CARDIOTHORACIC TRANSPLANTATION

BLOOD VERSUS CRYSTALLOID CARDIOPLEGIA FOR MYOCARDIAL PROTECTION OF DONOR HEARTS DURING TRANSPLANTATION: A PROSPECTIVE, RANDOMIZED CLINICAL TRIAL

Giovanni Battista Luciani, MD
Giuseppe Faggian, MD
Giuseppe Montalbano, MD
Gianluca Casali, MD
Alberto Forni, MD
Bartolomeo Chiominto, MD
Alessandro Mazzucco, MD

Objective: **To assess the safety and efficacy of myocardial protection of the donor heart during transplantation with the use of blood cardioplegia, a prospective randomized clinical trial was undertaken between January 1997 and March 1998.** ***Methods:*** **Forty-seven consecutive patients were assigned either to crystalloid (27 patients; group 1) or blood cardioplegia (20 patients; group 2). Comparison of recipient age (54 ± 11 years vs 55 ± 7 years; *P* = .9), sex (89% vs 90% male patients; *P* = .9), diagnosis (63% vs 65% dilated cardiomyopathy; *P* = .8), elevated pulmonary vascular resistance (30% vs 30%; *P* = .9), prior cardiac operations (22% vs 30%; *P* = .5), need for urgent heart transplantation (7% vs 20%; *P* = .2), donor age (32 ± 11 years vs 31 ± 13 years; *P* = .7), cause of death (33% vs 40% vascular; *P* = .5), and global myocardial ischemia (176 ± 51 minutes vs 180 ± 58 minutes; *P* = .5) showed no difference. Hemodynamically unstable donors (15% vs 45%; *P* = .02) were more prevalent in group 2.** ***Results:*** **Operative mortality rates (4% vs 5%; *P* = .8), high-dose inotropic support (41% vs 30%; *P* = 0.6), and postoperative mechanical assistance (11% vs 10%; *P* = 0.9) were comparable in the 2 groups. Prevalence of acute right heart failure (27% vs 0; *P* = .02) and of temporary complete atrioventricular block (52% vs 20%; *P* = .02) were greater in group 1. Spontaneous sinus rhythm recovery was more prevalent in group 2 (11% vs 40%; *P* = .02). Higher peak creatine kinase (1429 ± 725 u/L vs 868 ± 466 u/L; *P* = .01) and creatine kinase MB (144 ± 90 u/L vs 102 ± 59 u/L; *P* = .06) levels suggested more severe ischemic injury in group I.** ***Conclusion:*** **Use of blood cardioplegia was associated with a lower prevalence of right heart failure, cardiac rhythm dysfunction, and laboratory evidence of ischemia. (J Thorac Cardiovasc Surg 1999;118:787-95)**

The need for continued extension of donor selection criteria to meet the demand for heart transplantation is leading to increasing acceptance of "marginal" grafts.[1] At the same time, progress in the management of pretransplantation and posttransplantation morbidity has allowed extension of heart transplantation to a growing subset of high-risk recipients.[2] Not surprisingly, acute failure of the graft and elevated pulmonary vascular resistance still account for most early deaths after transplantation.[3] These observations have promoted a revived interest for methods to protect the heart from ischemia during transplantation. A review by Wheeldon and associates[4] has underscored the great diversity of techniques used for myocardial preservation. Based on an exhaustive body of experimental evidence,[5-9] a trend toward the application of myocardial reperfusion with the use of blood cardioplegia during heart transplantation is gradually emerging.[4] More recently, a novel method to protect the heart, which includes induction with blood cardioplegia in the donor

From the Division of Cardiac Surgery, University of Verona, Verona, Italy.

Received for publication Dec 30, 1998; revisions requested June 3, 1999; revisions received June 24, 1999; accepted for publication Aug 3, 1999.

Address for reprints: Giovanni Battista Luciani, MD, Division of Cardiac Surgery, University of Verona, O.C.M. Piazzale Stefani 1, Verona, 37126, Italy (E-mail: luciani@netbusiness.it).

0022-5223/99 $8.00 + 0 **12/1/101926**

The Journal of Thoracic and
Cardiovascular Surgery
November 1999

Table I. *Composition of cardioplegic solutions*

	Crystalloid	*Buckberg A2*	*Buckberg C3*
pH (room temperature)	7.6-7.8	7.5-7.7	7.5-7.7
Dose	15 mL/kg	15 mL/kg	150 mL · min^{-1} · m^{-2} for 3 min
Osmolarity (mOsm/L)	320	320	380
Temperature (°C)	10	10	34
Hematocrit (%)	—	24	24
Na^+ (mEq/L)	120	160	160
K^+ (mEq/L)	16	70	30
Cl^- (mEq/L)	160	170	30
HCO_3^- (mEq/L)	10	—	—
Ca^{2+} (mEq/L)	2.4	1	1
Mg^{2+} (mEq/L)	32	—	—
Glucose (g/L)	—	36	36
THAM (mEq/L)	—	70	70
CPD (mL)	—	60	230
Glutamate (mEq/L)	—	—	60
Aspartate (mEq/L)	—	—	60

THAM, Tromethamine; *CPD*, citrate phosphate dextrose.

and reperfusion in the recipient, has shown promising results.[10] The purpose of the present study was to compare the safety and efficacy of myocardial preservation with the induction and reperfusion of blood cardioplegia with standard crystalloid cardioplegia.

Patients and methods

Study design. Since June 1995, myocardial protection of the donor heart during transplantation was adopted. The technique was initially applied in a nonrandomized fashion. On the basis of the encouraging preliminary results observed in 21 selected recipients,[10] a prospective, randomized clinical trial was initiated. Between January 1997 and March 1998, all consecutive patients undergoing heart transplantation were asked to participate in the study. All 49 recipients who underwent transplantation during this time interval expressed their consent to the investigation and comprise the study population of this report. Two of the 49 patients were excluded because they underwent heterotopic heart transplantation. Random assignment to either standard (crystalloid; group 1) or modified (blood; group 2) cardioplegia was done according to the last digit (even versus odd number) of the medical record number of the patient.

Operative technique. All patients underwent orthotopic heart transplantation with the use of a modified technique, which entails left atrial cuff and direct bicaval anastomosis, as described by Blanche and associates.[11] Briefly, the donor underwent routine standard orthotopic heart transplantation. Attention was paid to the transection of the superior vena cava above the azygos vein. After donor heart was dissected, a double-outlet needle (Research Medical Inc, Midvale, Utah) was inserted in the donor's ascending aorta and secured with a 4-0 polypropylene purse-string suture. In group 1 patients, the needle was connected with standard St Thomas' Hospital II solution used to achieve cardiac standstill (Table I). Alternatively in group 2, 1 port of the needle was connected with a disposable cardioplegia bag where donor blood was collected and mixed with the Buckberg (A2) solution.[8] The bag was connected with a heat exchanger (Medtronic Bio-Medicus, Minneapolis, Minn) and a roller pump, which was used to cool the solution to 10°C and to infuse the solution at a constant pressure (60-80 mm Hg) through a line connected with the second port of the cardioplegia needle. After heparin bolus administration (3 mg/kg), 800 to 1000 mL of donor blood was slowly allowed to drain through the outflow port of the needle. Intercurrent episodes of systemic hypotension were treated with colloid fluid administration. The hematocrit of the induction solution was kept around 24% (Table I). The aorta was then crossclamped, and blood cardioplegic solution was administered through the antegrade route; the heart was decompressed through the right superior pulmonary vein and inferior vena cava. After the heart was excised, the graft was stored in cold (0°C-4°C) sterile saline solution. Recipient operation was performed under moderately hypothermic cardiopulmonary bypass. Attention was devoted to the site of caval cannulation, which was immediately below the origin of the superior vena cava and below the pericardial reflection of the inferior vena cava. Excision of the heart was carried out by transection of the superior vena cava at the atriocaval junction with a generous cuff of right atrium around the inferior vena cava. After section of the aorta and pulmonary artery trunk 2 cm above the semilunar valves, a left atrial cuff around the 4 pulmonary veins was tailored. Implantation of the graft was completed by anastomosis of the left atrial cuff, followed by the inferior vena cava, the main pulmonary artery, and the ascending aorta. Before the exposure of the graft to the recipient's own blood, a methylprednisolone bolus (1000 mg) was given intravenously. This time corresponded to aortic clamp release in group 1 patients, who did not receive any form of reperfu-

Table II. *Recipient and donor profile*

	Group 1	*Group 2*	P *value*
Patients (n)	27	20	
Recipient male sex (%)	89 (24/27)	90 (18/20)	.9
Recipient mean age (y)	54 ± 11	55 ± 7	.9
Diagnosis of dilated cardiomyopathy (%)	63 (17/27)	65 (13/20)	.8
Recipient elevated PVR, >4 Wood units (%)	30 (8/27)	30 (6/20)	.9
Prior cardiac operation (%)	22 (6/27)	30 (6/20)	.5
Urgent heart transplantation (%)	7 (2/27)	20 (4/20)	.2
Donor male sex (%)	78 (21/27)	70 (14/20)	.5
Donor mean age (y)	32 ± 11	31 ± 13	.7
Donor vascular death (%)	33 (9/27)	45(9/20)	.5
Unstable donor hemodynamics (%)	15 (4/27)	45 (9/20)	.02
Ischemic time (min)	176 ± 51	180 ± 58	.8
Bypass time (min)	135 ± 34	128 ± 23	.5

PVR, Pulmonary vascular resistance.

sion. In group 2 patients, the ascending aorta was again cannulated, and methylprednisolone was administered before warm (34°C) antegrade reperfusion with blood cardioplegic solution (Buckberg C3; Table I). Finally, the superior caval anastomosis was performed after aortic clamp removal.

Postoperative management and patient follow-up

Intraoperative management. Weaning from cardiopulmonary bypass was routinely performed with the aid of low-dose (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) dopamine and isoproterenol (0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$) infusion. An increase in the dose of catecholamine and the addition of epinephrine infusion were considered in case of intraoperative low-output syndrome. Intraaortic balloon pump (IABP) and ventricular assist device support were left as the last therapeutic measure in case of refractory circulatory insufficiency. Perioperative right heart failure was managed by mechanical hyperventilation and infusion of prostaglandin E_1 (0.01-0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$). In case of persistent right heart insufficiency, inhaled nitric oxide therapy (5-40 ppm) was commenced.

Posttransplantation immunosuppressive therapy. The same treatment protocol was applied to all recipients, regardless of the technique used for preservation of the heart. The protocol included oral cyclosporine (5-8 mg/kg per day) to maintain a whole blood trough level of 300 to 500 ng/dL, azathioprine (2-4 mg/kg per day) to maintain a total white blood cell count of 4000/mL, and oral prednisone (starting at a maintenance dose of 1 mg/kg per day and tapered to 0.5 mg/kg per day by month 3). Discontinuation of chronic steroid therapy was attempted after posttransplantation month 6. Surveillance of rejection was performed with a schedule of programmed endomyocardial biopsies, and treatment of a rejection was by means of pulse doses of methylprednisolone and/or augmentation of immunosuppression on an individual basis. Patient follow-up was based on examination during routine admissions for laboratory investigations, including endomyocardial biopsies, and was 100% complete.

Definition of variables and statistical analysis. Urgent heart transplantation was defined as any heart transplantation performed for in-hospital recipients who were receiving intravenous infusion of inotropic drugs and/or supported with IABP or ventricular assist device. Hemodynamic instability in the donor was defined as the presence of at least 1 episode of cardiac arrest or sustained (longer than 10 minutes) profound hypotension (≤50 mm Hg systolic pressure) requiring resuscitation, and/or the need for 2 or more inotropic agents, and/or the presence of supraventricular or ventricular tachyarrhythmias leading to hypotension (≤50 mm Hg systolic pressure) requiring either pharmacologic or electrical cardioversion. End points of the study were operative death (any death within 30 days or before discharge), the need for high-dose inotropic support (3 inotropic agents or 2 inotropic agents, 1 of which is epinephrine), mechanical life support (IABP, ventricular assist device), acute right heart failure (central venous pressure, >18 mm Hg; cardiac index, <2.0 L $\cdot min^{-1} \cdot m^{-2}$; left atrial pressure, <10 mm Hg; urine output, <1 mL $\cdot kg^{-1} \cdot h^{-1}$), acute graft failure (need for high-dose inotropic and/or mechanical life support in the absence of right heart failure), ventricular kinetics and shortening fraction at predischarge echocardiographic examination, spontaneous sinus rhythm recovery (resumption after clamp removal), induced sinus rhythm recovery (after intraoperative cardioversion), temporary complete atrioventricular block (need for temporary pacing of any duration, with recovery of sinus rhythm before discharge), permanent complete atrioventricular block (requiring permanent pacing), duration of ventilatory support, duration of intensive care stay, peak total and isoenzyme MB creatine kinase blood level, prevalence of histologic evidence of ischemia at first endomyocardial biopsy, late death, actuarial survival.

Values were expressed as mean ± SD. The χ^2 test was used to compare the distribution of binary variables, although the 2-tailed Student *t* test was used for comparison of continuous variables. Actuarial survival was calculated with the Kaplan-Meier product limit estimate, and curves were compared by means of the log-rank test. A *P* value less than .05 was considered indicative of a difference between variables not attributed to chance alone.

Table III. *Survival and graft function*

	Group 1	*Group 2*	P *value*
Early mortality (%)	4 (1/27)	4 (1/20)	.8
High-dose inotropic support (%)	41 (11/27)	30 (6/20)	.6
Mechanical life support (%)	11 (3/27)	10 (2/20)	.9
Acute graft failure (%)	15 (4/27)	30 (6/20)	.2
Acute right heart failure (%)	26 (7/27)	0 (0/20)	.01
Left ventricular shortening fraction (%)	32.8 ± 6.1	34.1 ± 5.8	.4
Left ventricular dysfunction (%)	11 (3/27)	0 (0/20)	.1
Right ventricular dysfunction (%)	11 (3/27)	0 (0/20)	.1
Late mortality (%)	0 (0/26)	5 (1/19)	.2
Follow-up (mo)	13.7 ± 4.8	15.0 ± 4.9	.7

Results

Recipient and donor population. Forty-seven patients qualified for the study; 27 patients received standard (crystalloid) cardioplegia, and 20 patients received modified (blood) cardioplegia for myocardial protection of their graft (Table II). Analysis of recipient demographic variables disclosed no significant difference. History of prior cardiac surgical procedures and of pulmonary hypertension were equally represented in the 2 groups. Need for urgent heart transplantation was 3-fold more common in group 2 recipients, although the difference did not reach statistical significance. The 47 donors assigned to recipients in the study also presented comparable demographic variables except for unstable hemodynamics, which was more prevalent in donors assigned to the modified myocardial protection. Bypass and ischemic times were similar; the latter ones averaged 3 hours in both groups.

Survival and graft failure. There was 1 early death in each group (4% [1/27 patients] vs 5% [1/20 patients]; $P = .80$); both patients had undergone operation on an urgent basis (Table III). The patient in group 1 was a 49-year-old man with ischemic cardiomyopathy (left ventricular ejection fraction, 20%), in whom postcardiotomy acute left ventricular failure developed after elective myocardial revascularization. After 6 days of mechanical life support with the use of a left ventricular assist device (LVAD) and IABP, the patient underwent heart transplantation. Weaning from bypass required the resumption of mechanical life support with LVAD and IABP because of acute graft failure. Shortly after the heart transplantation, the patient experienced the development of irreversible circulatory shock, which was caused by massive pulmonary embolism, which was found at postmortem examination. The patient in group 2 was a 45-year-old man with a history of treated Hodgkin lymphoma and an irradiation/chemotherapy-induced cardiomyopathy and chronic renal failure. Urgent heart transplantation was advised because of an acute congestive failure episode requiring in-hospital intravenous inotropic support. One week after successful heart transplantation, rapidly progressing renal failure developed, which required daily dialysis. The patient had a fatal, massive gastrointestinal hemorrhage during dialytic treatment 2 months after heart transplantation.

Prevalence of postoperative graft dysfunction, as gathered from the need for high-dose inotropic support (41% [11/27 patients] vs 30% [6/20 patients]; $P = .50$) and for mechanical life support (11% [3/27 patients] vs 10% [2/20 patients]; $P = .90$) was comparable in the 2 groups (Table III). Three patients in group 1 required mechanical support, including the 1 patient who died early. In detail, 1 patient required IABP and 1 patient required IABP and LVAD, respectively, for left heart failure; the third patient needed IABP and a right ventricular assist device for acute right heart failure. In group 2, 2 patients required IABP, both for acute left heart failure. The prevalence of acute graft failure was comparable between groups (15% [4/27 patients] vs 30% [6/20 patients]; $P = .30$). On the contrary, an analysis of right heart failure showed a significantly higher prevalence among group 1 recipients (26% [7/27 patients] vs 0% [0/22 patients]; $P = .02$). In addition, 3 of the 7 patients (43%) with acute right-sided insufficiency required advanced circulatory support, which included inhaled nitric oxide therapy in 2 patients and a right ventricular assist device in 1 patient (Table III). Assessment of ventricular function by means of 2-dimensional echocardiography before hospital discharge revealed a comparable shortening fraction of the left ventricle in the 2 groups. However, prevalence of at least moderate either right or left ventricular dysfunction, as judged by the severity of hypokinesis at 2-dimensional echocardiography, seemed higher in recipients who had crystalloid car-

Table IV. *Electrophysiologic findings*

	Group 1	*Group 2*	P *value*
Spontaneous sinus rhythm recovery (%)	11 (3/27)	40 (8/20)	.02
Temporary atrioventricular block (%)	52 (14/27)	20 (4/20)	.02
Duration of atrioventricular block (d)	3.2 ± 2.6	1.6 ± 0.9	.05
Permanent atrioventricular block (%)	4 (1/26)	(0/21)	.3
Incomplete right bundle branch block (%)	22 (6/27)	15 (3/20)	.2
Complete right bundle branch block (%)	33 (9/27)	30 (6/20)	.8

Table V. *Indices of myocardial ischemia*

	Group 1	*Group 2*	P *value*
CK-MB: hour 6 after transplantation (u/L)	144 ± 90	102 ± 59	.06
CK-MB: hour 24 after transplantation (u/L)	116 ± 83	100 ± 42	.7
CK: hour 6 after transplantation (u/L)	1430 ± 725	868 ± 466	.01
CK: hour 24 after transplantation (u/L)	1440 ± 851	832 ± 366	.02
Ischemic changes at EMB (%)	54 (14/26)	30 (6/20)	.1

CK, Creatine kinase; *MB*, MB isoenzyme; *EMB*, endomyocardial biopsy.

dioplegia, although the estimate did not reach statistical significance (Table III).

Electrophysiologic findings. Electrophysiologic findings were significantly different between the 2 patient groups (Table IV). Both spontaneous sinus rhythm recovery on aortic clamp removal (11% [3/27 patients] vs 40% [8/20 patients]; $P = .02$) and immediate recovery of regular atrioventricular conduction were more common in patients in group 2, as evidenced by the reduced need for temporary atrioventricular pacing (52% [14/27 patients] vs 20% [4/20 patients]; $P = .02$). In addition, the duration of the temporary atrioventricular block was significantly shorter in group 2 patients (1.6 ± 0.9 days vs 3.2 ± 2.6 days; $P = .05$). No patient in the group 2 versus 1 patient in group 1 required permanent pacing for complete atrioventricular block. The prevalence of minor conduction disturbances such as incomplete and complete right bundle branch block proved comparable in the 2 groups (Table IV).

Posttransplantation ischemia. Laboratory evidence of myocardial ischemia, as assessed by creatine kinase MB blood levels after heart transplantation, disclosed higher creatine kinase MB values in group 1 recipients at 6 hours, although the difference was marginally significant (144 ± 90 u/L vs 102 ± 59 u/L; $P = .06$) (Table V). The difference was not significant at 24 hours. On the contrary, blood levels of total creatine kinase, both at 6 and 24 hours, were significantly higher in group 1 recipients, suggesting greater generalized tissue injury. Histologic findings compatible with ischemic changes at the first endomyocardial biopsy tended to be more prevalent in group 1 recipients, although the difference did not reach statistical significance (54% [14/26 patients] vs 30% [6/20 patients]; $P = .13$).

Postoperative recovery and follow-up. The mean duration of mechanical ventilatory support was longer in group 1 recipients, although the figure did not reach statistical significance (33 ± 60 hours vs 25 ± 24 hours; $P = .58$; Table III). The duration of intensive care unit stay was comparable in the 2 groups, because of an institutional policy to keep the heart transplantation recipients in the unit until the day of the first endomyocardial biopsy (6.8 ± 6.3 days vs 6.8 ± 3.6 days; $P = .98$), thereby diminishing the importance of this index for the purpose of comparing outcome. Follow-up of hospital survivors ranged from 6 to 18 months, with no significant difference between the 2 groups (15.0 ± 4.9 months vs 13.7 ± 4.8 months; $P = .70$). There was only 1 late death in the modified protection group (0% [0/26 patients] vs 5% [1/19 patients]; $P = .30$) of noncardiac origin. The patient died 5 months after the transplantation of massive pulmonary embolism after an appendectomy procedure. Actuarial survival at 1 year was higher in group 1 (96% vs 90%) although the difference was not significant.

Discussion

The present prospective, randomized trial demonstrates that the prevalence of acute right heart failure and of atrioventricular conduction disturbance after heart transplantation are lower when induction and reperfusion blood cardioplegia are used for myocardial protection. The study, nevertheless, suggests that both

crystalloid and blood cardioplegic solutions allow satisfactory myocardial protection because the overall clinical outcome is similar in the 2 groups and compares well with currently reported results after heart transplantation.[3]

The necessity to improve methods of myocardial protection during heart transplantation is dictated by clinical evidence that suggests that acute graft failure remains a leading cause of early posttransplantation death.[3] Indeed, the recent extension of donor selection criteria, including the use of marginal donor organs,[1] can in part explain the inability to reduce the prevalence of acute graft failure. In addition, the continued expansion of the recipient pool, because of improvements in the management of posttransplantation complications, has selected a growing number of high-risk candidates, which further exacerbates the consequences of acute failure of the graft.[2] These considerations fully explain the crucial role of adequate myocardial protection in the current era.[4]

Investigations of innovative methods to protect the heart during heart transplantation have initially focused on the relative benefits of various crystalloid solutions. These solutions essentially differ in ionic composition, thereby resembling alternatively the intracellular milieu, the extracellular milieu, or an intermediate environment.[12-16] In spite of promising laboratory evidence that shows superior protection with the use of intracellular-like cardioplegic solutions,[12] available randomized clinical trials have been rare and have yielded conflicting evidence.[13-17] Indeed, although 2 prospective, randomized trials have demonstrated improved early results with the use of University of Wisconsin solution, albeit limited to prevalence of arrhythmias and release of creatine kinase,[14,15] further experimental studies have lessened the relevance of those findings.[16] In addition, the use of intracellular solutions has been postulated to cause chemical damage to the coronary endothelium to explain the observed higher prevalence of allograft vasculopathy.[17] At the same time, growing laboratory evidence has suggested a beneficial role for blood-based cardioplegic solutions in heart transplantation.[6-9] Moving from Buckberg's original work[5] on the use of blood cardioplegia for myocardial protection in cardiac surgical procedures, several groups have documented superior myocardial protection during heart transplantation in laboratory animals with the use of both blood cardioplegia for reperfusion[6,7,9] and warm blood cardioplegia for the induction of cardiac standstill.[8] These observations account for the emerging trend toward the use of some form of reperfusion in clinical heart transplantation, as reported by Wheeldon and associates.[4]

The application of blood cardioplegia to heart transplantation is relatively recent, and a variety of methods have thus far been adopted. Accordingly, Soots and associates[18] and Nataf and associates[19] have reported on the use of crystalloid cardioplegia induction, followed by cold blood maintenance in the graft and warm blood reperfusion before clamp removal. Although Soots and associates[18] have found significantly lower mortality rates in patients receiving blood compared with those patients with crystalloid cardioplegia, the estimates reported for both the control and the treatment group are excessively high (21% vs 10%). In addition, even early survival (50% ± 8% vs 64% ± 8% at 18 months) appears well below the accepted standard results after heart transplantation. In that study, factors other than myocardial protection must have played a relevant role. Likewise, the work by Nataf and associates[19] shows prohibitive early mortality rates (20% with the crystalloid versus 14% with the blood solution), although the rates are comparable in the 2 groups. The only significant difference reported is in terms of sinus rhythm recovery and duration of inotropic support. Most important, both series are collected in a retrospective, nonrandomized fashion, making even the weak differences irrelevant. An alternative myocardial protection strategy has been chosen by Pradas and colleagues,[20] who have reported on the use of cold crystalloid induction and continuous retrograde reperfusion during implantation. When comparing this method with standard crystalloid cardioplegia, the authors have found a higher prevalence of spontaneous sinus rhythm recovery, a lesser need for inotropic support, a shorter hospital stay, and a lower prevalence of ischemic changes at endomyocardial biopsy.[20] However, the ischemic time was significantly lower in recipients of blood cardioplegia, and mortality was twice as high (6% vs 14%). When added to the observation that this work is also retrospective and that the 2 patient groups were collected during different time intervals, conclusions can hardly expand on anything but the technical feasibility of the method.[20]

The only available prospective, randomized study on blood cardioplegia in heart transplantation compares the use of crystalloid induction and continuous retrograde warm blood reperfusion with standard crystalloid induction in 34 consecutive heart transplant recipients.[21] According to the authors, superiority of blood-based cardioplegia can be inferred from the higher prevalence of spontaneous defibrillation and the lower prevalence of early graft failure, the other differences not reaching statistical significance.[21] Nonetheless, a series of observations seem to weaken the conclusions. The trial simultaneously compares 2 alternative solu-

tions, administration routes and protocols. In addition, mortality rate(18%) and prevalence of acute graft failure rate (24%) in the control group are excessively high when matched with a short mean ischemic time (approximately 2 hours) and a young average recipient (47 ± 2 years) and donor (32 ± 2 years) age. These results compare poorly with current operative mortality rates after heart transplantation, as reported by the International Society for Heart and Lung Transplantation,[4] and with the authors' own experience with crystalloid cardioplegia before the randomized study.[21,22] It is reasonable to assume that factors other than myocardial protection may have come into play and that the results represent weak evidence favoring the use of blood cardioplegia in heart transplantation.[21]

The present study attempts to provide more rigorous information on the safety and efficacy of blood cardioplegia in heart transplantation. In an effort to simplify a comparison between myocardial protection methods, blood cardioplegic solutions in the donor and in the recipient have been administered through the antegrade route as for crystalloid cardioplegic solutions.[10] The original aspect of this technique is the use of blood cardioplegia to induce cardiac standstill in the donor, as advocated by previous experimental work on donor hearts with impaired hemodynamics[8] and by routine cardiac surgical practice.[5] Compared with previous randomized trials,[14,15,21] the present series includes a population of recipients with poorer pretransplantation conditions, as attested by the overall prevalence of pulmonary hypertension (30%), of prior cardiac operations (25%) and priority listing (12%), and a large proportion of marginal donors (27% with unstable hemodynamics). In addition, mean ischemic times are longer than generally reported, with mean values approximately 3 hours and extending to 5 hours of preservation. Despite these considerations, overall operative (2/47 patients; 4%) and late (1/45 patients; 2%) mortality rates favorably compare with current standard results after heart transplantation.[4] It can be assumed that both the population and the outcome described in this study are highly representative of the current practice of heart transplantation worldwide.

The present work demonstrates that both crystalloid and blood cardioplegia are generally safe methods for the protection of the myocardium during heart transplantation, because both are associated with satisfactory early and late survival in a difficult cohort of recipients and with suboptimal or even marginal donor organs. In detail, acute graft failure remains a definite early hazard with both methods of myocardial protection, although it is usually reversible if pharmacologic or mechanical support can effectively maintain the circulation. The prevalence of acute graft failure with blood cardioplegia appears slightly higher in our series (6/20 patients; 30%) than previously reported with other blood-based solutions (estimates ranging form 6% to 12%).[19-21] It must be emphasized, however, that, contrary to prior works, the definition of acute graft failure herein was inclusive of patients who eventually survived heart transplantation. Considering that no patient in the blood cardioplegia group experienced graft failure leading to death or retransplantation, our results favorably compare with existing data.[19-21] The present study further demonstrates that failure of the right heart is rare among recipients of blood cardioplegia but common among recipients of crystalloid cardioplegia; electrophysiologic changes typically associated with ischemia of the right heart (such as failure to recover sinus rhythm and atrioventricular conduction) are also rare. Acute right-sided circulatory insufficiency, particularly in the face of elevated recipient pulmonary vascular resistance, still represents a leading cause of early death after heart transplantation.[4] The observations reported here are even more relevant considering that as much as one third of recipients enrolled in the blood cardioplegia group had pretransplantation pulmonary hypertension. The fact that none of the cases of right-sided heart failure in the crystalloid cardioplegia group proved fatal is only indicative that advanced life support, including the use of inhaled nitric oxide and right ventricular assist devices (3 of 7 patients) may profoundly reduce the mortality rate in high-risk transplant recipients. Comparison of our results with previous studies is difficult with respect to acute right heart failure, because this complication is rarely quoted as such. Similarly to most series that suggest benefits of blood-based cardioplegic solutions,[18-21] the present work shows a higher prevalence of spontaneous sinus rhythm recovery and a lower prevalence of atrioventricular conduction disturbance. The alleged property of blood cardioplegia to enhance right heart protection, including the conduction tissue, may account for this finding. Although the overall prevalence of temporary atrioventricular block in the present series appears rather high for heart transplantation with the use of the bicaval anastomosis implantation technique, the overall need for permanent pacing (1/47 patients; 2%) was not significantly greater than estimates reported by Trento and associates[23] (0/100 patients) and identical to data presented by others[24] (1/50 patients; 2%). These findings match with the laboratory evidence of myocardial ischemia and with the histologic findings that suggest greater ischemic damage to the myocardium, albeit with a marginally significant difference. Comparison of these results with pre-

vious reports is worthwhile, because a prior work by Carrier and associates[21] has shown levels of creatine kinase MB, in transplant recipients who received crystalloid cardioplegia either with or without continuous retrograde blood reperfusion, which are similar to those found in recipients of crystalloid cardioplegia with no reperfusion in our study. Thus induction with cold blood and warm blood reperfusion gives better laboratory results of both crystalloid cardioplegia with no reperfusion and crystalloid cardioplegia with continuous retrograde blood reperfusion.

The clinical implications of the present results seem unclear from the study because overall outcome (death, need for inotropic support, mechanical ventilation, intensive care assistance) is comparable between groups. However, more careful analysis of data shows how recipients of blood cardioplegia were more commonly assigned marginal grafts (hemodynamically unstable). One might speculate that the myocardial protection protocol adopted herein may enable the reproduction of the early outcome obtained with ideal donor organs and ideal recipients even when large numbers of marginal donor organs are used in poor heart transplantation candidates. Accordingly, after the close of our study, blood cardioplegia has been routinely used in the presence of high-risk recipients (pulmonary hypertension, need for urgent transplantation, prior cardiac procedure), and/or marginal donor organs (donors older than 40 years, unstable hemodynamics, distant retrieval).

Limitations. The present study is influenced by several limitations. In fact, it reports the comparison of 2 different cardioplegic solutions and 2 different administration protocols (single induction versus induction and reperfusion), even though the administration route is the same (antegrade). The method requires the assistance of a perfusion technician, although the protocol can be performed without a portable pump, as well. There may be potential for harm to other organs because of the need for blood draw during the harvesting procedure. Nevertheless, the 2 methods reported herein reproduce the current standard for myocardial protection in heart transplantation versus the application of the Buckberg principles to heart transplantation. Furthermore, additional costs connected with the method may be balanced by decreased morbidity after heart transplantation, provided this is demonstrated. No organs were lost during the study from any of the 22 multiorgan donors who received induction blood cardioplegia.

In conclusion, the use of induction and reperfusion blood cardioplegia is associated with lower prevalence of posttransplantation right heart insufficiency, arrhythmias, and laboratory evidence of ischemia when compared with standard crystalloid cardioplegia. Adoption of this method of myocardial protection may be indicated to control early morbidity, particularly when poor donor organs are used in high-risk transplant recipients.

We thank the perfusion technicians, Tiziano Menon, Maddalena Tessari, Luigi Franchetto, Terenzio Marzocco, and Francesco Faggionato for their assistance in developing the myocardial protection protocol.

REFERENCES

1. Jeevanandam V, Furukawa S, Prendergast TW, Todd BA, Eisen HJ, McClurken JB. Standard criteria for an acceptable donor heart are restricting heart transplantation. Ann Thorac Surg 1996; 62:1268-75.
2. Livi U, Milano A, Bortolotti U, Casula R, Zenati M, Casarotto D. Results of heart transplantation by extending recipient selection criteria. J Cardiovasc Surg (Torino) 1994;35:377-82.
3. Hosenpud JD, Bennett LE, Keck BM, Fiol B, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: fifteenth official report—1998. J Heart Lung Transplant 1998;17:656-68.
4. Wheeldon D, Sharples L, Wallwork J, English T. Donor heart preservation survey. J Heart Lung Transplant 1992;11:986-93.
5. Buckberg GD. Strategies and logic of cardioplegic delivery to prevent, avoid, and reverse ischemic and reperfusion damage. J Thorac Cardiovasc Surg 1987;93:127-39.
6. Swanson DK, Myerowitz D, Watson KM, Hegge JO, Fields BL. A comparison of blood and crystalloid cardioplegia during heart transplantation after 5 hours of cold storage. J Thorac Cardiovasc Surg 1987;93:687-94.
7. Milliken JC, Billingsley AM, Laks H. Modified reperfusate after long-term preservation of the heart. Ann Thorac Surg 1989;47: 725-8.
8. Tixier D, Matheis G, Buckberg GD, Young HH. Donor hearts with impaired hemodynamics: benefit of warm substrate-enriched blood cardioplegic solution for induction of cardioplegia during cardiac harvesting. J Thorac Cardiovasc Surg 1991;102:207-13.
9. Fukushima N, Shirakura R, Nakata S, et al. Effects of terminal cardioplegia with leukocyte-depleted blood on heart grafts preserved for 24 hours. J Heart Lung Transplant 1992;11:676-82.
10. Luciani GB, Faggian G, Forni A, Montalbano G, Chiominto B, Mazzucco A. Myocardial protection during heart transplantation using blood cardioplegia. Transplant Proc 1997;29:3386-8.
11. Blanche C, Czer LS, Valenza M, Trento A. Alternative technique for orthotopic heart transplantation. Ann Thorac Surg 1994;57: 765-7.
12. Gott JP, Pan-Chih, Dorsey LM, Cheung EH, Hatcher CR Jr, Guyton RA. Cardioplegia for transplantation: failure of extracellular solution compared with Stanford or UW solution. Ann Thorac Surg 1990;50:348-54.
13. Karck M, Frantzen V, Schwalb H, Haverich A, Uretzky G. Prolonged myocardial protection with St. Thomas' Hospital solution and University of Wisconsin solution: the importance of preservation techniques. Eur J Cardiothorac Surg 1992;6:261-6.
14. Jeevanandam V, Barr ML, Auteri JS, et al. University of Wisconsin solution versus crystalloid cardioplegia for human

donor heart preservation: a randomized blinded prospective clinical trial. J Thorac Cardiovasc Surg 1992;103:194-9.
15. Stein DG, Drinkwater DC, Laks H, et al. Cardiac preservation in patients undergoing transplantation: a clinical trial comparing University of Wisconsin solution and Stanford solution. J Thorac Cardiovasc Surg 1991;102:657-65.
16. Kawai A, Morita S, Kormos RL, et al. A clinical trial comparing University of Wisconsin and cold cardioplegic solution with load-independent parameters. J Heart Lung Transplant 1994;13: 150-6.
17. Drinkwater DC, Rudis E, Laks H, et al. University of Wisconsin solution versus Stanford cardioplegic solution and the development of cardiac allograft vasculopathy. J Heart Lung Transplant 1995;14:891-6.
18. Soots G, Crepin F, Prat A, et al. Cold blood cardioplegia and warm cardioplegic reperfusion in heart transplantation. Eur J Cardiothorac Surg 1991;5:400-5.
19. Nataf P, Pavie A, Bracamontes L, Bors V, Cabrol C, Gandjbakhch I. Myocardial protection by blood cardioplegia and warm reperfusion in heart transplantation. Ann Thorac Surg 1992;53:525-6.
20. Pradas G, Cuenca J, Juffé A. Continuous warm reperfusion during heart transplantation. J Thorac Cardiovasc Surg 1996;111: 784-90.
21. Carrier M, Leung TK, Solymoss BC, Cartier R, Leclerc Y, Pelletier LC. Clinical trial of retrograde warm blood reperfusion versus standard cold topical irrigation of transplanted hearts. Ann Thorac Surg 1996;61:1310-5.
22. Drinkwater DC. Invited commentary. Ann Thorac Surg 1996; 61:1315-6.
23. Trento A, Takkenberg JM, Czer LS, et al. Clinical experience with one hundred consecutive patients undergoing orthotopic heart transplantation with bicaval and pulmonary venous anastomoses. J Thorac Cardiovasc Surg 1996;112:1496-502.
24. Dreyfus G. In discussion of Trento et al.[23]