Protective Effects of Retrograde Compared With Antegrade Cardioplegia on Right Ventricular Systolic and Diastolic Function During Coronary Bypass Surgery

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The effect of retrograde cardioplegia delivered through the right atrium on right ventricular performance has not been critically examined in humans. We randomized 20 patients with right coronary artery lesions to receive cold blood cardioplegia solution either retrograde through the right atrium (group 1, n=10) or antegradely (group 2, n=10). The patients were similar in age, sex, severity of coronary artery disease, cross-clamp time, and completeness of revascularization. Before operation, right ventricular function was assessed by radionuclide ventriculography, and 18–24 hours after operation, right ventricular volumes and performance were assessed at a constant-paced heart rate by simultaneous hemodynamic-radionuclide measurements, before and after a fluid challenge. Intraoperative right ventricular temperatures were not different between the groups. Right ventricular volumes and ejection fractions were not different at baseline. After operation, at similar heart rates and loading conditions, there was a trend for the antegrade group to increase right ventricular end-systolic volume (p<0.1) whereas the retrograde group had no change in this parameter from the preoperative state. Postoperative ventricular function curves (p=NS, retrograde versus antegrade) suggest equivalent systolic performance in both groups. Right ventricular diastolic performance showed no significant differences between the two groups, suggesting no detriment to compliance due to right ventricular distension during operation. This suggests that retrograde cardioplegia adequately protects the right ventricular myocardium during bypass surgery and may be used as an alternative procedure in situations where ventricular cooling is inadequate with antegrade delivery due to severe coronary artery disease or aortic valvular disease. (Circulation 1989;79: 1271–1281)

During coronary artery bypass surgery, myocardial protection, especially of the right ventricle, may be inadequate in the presence of severe coronary lesions that obstruct the antegrade delivery of cold cardioplegia.1–8 Asymmetric myocardial cooling has been reported to yield postoperative right ventricular dysfunction, which may contribute to postoperative morbidity and mortality.2–3 Retrograde coronary sinus perfusion was introduced in 1956 to facilitate surgery involving the aortic valve.9–11 This technique was introduced as a means of myocardial protection for coronary artery bypass surgery in 196712 and has recently received renewed interest.13–17 An innovative method of delivering retrograde cardioplegia through the right atrium was recently developed by Fabiani and associates.13 This technique has obviated the need to directly cannulate the coronary sinus and thus has eliminated concerns regarding coronary sinus rupture due to cannulation13,14,18 and concerns of inadequate right ventricular perfusion.19 In contrast to antegrade delivery, retrograde delivery of cardioplegia through the right atrium is not subject to the problem of limited distribution in the presence of coronary artery occlusive disease and thus allows more uniform cooling of the left ventricle.20,21 However, according to one study,

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retrograde cardioplegia causes greater microvascular injury and extracellular edema than is observed after antegrade cardioplegia delivery despite more uniform cooling.22 Retrograde cardioplegia delivered through the right atrium with pulmonary artery cross-clamping may also subject the right ventricle to injury by distension, leading to systolic or diastolic dysfunction or both.23 Thus, as this technique has become more widely used, we attempted to determine 1) the effectiveness of retrograde delivery of cardioplegia through the right atrium for protection of the right ventricular myocardium and 2) the effect of intraoperative distension on right ventricular systolic and diastolic function when compared with the standard technique of antegrade delivery.

Methods

Patient Population and Study Design

Twenty consecutive patients (18 men and two women, aged 45–76 years; mean±SD, 59±7 years) undergoing coronary artery bypass surgery were studied before operation and 18–24 hours after operation. All patients had significant (>70%) stenosis of the right coronary artery in addition to severe left coronary artery disease. No patient had significant valvular disease. All patients had preserved left ventricular systolic function (left ventricular ejection fraction >0.40). All patients were assessed by radionuclide ventriculography 24–48 hours before operation. Patients were randomized to receive either retrograde (group 1, n=10) or antegrade (group 2, n=10) delivery of cardioplegia. The same surgeon performed all operations (J.T.D.). After operation, a simultaneous radionuclide-hemodynamic assessment was performed by an observer (E.J.E.) who was unaware of the randomization. Written, informed consent was obtained from all participants, and the protocol and consent form were approved by the institutional human investigation review committee of Tufts New England Medical Center.

Operative Techniques

Induction and maintenance of anesthesia were achieved with fentanyl (75 μg/kg), pancuronium (100 μg/kg), lorazepam, and enflurane. Patients were ventilated with 100% oxygen. Ascending aortic and bicaval cannulae were used to establish cardiopulmonary bypass. The cavae were snared around the venous cannulae in all patients. Moderate systemic hypothermia (30° C) and hemodilution (20–25% hematocrit level) were maintained during cardiopulmonary bypass. The aortic root was routinely vented during the cross-clamp period. Topical hypothermia and multidose cold blood cardioplegia (4:1 dilution, blood:cardioplegia) were used for myocardial protection in all patients. The cardioplegia solution was composed of 500 ml D5/0.2N saline, 34 ml citrate-phosphate-dextrose (CPD) solution, 29 ml tromethamine (0.3 M) buffer, and potassium citrate-phosphate-dextrose (CPD) solution.

FIGURE 1. Schematic representation showing technique for retrograde delivery of cardioplegia (CP) through the right atrium. Ascending aortic and bicaval cannulation with snares to restrict warm venous return are used to establish cardiopulmonary bypass. An aortic root vent is used during the cross-clamp period. A cardioplegia administration catheter and a pressure monitor catheter are inserted into the right atrium (reprinted with permission).

sium. The potassium concentration of the initial infusion to induce asystole contained 30 ml (2 meq/ml) added potassium to result in a final concentration in the blood cardioplegia mixture of 25 meq/l. Subsequent infusions of antegrade or retrograde cardioplegia contained 15 ml (2 meq/ml) added potassium, resulting in a final concentration in the blood cardioplegia mixture of 12.5 meq/l. The hematocrit level of the infused cardioplegia varied as a function of the patient’s own hematocrit level, generally between 8% and 10%. The pH of the solution at a temperature of 4° C was 7.8, and the osmolality was 390 mosm.

In group 1 patients, a 14F Argyle left ventricular sump vent catheter (Sherwood Medical, St. Louis, Missouri) was inserted into the right atrium for instillation of cardioplegia solution with an Argyle Medicut sentinel line catheter (2.3 mm o.d.) (Sherwood Medical) for pressure monitoring (Figure 1). An initial dose of high potassium cardioplegia (400–600 cc blood-crystalloid at 8–10° C) was given through the aortic root to achieve quick cardiac...
arrest.24 The remainder of the first dose and the ensuing doses of low potassium cardioplegia were administered through the right atrium with the pulmonary artery clamped and the cavae snared (Figure 1). Right atrial pressures were monitored during cardioplegia administration, and flow was adjusted to maintain a mean right atrial pressure of less than 35–40 mm Hg. The group 2 patients received cardioplegia solution exclusively through the aortic root and vein grafts in standard antegrade fashion. Doses of antegrade and retrograde cardioplegia were delivered after completion of the distal anastomoses, and the left ventricular temperature was maintained below 18° C.

In all patients, temperatures were measured in the left ventricular apex and right ventricular free wall with standard epicardial temperature probes. Enough cardioplegia solution (2–3 l/patient) was given to bring left ventricular temperatures to 18° C or below. The volume of each infusion was determined by the left ventricular temperature. The flow rate of retrograde delivery was determined by right atrial pressure, with an upper limit of 35–40 mm Hg. In both groups, as more distal anastomoses were performed, the more times cardioplegia had to be infused to maintain adequate hypothermia; thus a larger total infusion volume was produced. For longer cases, requiring more distal anastomoses, larger volumes of crystalloid-blood cardioplegia were given. Distal anastomoses were completed first. In group 2, the completed vein grafts were intermittently perfused with cardioplegia. In all patients, the vein grafts were perfused with systemic blood while the proximal anastomoses were constructed.

All patients received a bypass graft to the right coronary artery or posterior descending artery and at least one graft to the left coronary artery system (Table 1). Reperfusion with antegrade delivery of blood through the newly constructed vein grafts was performed for 20 minutes before weaning from cardiopulmonary bypass. During operation, catheters were placed in a radial artery, and a balloon-tipped catheter was positioned in the pulmonary artery for postoperative hemodynamic measurements. Epicardial pacing wires were secured onto the right atrial wall. All patients received vasopressors or inotropic medications as necessary in the first 12–20 hours after operation. However, these medications were discontinued for at least 2 hours before all postoperative studies.

**Postoperative Protocol**

All patients were studied in the cardiothoracic intensive care unit 18–24 hours after operation. All patients were studied while intubated with 5 mm Hg of positive end-expiratory pressure to ensure uniformity in intrathoracic positive pressure between groups. Radionuclide ventriculography (both before operation and after operation) was performed with previously described methods.25–30 In vivo red blood cell labeling was performed by injecting 15–25 mCi technetium-99m (99mTc) after administration of intravenous stannous pyrophosphate. Serial-gated radionuclide ventriculograms were obtained with an Anger scintillation camera (Siemens Gammasonics, Chicago, Illinois) and a 25° slant-hole straight-bore collimator positioned in a modified left anterior oblique projection with 25° caudal angulation. The camera was positioned to maximize interventricular and right atrioventricular separation. Data acquisition was gated to the patient's electrocardiogram, with each cardiac cycle divided into 24 frames. Six to 10 million counts were obtained during an 8-minute acquisition period, with a 15% window centered at the 99mTc photopeak. Images were processed on a dedicated nuclear medicine computer in a 64×64 matrix.

During the postoperative study, each patient underwent one baseline scan with simultaneous hemodynamic measurements and thermodilution cardiac output determinations. At baseline and at all subsequent data points, pressure measurements and heart rate determinations were recorded during the first 2 minutes and last 2 minutes of each scan acquisition, with each pair of measurements averaged. Thermodilution cardiac output was determined as a mean of three measurements with less than 15% variation.

After baseline measurements and scan acquisition, the patients were atrially paced at 100 beats/min for 10 minutes. Repeat hemodynamic-radionuclide measurements were made during continued atrial pacing. Normal saline, 300–700 ml, was then infused to raise right atrial and pulmonary capillary wedge pressures 2–5 mm Hg. While the patient was still being atrially paced at 100 beats/min, repeat hemodynamic-radionuclide measurements were performed. After repeat measurements, 300–700 ml additional normal saline was infused quickly to raise the mean pulmonary capillary wedge pressure and mean right atrial pressure an additional 2–5 mm Hg while a mean pulmonary capillary wedge pressure of <20 mm Hg was maintained. Repeat radionuclide and hemodynamic measurements were again performed.

**Radionuclide Analysis**

Radionuclide studies were analyzed with previously described methods.25–30 The right ventricular end-diastolic region was initially drawn on the end-diastolic frame. A summation of stroke volume and paradox images, which aided in delineating the right atrioventricular plane, was used to redraw the right ventricular region, if necessary.25–27,29 In drawing the right ventricular end-systolic region, the right atrioventricular separation was delineated based on examination of the end-systolic image and of an endless loop movie format display.25,27 Background was subtracted from end-diastolic and end-systolic regions with counts per pixel in a paraventricular background region26 at the end-systolic frame. We have validated this method for quantifying right ventricular function in patients with right ventricu-
lar pressure overload, volume overload, and depressed systolic function.25

Right ventricular ejection fractions were calculated as follows: ejection fraction=end-diastolic counts−end-systolic counts/end-diastolic counts.

Left ventricular analysis was performed with previously described methods.28,30 The left ventricular end-diastolic region was initially drawn on the end-diastolic frame, and background regions were defined by a previously described computer algorithm.28 The left ventricular region was redrawn, if necessary, on an ejection fraction image, and background regions were redefined as before. Background was subtracted from the region of interest with average counts per pixel in the paraventricular background region at the end-systolic frame, and left ventricular ejection fraction was calculated in a similar fashion to the right ventricle.

Right ventricular end-diastolic volume index (RVEDVI) was calculated with the radionuclide-derived right ventricular ejection fraction (RVEF) and thermodilution-determined stroke volume index (SVI) (cardiac index/heart rate): RVEDVI=SVI/RVEF.

Right ventricular end-systolic volume index (RVESVI) was calculated by subtracting the SVI from the RVEDVI.

Left ventricular end-diastolic volume index (LVEDVI) and left ventricular end-systolic volume index (LVESVI) were determined in a similar manner: LVEDVI=SVI/LVEF; and LVESVI=LVEDVI-SVI, where SVI is the thermodilution determined stroke volume index, and LVEF is left ventricular ejection fraction.

This calculation tends to underestimate ventricular volumes in the presence of valvular regurgitation. However, patients with preoperative clinical hemodynamic or angiographic evidence of valvular disease were excluded, and no patient had postoperative clinical or hemodynamic evidence of mitral or tricuspid regurgitation.

Preoperative left and right ventricular volumes were calculated as follows: Preoperative volume= postoperative volume×(Cpreoperative/Cpostoperative), where C is background corrected ventricular end-diastolic or end-systolic radionuclide counts.

Intraobserver variability of our radionuclide measurements has been tested by analysis of duplicate scans in a series of 10 patients. Coefficients of variation for left and right ventricular ejection fractions were 3.9% and 3.3%, respectively (percentage of measured ejection fraction). The correlation coefficient between duplicate measurements was 0.99.

Right ventricular stroke work index (RVSWI) was calculated as follows: RVSWI=(MPSP−MRAP)×SVI×0.0136, where MPSP is mean pulmonary artery systolic pressure, MRAP is mean right atrial pressure, and SVI is stroke volume index.

Systolic function was assessed by examining the relation of right ventricular stroke work index and stroke volume index versus right ventricular end-diastolic volume index.

Diastolic function was assessed by examining the relation of mean right atrial pressure to right ventricular end-diastolic volume index and the natural logarithm of mean right atrial pressure to right ventricular end-diastolic volume index.

Statistics

All measurements are expressed as mean±SD unless otherwise indicated. Changes from the preoperative state to the postoperative state (radionuclide measurements) were analyzed by a two-factor repeated measures analysis of variance. If a differential effect for groups across time was found (p<0.1), pairwise comparisons before operation to after operation were made with a Bonferroni’s adjustment.

Baseline hemodynamic indexes after operation were compared by a Student’s unpaired t test. Comparisons between groups (retrograde versus antegrade) at preoperative baseline were made by the Student’s unpaired t test. Statistical significance was set at a level of p<0.05.

The relation of the natural logarithm of mean right atrial pressure to right ventricular end-diastolic volume index31 has previously been shown to be linear. For this reason, differences between groups were examined in the following way. A regression analysis for each patient was determined, and the mean slopes and intercepts for the two groups were compared by the Student’s unpaired t test.

Analysis of ventricular function relations (right ventricular stroke work index and right ventricular stroke work index versus right ventricular end-diastolic volume index) and diastolic function relations (mean right atrial pressure versus right ventricular end-diastolic volume index) were compared by repeated-measures analysis of covariance with the right ventricular end-diastolic volume index as the covariate for both analyses. We used this statistical test (repeated measures analysis of covariance) to study the effect of a change in right ventricular end-diastolic volume index (the independent variable) on right ventricular stroke volume, right ventricular stroke work index, and mean right atrial pressure (dependent variables) in two groups over time.

We postulated that retrograde cardioplegia was at least as good as antegrade cardioplegia in preserving right ventricular function. Power analysis indicated that randomizing 20 patients yielded an 80% power of documenting that antegrade cardioplegia was superior to retrograde if the difference in right ventricular ejection fraction between the two treatment groups was greater than or equal to 0.07. Because the trends in our data were in the direction that actually favored retrograde cardioplegia, we conservatively chose to apply a two-tailed t test to
Table 1. Patient Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (retrograde)</th>
<th>Group 2 (antegrade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>59±8</td>
<td>59±6</td>
</tr>
<tr>
<td>Age range (yr)</td>
<td>49–76</td>
<td>45–66</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>9/1</td>
<td>9/1</td>
</tr>
<tr>
<td>Patient grafts (4 grafts/3 grafts/2 grafts)</td>
<td>1/7/2</td>
<td>0/7/3</td>
</tr>
<tr>
<td>Left main coronary artery lesions (&gt;50%)</td>
<td>1/10</td>
<td>0/10</td>
</tr>
<tr>
<td>Internal mammary artery grafts</td>
<td>7/10</td>
<td>8/10</td>
</tr>
<tr>
<td>Thromboendarterectomy of right coronary artery</td>
<td>1/10</td>
<td>1/10</td>
</tr>
<tr>
<td>Cross-clamp time (min)</td>
<td>48±7</td>
<td>49±13</td>
</tr>
<tr>
<td>Duration of cardiopulmonary bypass (min)</td>
<td>113±13</td>
<td>125±24</td>
</tr>
<tr>
<td>Total volume of crystalloid cardioplegia infused (ml)</td>
<td>660±125*</td>
<td>450±67†</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82±11</td>
<td>84±10</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.9±0.1</td>
<td>1.9±0.1</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD.

*Volume includes 108±61 ml given as initial aortic dose.

†p<0.005 vs. retrograde.

Examine the significance of differences between the two treatment groups.

Results

Preoperative and intraoperative patient data are summarized in Table 1. Patients in both groups were not significantly different in age, sex, completeness of revascularization, cross-clamp time, and duration of cardiopulmonary bypass. There were, however, significant differences between the retrograde and antegrade groups in mean volume of crystalloid cardioplegia infused (Table 1). These differences did not result in any perioperative difficulties, such as hyperkalemia.

Intraoperative myocardial temperatures are depicted in Figure 2. There were no significant differences in intraoperative right ventricular or minimal left ventricular temperatures. Maximal and, therefore, mean left ventricular temperatures were slightly higher in the retrograde group. Intra-aortic counterpulsation support was required only for one patient (from the retrograde group) after operation, and the patient was weaned from this support in less than 24 hours. After operation, there were no deaths, and the hospital stays were similar in both groups. One patient from the retrograde group sustained a perioperative myocardial infarction by electrocardiography (new Q waves) but was not catheterized after operation to determine whether this was a function of early graft closure or inadequate myocardial protection.

Preoperative Radionuclide Assessment

The antegrade and retrograde groups were not significantly different in preoperative left and right ventricular ejection fractions and volumes (Table 2).

Figure 2. Bar graphs showing right and left ventricular myocardial temperatures (mean±SEE). There was no significant difference in right ventricular temperatures measured only in one area of the right ventricular free wall. The retrograde group had a slightly warmer left ventricular mean temperature, primarily due to higher maximal temperatures. There was no significant difference in minimal left ventricular temperatures. NS, not significant.
### Table 2. Preoperative and Postoperative Hemodynamic-Radionuclide Findings

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (retrograde)</th>
<th>Group 2 (antegrade)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>—</td>
<td>81±12</td>
</tr>
<tr>
<td>RA pressure (mm Hg)</td>
<td>—</td>
<td>9±4</td>
</tr>
<tr>
<td>PA systolic pressure (mm Hg)</td>
<td>—</td>
<td>24±6</td>
</tr>
<tr>
<td>PA end-systolic pressure (mm Hg)</td>
<td>—</td>
<td>16±4</td>
</tr>
<tr>
<td>Mean pulmonary capillary wedge</td>
<td>—</td>
<td>10±3</td>
</tr>
<tr>
<td>pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial systolic pressure (mm Hg)</td>
<td>—</td>
<td>114±15</td>
</tr>
<tr>
<td>Arterial end-systolic pressure</td>
<td>—</td>
<td>62±11</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>—</td>
<td>3.2±0.7</td>
</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>—</td>
<td>39±4</td>
</tr>
<tr>
<td>RVEF</td>
<td>0.56±0.08</td>
<td>0.60±0.09</td>
</tr>
<tr>
<td>RVEDVI (ml/m²)</td>
<td>71±32</td>
<td>66±11</td>
</tr>
<tr>
<td>RVESVI (ml/m²)</td>
<td>31±14</td>
<td>27±10</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.50±0.07</td>
<td>0.58±0.10†</td>
</tr>
<tr>
<td>LVEDVI (ml/m²)</td>
<td>86±35</td>
<td>68±13‡</td>
</tr>
<tr>
<td>LVESVI (ml/m²)</td>
<td>44±22</td>
<td>30±11†</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD.
Pre, preoperative; Post, postoperative; RA, right atrial; PA, pulmonary artery; RV, right ventricular; EF, ejection fraction; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; LV, left ventricular.

*p=NS vs. retrograde group; †p<0.01 vs. preoperative (baseline); §p<0.1 vs. preoperative (baseline).

Postoperative Baseline Assessment

After operation, there was no difference in baseline heart rate between the groups (mean±SD, 81±12 vs. 83±12 beats/min; p=NS). Changes in right ventricular volumes and ejection fraction can be seen in Table 2 and Figure 3. Right ventricular ejection fraction did not change in either group. Right ventricular end-systolic volume tended to increase in the antegrade group (from 25±8 to 30±8 ml/m², p<0.1) and did not change in the retrograde group (from 31±14 to 27±10 ml/m², p=NS). This occurred at a similar afterload (pulmonary artery end-systolic pressure) in both groups after operation (retrograde versus antegrade; 16±4 versus 19±4 mm Hg, p=NS). However, these differences between groups were not significant. The right ventricular end-diastolic volume increased in the antegrade group (from 57±15 to 67±14 ml/m², p<0.01) but did not change appreciably in the retrograde group (from 71±32 to 66±11 ml/m², p=NS).

To compare postoperative right ventricular systolic and diastolic function in the two patient groups, we performed volume loading and examined the following relations at a constant (atrial)-paced heart rate of 100 beats/min: 1) right ventricular stroke volume index versus right ventricular end-diastolic volume index, 2) right ventricular stroke work index versus right ventricular end-diastolic volume index, 3) mean right atrial pressure versus right ventricular end-diastolic volume index, and 4) the natural logarithm of mean right atrial pressure versus right ventricular end-diastolic volume.

Postoperative Right Ventricular Systolic Function

Examination of the ventricular function curves revealed the retrograde curves to lie leftward and upward from the antegrade curves although this shift was not significant (p=0.35 for right ventricular stroke volume index versus right ventricular end-diastolic volume index; p=0.47 for right ventricular stroke work index versus right ventricular end-diastolic volume index).

Postoperative Right Ventricular Diastolic Function

Postoperative diastolic function was assessed by examining the relation between mean right atrial pressure and the natural logarithm of mean right atrial pressure versus right ventricular end-diastolic volume index (Figure 4). As can be seen in Figure 4A, there was no significant difference (p=NS) in right ventricular chamber stiffness between the groups. Comparison of slopes of the line defined by the relation of the natural logarithm of mean right atrial pressure versus right ventricular end-diastolic volume index (Figure 4B) revealed no significant differences. Previous investigators have shown that the slope of this relation is directly proportional to chamber stiffness.31

Postoperative Left Ventricular Function

Postoperative assessment of left ventricular function was likewise studied and has been previously reported in detail.21 The mean left ventricular ejection fraction for the retrograde group increased from 0.50±0.07 to 0.58±0.10 (p<0.01), whereas it did not change for the antegrade group (from
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FIGURE 3. Bar graphs showing right ventricular volumes and ejection fractions for retrograde and antegrade groups, both before operation and after operation (mean±SEE). As is evident, there was no difference between groups in right ventricular volumes or ejection fraction preoperatively. After operation, the right ventricular end-diastolic volume index (RVEDVI) and right ventricular end-systolic volume index (RVESVI) increased only in the antegrade group despite similar loading conditions. There was no change in ejection fractions for both groups. NS, not significant.

0.50±0.06 to 0.53±0.06, p=NS) (Figure 5). This improvement in ejection fraction was due primarily to a reduction in left ventricular end-systolic volume index in the retrograde group (from 44±22 to 30±11 ml/m², p<0.01). Although there was a trend toward smaller left ventricular end-systolic volumes in the antegrade group (from 40±10 to 34±11 ml/m²), this change was not significant (p=0.09). The disproportionate decrement in left ventricular end-systolic volume in the retrograde group occurred at a similar preload (left ventricular end-diastolic volume index) and afterload (systemic end-systolic pressure) as in the antegrade group. Left ventricular end-diastolic volume index tended to decrease in both groups before operation, but this was also not significant (p<0.1).

Discussion

We have previously shown that retrograde delivery of cardioplegia will effectively preserve left ventricular myocardium during coronary artery bypass surgery and may even be superior to antegrade delivery in cases of severe proximal coronary artery stenosis or aortic insufficiency. However, theoretical considerations of right ventricular distension or microscopic myocardial damage due to direct infusion of the cardioplegia solution into the right atrium and ventricle have prompted this investigation of postoperative right ventricular systolic and diastolic function.

Preoperative assessment of right and left ventricular function by radionuclide scan revealed equivalent volumes and ejection fractions. Although loading conditions were not assessed before operation, mean right and left ventricular volumes were larger in the retrograde group than in the antegrade group
The increase in right ventricular end-diastolic volume index in the antegrade group may represent either a Frank-Starling increase in preload to compensate for some degree of systolic dysfunction (i.e., an increase in end-systolic volume) due to inadequate protection or a preferential reduction in diastolic chamber stiffness in the antegrade group due to resolved preoperative ischemia or both. The retrograde group had no significant change in postoperative right ventricular end-diastolic volume and had an equivalent postoperative right ventricular end-diastolic volume to the antegrade group at a similar right atrial pressure. This suggests no difference in postoperative right ventricular chamber stiffness despite the use of the retrograde technique.

**Postoperative Right Ventricular Systolic Function Assessment**

Examination of the ventricular function curves for the two groups revealed a leftward and upward shift of the retrograde curve when compared with the antegrade curve although this shift was not significant. Thus, retrograde delivery of cardioplegia resulted in postoperative right ventricular systolic function, which was just as good if not better than standard antegrade delivery.

**Postoperative Right Ventricular Diastolic Function Assessment**

Evaluation of the relation between right atrial pressure and right ventricular end-diastolic volume index can be seen in Figure 4A. There were no significant differences after the operation between the antegrade and retrograde groups despite mild right ventricular distension during the operation in the latter group. This suggests no postoperative difference in chamber stiffness between groups 1 and 2. The relation of the natural logarithm of right ventricular end-diastolic pressure to right ventricular end-diastolic volume index is linear, with the slope (k) representing myocardial chamber stiffness. We analyzed a similar relation, assuming right ventricular end-diastolic pressure to be reflected by mean right atrial pressure (Figure 4B). Linear regression analysis of the slope of this line for patients in both groups revealed no significant differences between the mean slopes (p=NS). Thus, despite mild right ventricular distension due to cardioplegia infusion, retrograde delivery of cardioplegia through the right atrium does not result in right ventricular diastolic impairment when a mean infusing pressure of less than 40 mm Hg is used with care to not overdistend.

**Efficacy of Retrograde Delivery of Cardioplegia**

Inadequate perfusion of regional myocardium beyond obstructed coronary arteries with inadequate cooling of the right ventricle is a known consequence of antegrade delivery and may result in postoperative right ventricular dysfunction or death or both. Clinical studies with temperature
mapping by thermographic analysis have shown more uniform ventricular cooling with retrograde coronary sinus delivery when compared with the standard antegrade technique. As can be seen in Figure 2, the right ventricle was not significantly cooler in the retrograde group than in the antegrade group. Because temperatures were measured in only one area in both ventricles, it is not known in these patients whether the retrograde technique produced more uniform cooling of the right ventricle. However, superior uniformity of cooling is the best explanation for the well-preserved postoperative left ventricular systolic function in the retrograde group. Measurement of temperatures in other areas of the right and left ventricles theoretically may have revealed significantly warmer temperatures in the antegrade group, especially in the left ventricle. No patient in either group was difficult to cool although the theoretical advantage of retroperfusion may be accentuated in situations where antegrade delivery is inhibited, such as severe left main coronary artery disease or repeat coronary artery bypass operation.

**Direct Versus Indirect Retrograde Infusion**

Despite the theoretical benefits of performing retrograde infusion of cold cardioplegia, the technique of direct coronary sinus cannulation can be cumbersome, requiring an atriotomy and special coronary sinus catheters. This new indirect technique, described by Fabiani and associates, and used in the patients participating in this study, has some significant benefits over direct coronary sinus cannulation. First, this technique requires no atriotomy, thus reducing operative time and possibly reducing postoperative arrhythmias. Second, direct cannulation of the coronary sinus may result in damage to the ativoventricular node or coronary sinus itself. The technique presented herein obviates the need for direct sinus cannulation and, thus, removes the danger of injuring these structures. Third, there is concern that right ventricular free wall and part of the interventricular septum may be inadequately protected by direct cannulation of the coronary sinus due to the anatomic patterns of venous drainage of these structures and obstruction of proximal coronary veins by the coronary sinus balloon catheter. Direct infusion of the cold cardioplegia solution into the right atrium and ventricle ensures adequate cooling of the right ventricle directly while providing adequate cooling of the left ventricle.

Previous investigators have suggested that this method does not provide as much myocardial protection as continuous retrograde coronary sinus cardioplegia. Several important differences exist between these findings and ours. First, our study was performed in humans and not in dogs. Second, we gave one dose of high potassium antegrade cardioplegia to induce quick cardiac arrest and avoid ischemia whereas in the canine study, ventricular fibrillation and incomplete cardiac arrest were present in the atrial cardioplegia group throughout the period of cross-clamping. Third, the canine study examined ventricular function very early after operation, whereas we waited 18–24 hours after operation to assess performance. It has been well documented that there is myocardial depression and an increase in the ratio of myocardial oxygen extraction to cardiac work after operation, an effect which is probably due to either stunned, ischemic cardiac tissue, ultrastructural damage, accumulation of inhibitors, or a loss of adenine nucleotides. However, this effect has been documented to be mostly resolved 24 hours after operation. Thus, we studied patients only after a sufficient amount of time had passed to allow resolution of the acute ischemic changes associated with bypass surgery. Fourth, the authors of the canine study claimed they had difficulty reducing right ventricular myocardial temperatures below 16°C. We were easily able to cool the right ventricle to 15°C with this technique; we did not cool it below this temperature since our protocol for myocardial protection does not require temperatures below this. The authors of the canine study report poor recovery of right ventricular function, which they felt was due to right ventricular distension. As is shown by our data, mild distension of the right ventricle by the use of this technique does not result in severe systolic or diastolic dysfunction although we used great care to maintain low maximal right ventricular perfusion pressures and did not allow a large amount of distension. As in the canine study, the use of this technique resulted in adequate left ventricular protection as shown by a reduction in postoperative left ventricular end-systolic volume index only in the retrograde group (at similar postoperative afterloads) and an increase in left ventricular ejection fraction only in the retrograde group.

**Limitations to the Study**

The major limitation to this study was the difficulty in evaluating right ventricular volumes. The radionuclide method used to evaluate ejection fraction has previously been validated in our laboratory and has been shown to be reproducible. However, the errors in making three independent measurements (right ventricular ejection fraction, thermodilution cardiac output, and heart rate) can result in some error of measurement. Although we eliminated any patients with evidence of regurgitant lesions, some occult tricuspid insufficiency may have been present.

The design of our study did not allow for a preoperative hemodynamic-radionuclide study. A radionuclide evaluation alone was done for patient comfort. Thus, we cannot discount the possibility that discrepant loading conditions could have been present in the baseline state. However, with similar ejection fractions and volumes in the two groups in a blind and randomized trial, it is most unlikely that
severe discrepancies existed. In addition, there was more scatter in the baseline volume data than anticipated before our commitment to randomize 20 patients. Thus, larger studies are warranted to confirm our findings.

The assessment of diastolic chamber stiffness in the clinical setting often has significant limitations. Ideally, measurement of multiple pressure-volume points would permit normalization of chamber volumes and calculation of $V(dP/dV)$ at common pressures. However, the application of such a calculation permits the comparison of ventricles with discrepant volumes. In this study, normalization for different chamber volumes is not necessary because both groups had diastolic chamber volumes that were not significantly different.

In addition, we cannot rule out the possibility that a slight upward parallel shift in the relation of the natural logarithm of mean right atrial pressure to right ventricular end-diastolic volume suggests a mild increase in chamber stiffness in the retrograde group, even in the presence of equivalent slopes (k). However, as the slope (k) and intercepts of the two groups were not significantly different, it is doubtful that such a shift is meaningful.

It is also possible that the presence of a pericardiotomy in all patients obscured an effect of right ventricular distension on diastolic chamber stiffness in the retrograde group. However, such an effect would not be considered clinically relevant because all bypass patients undergo pericardiotomy and should be studied in the state that is most clinically applicable.

In addition, this study does not allow a complete resolution to the question of whether right ventricular distension per se is deleterious to postoperative right ventricular function. For this comparison, a study design comparing coronary sinus with right atrial cardioplegia administration would have been more appropriate. However, our intent was not to compare methods of retrograde delivery but rather to compare the current standard technique of antegrade cardioplegia delivery with one of the two retrograde techniques currently in use. We chose this method of retrograde delivery for its advantages of direct right ventricular cooling and reduced incidence of coronary sinus damage and of heart block. In addition, a recent animal study at our institution has compared right ventricular systolic performance after right atrial retrograde, coronary sinus, and aortic root cardioplegia delivery. This animal study has shown that right ventricular distension is not detrimental to systolic performance and better preserves the right ventricle when compared with the other methods of cardioplegia delivery.

Summary

We randomized 20 consecutive patients to receive either retrograde delivery of cardioplegia through the right atrium or standard antegrade delivery. Postoperative assessment of both groups revealed an increase in right ventricular end-diastolic and to a lesser degree end-systolic volume only in the antegrade group at similar postoperative loading conditions to the retrograde group. Analysis of ventricular function curves after operation suggested as good, if not slightly better, systolic performance as in the retrograde group. Analysis of diastolic performance revealed no significant difference between the groups. Left ventricular protection was excellent with the retrograde technique. These facts suggest that myocardial protection, especially in the right ventricle, was at least as good or better than that in the antegrade group and right ventricular distension and microscopic injury, which has previously been reported, is not clinically a significant concern when this technique is used. This technique may be advantageous 1) when antegrade delivery results in insufficient ventricular cooling because of a tight left main coronary artery lesion or severe three vessel coronary artery disease and especially when repeat bypass operations are performed, 2) as an alternative to direct coronary artery ostial cannulation for aortic valve procedures or in patients with aortic insufficiency, and 3) for mitral valve operations where repeated doses of antegrade cardioplegia could result in coronary air embolism and necessitate the removal of air from the aortic root.

Larger trials, studying patients with severe three vessel or left main coronary artery disease or with valvular heart disease, need to be conducted.

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