroperfusion catheter was pulled back into the PTFE tube and the proximal portion of the PTFE tube was made occlusive about the catheter.

**Dr. Gundry.** Is there any reason that you did not initially position the balloon, even though it was a leaking balloon, at the coronary ostium?

**Dr. Rudis.** Yes, in the experiment we tried to mimic the clinical situation by placing the catheter where we generally put it during clinical retroperfusion. In most cases this will be distal to the posterior intraventricular vein in the coronary sinus.

**Dr. Gundry.** In regard to the amount of regurgitation, Dr. Felipe Menasche recently published an article in *The Annals of Thoracic Surgery* comparing an autoinflating balloon with a manually inflating balloon using exactly the same method that you have used, collecting all effluent from the coronary sinus through a PTFE tube. In that study he found a 30% regurgitant fraction using the autoinflating balloon and a 0% regurgitant fraction using the manually inflating balloon. Did you ever consider using a manually inflating balloon in your study to compare the leak rate caused by the autoinflating balloon versus the position of the balloon at the coronary sinus ostium?

**Dr. Rudis.** The results of this study, as well as Dr. Menasche's study, certainly suggest that a significant amount of cardioplegic solution is simply regurgitated back into the right atrium if there is no mechanism to make the retroperfusion catheter occlusive. Thus, if a purse-string suture is placed about the coronary sinus ostium or a manually inflating catheter is properly used, regurgitation can be eliminated and efficacy improved.

Distribution is an entirely different matter. We believe that the improvement in cardioplegic distribution seen for the right ventricle in these studies was related to the equal pressure perfusion of the posterior intraventricular vein when compared with the distal coronary sinus. Clinically, this can be achieved by placing a purse-string suture about the coronary sinus ostium and introducing any type of retroperfusion catheter into the coronary sinus. If a manually inflating catheter is used, one must be certain that this is placed in the coronary sinus proximal to the posterior intraventricular vein to achieve equal pressure perfusion of this vein. As I am sure you know, the distance between the ostium of the coronary sinus and the posterior intraventricular vein is frequently very short. This often makes positioning of the manually inflating retroperfusion catheter suboptimal for perfusion of the posterior intraventricular vein. For these reasons we did not consider using the manually inflating catheter placed at the coronary sinus ostium for these experiments.

**Dr. Gundry.** Last, you may be aware that at this year's Society of Thoracic Surgeons meeting we showed in 141 human patients that there was equal distribution of nutrient blood flow to the right ventricle and left ventricle with high-flow continuous retrograde cardioplegia. We have suggested that one can overcome the limitations of balloon placement by large volumes of retrograde cardioplegic solution, literally stuffing all the available accesses out from the heart. Have you thought about whether changing the volumes of infused solution during your study would have made any difference?

**Dr. Rudis.** Volume of flow is governed by perfusion pressure, which in these experiments was kept between 30 and 40 mm Hg. In the laboratory we have increased flow by allowing higher pressures. Unfortunately, we have not found that this significantly affects distribution, and on histologic examination we have noted edema formation and actual venous disruption with higher pressures. Thus we would advocate careful catheter positioning as opposed to increasing pressure/flow to improve distribution.

**Dr. George Cimochowski** *(Wilkes-Barre, Pa.).* We have been interested in this problem for 3 years. When we routinely used warm retrograde cardioplegia and the manually inflating balloon, as Dr. Gundry suggested, stone heart with hypertrophied ventricles developed in

three patients. We solved the problem in two ways. First, we switched to warm-cold-warm antegrade/retrograde cardioplegia, giving cold solution in the retrograde mode. Second, we designed a new large-volume catheter with Research Medical, Inc., Midvale, Utah. At the autopsy suite and the operating room we saw that even with the regular balloon manual catheter there was significant regurgitation of the cardioplegic solution in patients with valve disease and hypertrophy.

**Dr. Rudis.** It does appear as though both small and large hearts regurgitate about the coronary sinus when autoinflating retroperfusion cannulas are used. This problem is likely to be greater if the coronary sinus is grossly enlarged, as it often is in massively hypertrophied hearts. Cannulas that can deliver high volumes (300 to 450 ml/min) are required in massively hypertrophied hearts if one is to maintain a perfusion pressure of 30 to 40 mm Hg. We do believe this is important.