LEFT VENTRICULAR DIASTOLIC FUNCTION AFTER CORONARY ARTERY BYPASS GRAFTING: A CORRELATIVE STUDY WITH THREE DIFFERENT MYOCARDIAL PROTECTION TECHNIQUES

Pierre A. Casthely, MD^{a, b}
Chirag Shah^{a, b}
Haroutune Mekhjian, MD^c
Daniel Swistel, MD^c
Thil Yoganathan, MD^{a, b}
Claudia Komer, MD^{a, b}
Ricardo A. Miguelino, MD^{a, b}
Ramon Rosales, MD^{a, b}

Background: This study was designed to examine the effect of myocardial protection on diastolic function after cardiac operations. **Methods:** Subjects were patients with normal preoperative diastolic function who were scheduled for coronary artery bypass grafting. Group I received antegrade cardioplegia; group II received antegrade and retrograde cardioplegia; and group III was protected with ventricular fibrillation and intermittent aortic crossclamping. Operations were performed with mild hypothermia and ventricular venting through the left superior pulmonary vein in all cases. Left ventricular diastolic function was evaluated with pulsed-wave Doppler transesophageal echocardiography (samples at the mitral valve leaflet; four-chamber view) and left superior pulmonary vein flow velocity. The flow patterns were stored on videotape and sent to an independent investigator for analysis. Left ventricular ejection fraction was calculated with transesophageal echocardiography (short-axis view, two-dimensional and M-mode). **Results:** Left ventricular diastolic function, as measured by the ratio between the peak velocities during early filling and atrial contraction and by systolic diastolic superior pulmonary venous flow ratio, was significantly impaired in all three groups 5 minutes after discontinuation of cardiopulmonary bypass. At 1 hour after operation, these values had returned to control levels only in group III. There was an increased incidence of supraventricular arrhythmias in group III. There were no significant hemodynamic differences among the three groups. **Conclusions:** Left ventricular diastolic function was severely impaired after cardiopulmonary bypass. The degree of impairment depended on the myocardial protection used. The impairment in diastolic function was less when ventricular fibrillation and intermittent aortic crossclamping were used, and greater when antegrade and retrograde cardioplegia were used. (*J Thorac Cardiovasc Surg* 1997;114:254-60)

Inadequate myocardial protection resulting in perioperative cardiac damage and dysfunction has always been the major cause of morbidity and

mortality after cardiac operations.¹ Advances in cardioprotective techniques, including oxygenated crystalloid and blood cardioplegia and antegrade and retrograde delivery of cardioplegic solution, have evolved through an improved understanding of the pathophysiology of the intraoperative ischemic and reperfusion injury.² These techniques have reduced the incidence of low-output syndrome, the leading cause of postoperative death.

Transesophageal echocardiography (TEE) provides a variety of information during cardiac operations.³⁻⁵ The use of pulsed-wave Doppler echocardiography for the assessment of diastolic dysfunction in the diagnosis of various cardiac disease has been gaining popularity. Diastolic dysfunction may precede systolic dysfunction during myocardial ischemia.⁶ Transmitral flow determined by TEE has been reported to correlated well with left

From Seton Hall University^a and the Divisions of Cardiac Anesthesia^b and Cardiac Surgery,^c St. Joseph's Hospital and Medical Center, Paterson, N.J.

Work performed in the Department of Anesthesiology, Division of Cardiac Anesthesia and Division of Cardiac Surgery, St. Joseph's Hospital and Medical Center, Paterson, N.J.

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Address for reprints: Pierre A. Casthely, MD, Professor of Anesthesiology, Division of Cardiac Anesthesia, Seton Hall University, Postgraduate Medical School, St. Joseph's Hospital and Medical Center, 703 Main St., Paterson, NJ 07503.

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ventricular diastolic function.⁷ This study was designed to examine the effect of myocardial protection on diastolic function after cardiac operations.

Methods

This observational study was approved by the Human Research Committee of St. Joseph's Hospital and Medical Center. Sixty patients scheduled for elective coronary artery bypass grafting (CABG), ranging in age from 36 to 60 years, were studied. They were all in American Society of Anesthesiologists class III and had good ventricular function with an ejection fraction greater than 0.4 before operation. Patients with a history of hypertension, myocardial infarction, mitral valve and aortic valve disease, or esophageal pathology were excluded from this study. The patients were medicated before operation with morphine sulfate (1 mg/kg) and scopolamine (0.4 mg). Preoperative monitoring included an arterial line, electrocardiography, pulse oximetry, and a pulmonary artery catheter.

The patients were divided into three equal groups by the cardiac surgeon according to the myocardial protection and the operating room (OR) used. Group I received antegrade cardioplegia (OR 10); group II received antegrade and retrograde cardioplegia (OR 12); and group III patients were protected with ventricular fibrillation and intermittent aortic crossclamping (OR 9). All operations were performed with mild hypothermia (blood temperature 28° C) and ventricular venting through the left superior pulmonary vein. Iced saline solution was also applied to the heart when blood temperature was 30° C to produce topical hypothermia. Myocardial temperature was measured as soon as the aortic crossclamp was applied (blood temperature 30° C) with a Mon-A-Therm myocardial needle (Mallinckrodt Medical, St. Louis, Mo.). The myocardial temperature was maintained around 5° to 7° C while the distal anastomosis was being performed. This ventricular vent was withdrawn into the left atrium to monitor left atrial pressure when CPB was discontinued. Antegrade or retrograde blood cardioplegia was prepared by mixing 1080 ml blood with 25 mEq sodium bicarbonate and 30 mEq potassium chloride and delivered at 4° to 8° C. Antegrade cardioplegia was administered at a rate of 300 ml/min, which generated a line pressure of 200 to 250 mm Hg, through a 14-gauge catheter inserted into the ascending aorta after aortic crossclamping. Then antegrade cardioplegia was also delivered through vein grafts with vein introducers after each distal anastomosis.

Patients in group III also received 100 ml pump blood infused at 50 ml/min through each vein graft after each distal anastomosis. Retrograde cardioplegia was administered through a coronary sinus catheter with insertion stylet, pressure-monitoring lumen, and self-inflating balloon at a rate of 150 ml/min for 2 to 3 minutes, which generated a line pressure of 50 to 80 mm Hg. The catheter was always inserted during partial cardiopulmonary bypass (CPB).

Anesthesia was induced with midazolam, sufentanil, and vecuronium. After endotracheal intubation, a 9 mm TEE biplanar probe was inserted into the esophagus and connected to a Toshiba TEE machine (SSH-140A system

with 9 mm 5 MHZ PEF-510 SB; American Medical System, Inc., Chicago, Ill.) for the evaluation of transmural blood flow. Assessment of left ventricular diastolic function was performed with pulsed-wave Doppler echocardiography. The transducer was manipulated to obtain a four-chamber view. The pulsed-wave sample volume was placed at the tips of the mitral valve leaflets to obtain the highest velocity. Doppler measurements included peak velocity during early filling (E), peak velocity during atrial contraction (A), the E/A ratio, and deceleration time (DT). The endoscope was then slightly withdrawn, and the tip was flexed and turned to the left to obtain a clear view of the left upper pulmonary vein as it emptied into the left atrium (sample volume 1 to 2 cm into the pulmonary vein from its junction with the left atrium). Three consecutive pulmonary vein velocity curves were analyzed. The height of the retrograde velocity at atrial contraction and the peak forward flow velocity during ventricular systole and diastole were measured. DT of early diastolic filling was measured in a manner similar to that of the DT for the mitral velocities. Left ventricular ejection fraction was calculated by means of a transgastric short-axis view (midpapillary muscle). All measurements were recorded on a videocassette recorder and on a strip chart at a recorder speed of 50 mm/sec. Mitral valve flow patterns and pulmonary flow velocity were then sent to an independent investigator for analysis. Samples were taken (1) 5 minutes before CPB, (2) 5 minutes after discontinuation of CPB, and (3) 1 hour after discontinuation of CPB. The measurements were performed in triplicate and randomly redistributed within the respiratory cycle.

After adequate heparinization, the patients were cannulated and CPB was instituted. After discontinuation of CPB during a steady-state period, all peak flow velocities and hemodynamic values were measured and compared with the preoperative values. Simultaneous calculations of cardiac index (CI), heart rate (HR), and mean arterial pressure (MAP) were also made.

Statistical analyses were performed with two-way analysis of variance for repeated measures, where the two factors were cardioplegic technique (antegrade, retrograde, or both antegrade and retrograde) and CPB (before, 5 minutes after, and 1 hour after). All values were expressed as means plus or minus the standard error. Multiple comparisons within and between groups were performed with Student's *t* tests, followed by Bonferroni corrections. A probability value less than 0.05 was considered significant.

Results

All patients had normal diastolic relaxation before operation. Left ventricular diastolic function, as measured by the E/A ratio, was impaired after CPB. The E/A ratio was significantly less altered after CPB in group III than in groups I and II. In group I, the E/A ratio decreased from 1.40 ± 0.2 before CPB to 0.67 ± 0.04 ($p = 0.01$) and 0.72 ± 0.05 ; $p = 0.02$) 5 minutes and 1 hour after CPB, respectively (Table I).

The greatest decrease in E/A ratio occurred in

Table I. Mitral and pulmonary vein flow velocities during CABG

		Before CPB	5 min after CPB	1 hour after CPB
E/A ratio	I	1.4 ± 0.2	0.67 ± 0.04*	0.72 ± 0.05
	II	1.45 ± 0.15	0.51 ± 0.03*	0.54 ± 0.03*
	III	1.35 ± 0.18	0.91 ± 0.05*†	1.15 ± 0.03†
DT	I	120 ± 10	196 ± 18*	205 ± 19*
	II	127 ± 11	220 ± 15*	225 ± 20*
	III	130 ± 15	160 ± 14**†	140 ± 12*
S (m/sec)	I	0.45 ± 0.14	0.46 ± 0.15	0.47 ± 0.16
	II	0.43 ± 0.15	0.44 ± 0.16	0.43 ± 0.13
	III	0.42 ± 0.13	0.50 ± 0.10*†	0.48 ± 0.10
D (m/sec)	I	0.33 ± 0.14	0.25 ± 0.06*	0.26 ± 0.07
	II	0.35 ± 0.15	0.24 ± 0.05*	0.22 ± 0.04
	III	0.34 ± 0.13	0.29 ± 0.07*†	0.32 ± 0.13†
S/D ratio	I	1.36 ± 0.16	1.84 ± 0.15*	1.80 ± 3
	II	1.22 ± 0.15	1.83 ± 0.16*	1.95 ± 3
	III	1.23 ± 0.14	1.40 ± 0.15*†	1.50 ± 16†

S, Systolic pulmonary vein flow velocity; D, diastolic pulmonary vein flow velocity; S/D, ratio of systolic/diastolic pulmonary vein flow velocity.

* Significance within group.

† Significance between groups.

group II. The E/A ratio decreased from 1.45 ± 0.15 to 0.51 ± 0.03 ($p = 0.005$) and 0.54 ± 0.03 ($p = 0.005$) 5 minutes and 1 hour after CPB, respectively. In group III, the E/A ratio decreased from 1.35 ± 0.18 to 0.91 ± 0.05 at 5 minutes after CPB ($p = 0.03$) and returned to near-baseline value 1 hour after CPB (1.15 ± 0.03 ; $p = 0.06$). The DT after CPB was highest in group II. One hour after CPB, the DT made a steady recovery toward baseline value in group III. There were no differences in diastolic and systolic pulmonary venous flow velocity in the preoperative period among the three groups of patients studied. The systolic pulmonary venous flow velocity significantly increased 5 minutes ($p = 0.01$) and 1 hour after CPB ($p = 0.02$) only in group III. The diastolic portion of pulmonary venous flow decreased significantly after 5 minutes of CPB in all three groups of patients studied ($p = 0.005$), with the greatest decrease occurring in groups I and II. Sixty minutes after CPB, diastolic pulmonary venous flow was back to control values only in group III. The decrease in the diastolic portion of pulmonary venous flow was associated with a simultaneous increase in the reverse flow from atrial contraction. There were no significant differences in age, sex, MAP, and CI in the preoperative period among the three groups studied. CI in the postoperative period, however, was significantly higher in group III ($p = 0.05$) than in groups I and II (Table II). The average

Table II. CIs During CABG

		Before CPB	5 min after CPB	1 hour after CPB
MAP (mm Hg)	I	76 ± 5	74 ± 4	76 ± 7
	II	79 ± 7	77 ± 6	78 ± 4
	III	75 ± 6	76 ± 5	75 ± 5
CI (L/min/m ²)	I	2.20 ± 0.20	2.25 ± 0.15*	2.27 ± 0.30
	II	2.17 ± 0.25	2.27 ± 0.30*	2.35 ± 0.34
	III	2.20 ± 0.3	2.35 ± 0.25*†	2.40 ± 0.30*†
LVEF (%)	I	62 ± 8	66 ± 4	67 ± 6
	II	60 ± 5	64 ± 7	69 ± 2
	III	66 ± 7	65 ± 5*†	69 ± 7*†
HR (beats/min)	I	82 ± 5	92 ± 6	88 ± 7
	II	87 ± 12	90 ± 5	87 ± 6
	III	85 ± 10	89 ± 7	91 ± 8
LA	I	8 ± 2	15 ± 4*	15 ± 3*
	II	9 ± 1	16 ± 3*	14 ± 3*
	III	9 ± 2	8 ± 3†	9 ± 2†

LVEF, Left ventricular ejection fraction; LA, left atrial pressure.

* Significance within group.

† Significance between groups.

bypass time was 99 ± 4 minutes in group I, 101 ± 5 minutes in group II, and 91 ± 2 minutes group III. The average aortic crossclamp time was 52 ± 4 minutes in group I, 50 ± 3 minutes in group II, and 40 ± 1 minutes in group III ($p = 0.05$).

The average amount of cardioplegic solution used was 2295 ± 105 ml in group I and 2520 ± 250 ml in group II (1590 ml antegrade and 930 ml retrograde). The line pressure generated by the cardioplegic infusion was 200 to 250 mm Hg for the antegrade infusion and 50 to 80 mm Hg for the retrograde. The cardioplegic solution was administered at a rate of 350 ml/min for the antegrade infusion and 150 ml/min for the retrograde. There were no differences among the three groups in the number of vessels bypassed or in which arteries were bypassed. All patients were weaned from CPB with dobutamine (Dobutrex 3 μ g/kg/min), which was discontinued 6 to 8 hours after operation. No new regional abnormalities in wall motion were found in our patients during the postoperative period. Cardiac enzyme activities were normal in all the patients studied. The incidence of supraventricular arrhythmias during the 24-hour postoperative period was highest in group III and lowest in group II (Table III). The incidence of ventricular arrhythmias was similar in all three groups studied. Heart block was more common in groups I and II than in group III (Table III).

Table III. Arrhythmias 24 hours after operation

	Supraventricular arrhythmias	Ventricular arrhythmias
Group I	1	4
Group II	1	2
Group III	7	1

Discussion

The factors that determine the velocity of blood flow across the mitral valve can be understood more clearly by examining the basic hydrodynamic principles that govern this process. A typical normal mitral flow velocity is shown in Fig. 1. The E wave is caused by the difference in pressure between the atrium and the ventricle, the A wave is caused by atrial contraction, and the DT is caused by left ventricular compliance. In the presence of abnormal relaxation, atrial contraction occurs with an incompletely empty left atrium and blood is propelled into the left ventricle with increased velocity, accounting for the heightened A wave and consequent decreased E/A ratio. The DT is the time from the mitral valve E velocity to the intersection of an interpolation of this decline in velocity to the baseline. Blood flow in the pulmonary veins is biphasic, with peaks of forward flow occurring in both systole and diastole and inverse diastolic flow occurring during atrial contraction (Fig. 2).^{8,9}

We found significant impairment in diastolic function after CABG in patients who had good preoperative systolic and diastolic function. The least impairment occurred with patients in whom ventricular fibrillation and intermittent aortic crossclamping were used. Diastolic function returned to normal value 1 hour after termination of CPB in group III. There were also no differences in HR, CI, or MAP among the three groups studied. Although systolic pulmonary vein flow velocity was normal in groups I and II after operation, it was significantly higher in group III. These changes in systolic pulmonary flow velocity were strongly related to changes in CI and left atrial pressure (Table I). It is well known that there is an inverse relationship between the left atrial pressure and pulmonary venous systolic flow.^{10,11} This is one of the reasons that determination of systolic pulmonary venous flow velocity was proposed as a rapid method to estimate left ventricular filling pressures in patients undergoing CABG.^{10,11}

Pulmonary diastolic flow decreased significantly in all three groups of patients 5 minutes after

Fig. 1. Mitral flow velocity during CABG.

discontinuation of CPB and returned toward control value 60 minutes after CPB only in group III. The decrease in diastolic pulmonary vein blood flow was significantly less in group III. The increase in systolic diastolic pulmonary venous flow ratio resulted mainly from the decrease in diastolic blood flow, rather than from an increase in systolic blood flow. The decrease in diastolic flow of the pulmonary vein was simultaneous associated with an increase in the reverse flow from atrial contraction. The average aortic crossclamping time and CPB duration were higher in groups I and II than in group III.

A wide variety of methods are used to maintain myocardial integrity and energy stores during cardiac operations. Myocardial preservation techniques include topical hypothermia, retrograde and antero-grade cardioplegia, and ventricular fibrillation.¹²⁻¹⁵ All of these methods provide excellent myocardial protection, resulting in little decrease in systolic function.

Fig. 2. Pulmonary vein flow velocity during CABG. S, Systolic flow; D, diastolic flow.

The immediate effect of myocardial protection on ventricular relaxation in human beings is not well known. Any impairment could predispose the ventricle toward delayed or incomplete relaxation, which would affect postbypass ventricular compliance and filling.

Cardiac preconditioning represents a robust, endogenous mechanism that convincingly augments postischemic ventricular function (principally through limitation of infarct size), attenuates dysrhythmias, and may confer metabolic recovery. It also improves contractile function and active relaxation compared with that seen in myocytes that were not preconditioned and preserves β -adrenergic responsiveness after arrest and rewarming.¹⁶

The effects of CABG on cardiovascular function are controversial. CABG restores blood flow to ischemic myocardium, which results in immediate improvement in systolic function.¹⁷⁻¹⁹ This was seen in our patients. Our study showed an improvement in systolic function, but diastolic function was severely impaired. The impairment in diastolic function was not severe enough to produce a decrease in global ventricular function. This severe decrease in diastolic function seen in groups I and II could be attributable to cellular changes such as edema in the myocardium as a result of the cardioplegic solution. That the impairment in diastolic function was worse in group II than in group I may be attributable to the fact that patients in group II received more car-

dioplegic solution than did those in group I. Also, despite persistent abnormal diastolic relaxation 1 hour after CPB in groups I and II, patients in group III had a better CI than did patients in groups II and I. Their systolic and diastolic function may have been preserved by the phenomenon of preconditioning. The preconditioning effect of a brief period of ischemia is essential for the understanding and value of intermittent aortic crossclamping as a safe operative technique. Considerable evidence relates the basic mechanism of increased tolerance to ischemia during intermittent aortic crossclamping to the cardioprotective effect of adenosine by means of A_2 receptor stimulation.²⁰

Experimental testing of prebypass ischemia before prolonged aortic crossclamping with cold cardioplegia shows worsened, rather than improved, recovery.¹⁹ It is possible that the mechanisms responsible for ischemic preconditioning are retarded by deep hypothermia and are effective only with intermittent ischemia with mild hypothermia, especially in conjunction with drugs that affect adenosine metabolism, block calcium channels, and open potassium channels.²¹⁻²³ Aortic crossclamping time or duration of CPB may account for part of the discrepancy in diastolic function found in our patients because both were shorter in group III.

There were significant differences in the types and numbers of arrhythmias among the three groups studied. Contrary to previous reports,²⁴ we found an

increased incidence of supraventricular dysrhythmias 24 hours after operation in patients in whom the myocardium was protected with intermittent ischemic arrest. There were more ventricular arrhythmias when cardioplegic solution was used (Table II). There was no increase in the incidence of postoperative myocardial infarction or of new abnormalities in regional wall motion in the three groups of patients studied.

HR is especially important,²⁵ but our results showed no difference in HR before and after CPB or among the three groups studied. HR thus cannot account for the discrepancies found among our patients. There were also no significant differences in age or MAP among the three groups studied.

This study, however, has limitations. We studied the differences in diastolic function among the three groups for only a limited period (up to 1 hour) after CPB. We are now studying the long-term effects of myocardial preservation techniques on diastolic function after CABG to verify any restoration of normal diastolic function in groups I and II.

Caution should be used during the interpretation of transmitral Doppler velocity patterns because of the complex nature of diastolic function.^{26, 27} It is important to remember that a variety of technical and physiologic factors (for example, sample volume size and position, phase of respiration, HR, and signal quality) may limit our ability to interpret and report apparent abnormalities in diastolic function. Physiologic variables that may influence the Doppler evaluation of diastolic function include preload, afterload, left ventricular function, arrhythmias, and the presence of mitral valve disease. Alterations in loading conditions have been demonstrated to affect transmitral diastolic flow velocity.

Conclusion

Left ventricular diastolic function was impaired after CABG in patients with normal preoperative diastolic and systolic function. The impairment depended on the myocardial protection used. The impairment was minimal when ventricular fibrillation and intermittent aortic crossclamping was used; it was highly significant when retrograde and antero- grade cardioplegia were used. The objective of cardioprotective approaches during cardiac operations is complete avoidance of myocardial stunning and necrosis. The evolution of cardioprotective strategies has been accomplished by surgeons adopting adversarial positions (ischemia vs antero-

cardioplegia vs retrograde cardioplegia), rather than through a compromising approach. This study should serve as a reminder that ventricular fibrillation and intermittent aortic crossclamping, one of the oldest myocardial preservation techniques available, should not be completely abandoned because it preserves diastolic function better than do the newest techniques available.

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