Continuous retrograde blood cardioplegia is associated with lower hospital mortality after heart valve surgery

Willem J. Flameng, MD, PhD^a

Paul Herijgers, MD, PhD^a

Sarah Dewilde, MSc^b

Emmanuel Lesaffre, PhD^b

Objective: Myocardial preservation studies comparing blood and crystalloid cardioplegia techniques were almost exclusively performed on patients undergoing coronary bypass, and they were unable to show a difference in hospital mortality. We investigated possible factors, including cardioplegia techniques, influencing hospital mortality in patients undergoing cardiac valve surgery.

Methods: We evaluated hospital mortality in 1098 consecutive patients undergoing cardiac valve surgery by using a multivariate logistic regression with propensity score balancing of the groups. In 25% of the patients, multiple valve or Bentall procedures were performed, and in 46% of all patients, coronary bypass grafting was associated with valve surgery. A first cohort of 504 consecutive patients were operated on by using single-shot antegrade cold crystalloid cardioplegia, and a second cohort of 594 patients were operated on by using continuous retrograde cold blood cardioplegia.

Results: After correction for patient-related and operative risk factors, lower hospital mortality was found in patients who received retrograde blood cardioplegia ($P = .020$). The odds ratio of in-hospital death when using blood cardioplegia was 0.44 (95% confidence interval, 0.22-0.88). Further predictors of hospital mortality were age, advanced New York Heart Association functional class, cardiopulmonary bypass time, reoperation, active endocarditis, and renal failure.

Conclusions: This study shows that continuous retrograde blood cardioplegia is associated with lower hospital mortality in heart valve operations.

From Cardiac Surgery^a and Biostatistical Centre,^b Katholieke Universiteit Leuven, Belgium.

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Address for reprints: W. Flameng, MD, PhD, Department of Cardiac Surgery, U.Z. Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium (E-mail: Willem.Flameng@med.kuleuven.ac.be).

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Most clinical studies on cardioplegia techniques have been done in patients undergoing coronary artery bypass grafting. Nevertheless, the advent of off-pump coronary artery bypass surgery has reduced the necessity for it. On the contrary, few studies have been performed in patients undergoing valve surgery in which cardioplegia is still fundamental. There is a wide range of cardioplegia practices with significant intersurgeon and international differences. Major controversies involve the temperature of cardioplegic solutions, intermittence of delivery, and direction of flow. Properly designed randomized clinical trials would be the ideal method for testing the outcome of different methods of myocardial protection, but in cardiac surgery most improvements occurred because of progressive changes in current practice. In the early 1990s, the most common technique used in Europe was cold antegrade crystalloid cardioplegia. In the United Kingdom, for example, in 1992, 58% of the surgeons used crystalloid cardioplegia, 77% used antegrade cardioplegia, and 98% used cold cardioplegia.¹

Because experimental studies showed that blood cardioplegia was advantageous over crystalloid cardioplegia,² blood cardioplegia gained interest. Obviously, excellent protection can be obtained with the use of cold,³ warm,^{4,5} and tepid^{6,7} cardio-

TABLE 1. Type of intervention

	Crystalloid		Blood		Total
	–CABG	+CABG	–CABG	+CABG	
Single valve					
Aortic	120	138	130	140	528
Mitral	67	69	76	74	286
Tricuspid	6	2	1	0	9
Double valve	55	26	79	42	202
Triple valve	6	5	25	4	40
Bentall + other complex	8	2	22	1	33
Total	262	242	333	261	1098

CABG, Coronary artery bypass grafting.

plegia. Furthermore, the rate of administration of cardioplegia (continuous or intermittent) seemed to matter more than the means of administration (antegrade or retrograde).

In our institution, before November 7, 1994, we used antegrade, single-shot cold crystalloid cardioplegia for all isolated valves or valves combined with coronary bypass operations. At this date, we switched to continuous cold retrograde blood cardioplegia. Because all the patients were operated on at one institution by one surgeon (W.F.) and because the patient population was not supposed to have changed dramatically over time, we decided to analyze, in a retrospective way, early outcome in more than 1000 cardiac valve operations. The objective of the study was to ascertain whether the use of continuous retrograde blood cardioplegia improved our results in terms of hospital mortality.

Methods

Patient Population

The study consists of 1098 consecutive adult patients operated on by one surgeon (W.F.) at the KULeuven between November 4, 1991, and September 18, 1997. Nine hundred thirty-eight underwent primary operations, and 160 underwent reoperations. All patients undergoing valve surgery solely or combined with coronary bypass grafting were included. The type of valve surgery and its distribution between the groups is listed in Table 1. Excluded were interventions with deep hypothermia and circulatory arrest, cardiac transplantations, and non-valve-related operations. Twenty percent of the valve procedures were reconstructions.

From November 4, 1991, until November 6, 1994, all patients ($n = 504$) were operated on with antegrade cold hyperkalemic crystalloid cardioplegia⁸ combined with topical cooling of the heart. From November 7, 1994, until September 18, 1997, all patients ($n = 594$) were operated on with retrograde cold blood cardioplegia. The distribution of the type of interventions did not significantly differ between the patient populations (ie, the crystalloid or blood cardioplegia groups ($P > .05$)). However, there was a tendency to operate on more double-, triple-, and complex valve cases in the most recent series. Also, patient characteristics differed between the groups: New York Heart Association (NYHA) function class, body mass index (BMI), incidence of pulmonary hypertension, and arterial hypertension were higher in the blood cardioplegia group, and incidence of angina was lower ($P < .05$).

Cardioprotective Methods

As mentioned above, single-shot crystalloid cardioplegia was used before November 6, 1994, in 504 consecutive patients. This hyperkalemic cardioplegic⁹ solution was delivered only by means of antegrade infusion in the aortic root until septal temperature reached 8°C. A minimum of 800 mL was used. Cooling of the heart was maintained by means of topical application of slush ice. The crystalloid cardioplegia was basically an oxygenized hyperkalemic solution. General cooling was applied to a rectal temperature of 28°C. No multidose methods were used. In cases of significant aortic regurgitation, direct coronary perfusion was used.

After November 6, 1994, retrograde blood cardioplegia was used in 594 consecutive patients. A mixture of 3 volumes of blood and one volume of crystalloid cardioplegia⁹ was infused at a temperature of 10°C through the coronary sinus at a rate of 300 mL/min until the septal temperature reached 15°C and cardioplegic arrest was obtained. Then the infusion rate was diminished to a minimum dose, allowing continuous cardiac arrest. General cooling was applied to 28°C.

Statistical Methods

χ^2 Tests and Student unpaired t tests were used to evaluate differences between the blood and crystalloid cardioplegia groups in terms of patient characteristics, operative data, and mortality. χ^2 Tests and Student unpaired t tests were used to evaluate differences between the dead and surviving patients in terms of patient characteristics and operative data. The variables included were age, BMI, sex, left ventricular function, aortic crossclamp time, cardiopulmonary bypass (CPB) time, smoking, diabetes, renal failure, arterial hypertension, pulmonary hypertension, transient ischemic attack, cardiovascular accident, chronic obstructive lung disease, NYHA class, reoperation, myocardial infarction, angina, cardiogenic shock, heart rhythm, aneurysm of ascending aorta, type of operation (valve, valve plus coronary artery bypass grafting, or ascending aorta replacement), aortic valve replacement, mitral valve replacement, tricuspid valve replacement, active infectious endocarditis, associated procedures, emergency status, number of coronary vessels diseased, left main stem lesion, type of cardioplegia, and mortality.

A logistic regression was used to establish the relationship between hospital mortality and the covariates. Because this is not a randomized study, an additional multivariate logistic regression approach was used in which a propensity score model was used to

correct for imbalances in preoperative variables between the groups.¹⁰ Extensive preparative modeling with propensity score models with continuous propensity scores or divided into 5 quintiles, with models based on all or only the most significant differences between the 2 treatment groups, was performed and checked for being multicollinear. After this preparative modeling, a propensity score model was built on the basis of the preoperative variables that differed between the treatment groups at a P value of less than .1 (BMI, sex, CPB, arterial hypertension, pulmonary hypertension, NYHA class, angina, and mitral valve replacement). In the propensity score model we included the 8 main effects and all 2-factor interactions and the squares of each effect, which amounted to 36 variables altogether. We divided the predictive values from this model, the propensity scores, into 5 quintiles. The final model to predict mortality is based on these quintiles together with a stepwise selection of all significantly different variables between the 2 mortality groups (age, BMI, left ventricular function, CPB, aortic crossclamp, renal failure, active endocarditis, NYHA class, reoperations, cardiogenic shock, heart rhythm, aortic aneurysm, type of operation, tricuspid valve replacement, ascending aorta replacement, combined carotid artery surgery, emergency, number of coronary vessels diseased, left main stem lesion, and type of cardioplegia management). All statistical analyses were performed with SAS software.

Results

Operative Characteristics

Mean $\pm$ SD aortic crossclamp time was not different between the treatment groups: 76.7 ± 25.7 minutes in the crystalloid cardioplegia group and 76.0 ± 30.5 minutes in the blood cardioplegia group ($P = .66$). CPB time, however, was significantly shorter in the blood cardioplegia group (110.0 ± 43.6 minutes) than in the crystalloid cardioplegia group (125.5 ± 44.1 minutes, $P < .0001$).

Prediction of Hospital Mortality

Univariate analysis. The relationship between hospital mortality and the following categorical variables was univariately analyzed: blood cardioplegia, age, sex, BMI, diabetes, type of operation, preoperative NYHA function class, left ventricular function score, renal insufficiency, pulmonary hypertension, arterial hypertension, active endocarditis, reoperation, angina, cardiogenic shock, aneurysm of the ascending aorta, carotid artery surgery, emergency conditions, number of coronary vessels diseased, left main stem lesion, crossclamp time, CPB time, and cardiac rhythm. The nonuse of blood cardioplegia resulted in a hospital mortality of 8.5% versus 5.2% when blood cardioplegia was used ($P = .03$). Furthermore, patients who died were significantly older, had worse ventricular function, had longer aortic crossclamp and CPB times, had more renal failure, had more active endocarditis, had a higher NYHA class, had received more often a previous cardiovascular intervention, were more often in cardiogenic shock ($P < .001$), had a pacemaker rhythm preoperatively ($P < .01$), more fre-

quently had aorta ascendens replacements ($P < .02$), needed more tricuspid valve replacement or carotid artery surgery ($P < .01$), had a significantly higher number of diseased coronary vessels ($P < .001$), were more likely to have a left main stem stenosis ($P < .02$), and underwent additional coronary artery bypass grafting surgery ($P < .02$).

Multivariate analysis. Stepwise selection of all significantly different variables between the 2 mortality groups yielded the following effects: CPB time ($\chi^2 = 58.55$, $P < .001$), NYHA class ($\chi^2 = 14.38$, $P < .001$), age ($\chi^2 = 15.13$, $P < .001$), active endocarditis ($\chi^2 = 9.43$, $P = .002$), reoperation ($\chi^2 = 7.15$, $P = .007$), blood cardioplegia ($\chi^2 = 6.03$, $P = .014$), and renal failure ($\chi^2 = 5.51$, $P = .019$). As a result, our final model to estimate mortality will contain these variables: CPB time, age, NYHA class, active endocarditis, reoperation, renal failure, and blood cardioplegia. We then add the propensity score quintiles in the model, where we try to correct for the nonrandomization.

The addition of the quintiles does not change the model very much: the R^2 augments from 0.2769 to 0.2965, the parameter estimates are almost the same in both models, the Hosmer and Lemeshow test indicates that the model has a good fit (0.1436), and there is no multicollinearity in the model. For the analysis of maximum likelihood estimates, see the Appendix.

First, we should remark that the stepwise selection mechanism chose blood cardioplegia as a significant predictor of mortality out of 20 possible variables. This variable has a P value of .020 and is thus highly significant in predicting mortality. Although we corrected for the effects of age, CPB time, NYHA class, reoperations, renal failure, and active endocarditis on mortality and, moreover, we balanced the treatment groups for a whole range of variables with the propensity score, we still find a significant treatment effect.

The odds of mortality when being operated on with blood cardioplegia are 44% of the odds of mortality when operated on with crystalloid cardioplegia. Therefore patients being operated on with crystalloid cardioplegia have a more than double chance of dying after valve surgery than if blood cardioplegia is used. The 95% confidence interval for this odds ratio is 0.218 to 0.876.

Discussion

These results show that hospital mortality in valve operations and combined valve and coronary bypass operations can be influenced by the choice of the myocardial protection technique. In a comparable study in mainly coronary bypass operations, Loop and colleagues⁹ could not show this effect, although a significant reduction in morbidity was demonstrated with the use of blood cardioplegia. Our study shows that in absolute figures hospital mortality is reduced from 8.5% to 5.2% in the cohort of patients operated on with blood cardioplegia instead of crystalloid cardioplegia. The multivariate analysis revealed the use of retrograde blood

cardioplegia as an independent predictor of hospital mortality, with an odds ratio of 0.44 and a 95% confidence interval of 0.218 to 0.876. Therefore in the worst case patients being operated on with blood cardioplegia have a reduced chance of mortality of greater than 10% and, in the best case, a reduction of almost 80%. This means that independent from any other factor, blood cardioplegia reduces hospital mortality by approximately 50%. In addition to this, other independent factors increasing hospital mortality are age, NYHA function class, CPB time, active endocarditis, reoperations, and renal failure. Most of these factors were already identified earlier.¹¹

Another interesting finding is that in the univariate analysis aortic crossclamp time, duration of CPB, and the complexity of the operation are significantly related to hospital mortality. An isolated (single or multiple) valve procedure has an overall hospital mortality of 4.3%, and a combined valve and coronary bypass operation has a mortality of 7.8% when the main stem is normal and a mortality of 13.6% when the left main stem is involved. In the multivariate analysis, however, aortic crossclamp time and type of operation are no longer significant predictors of hospital mortality.

It must be noted that the addition of propensity scores did not change the conclusions of the present study. The magnitude and significance of the effects of the influencing factors barely changed. No additional predictors were found, nor were predictors deleted from the model with or without propensity score quintiles included.

In addition to the choice of crystalloid or blood cardioplegia, other factors can differ between current cardioplegia techniques. These involve temperature, intermittence of delivery, and direction of flow. Two different routes of application are available, antegrade and retrograde, as well as the combination of both. Although retrograde cardioplegia is increasing in popularity, concerns have been raised about the adequacy of perfusion of the right ventricle. It was shown by Menasché and coworkers¹² and our group¹³ that right ventricular function is adequately preserved after coronary sinus cardioplegia. Furthermore, we could show that in the presence of coronary artery obstruction, retrograde delivery was superior to antegrade delivery.¹⁴ However, Arom and associates¹⁵ evaluated the 2 different routes of cardioplegia in more than 7000 patients and found that retrograde cardioplegia alone provides myocardial protection and safety that is just as good as that provided by an antegrade-retrograde approach in either low-risk or high-risk patients.

Controversy still exists as to whether blood cardioplegia should be warm or cold. In a large randomized trial in 1700 coronary bypass operations, warm versus cold antegrade blood cardioplegia was compared, and a favorable cardiac outcome with warm heart surgery was demonstrated.⁴ In

another randomized trial involving 1001 patients, continuous warm blood cardioplegia was shown to have similar mortality and cardiac outcome as antegrade cold crystalloid cardioplegia, but strokes and total neurologic events were greater in the warm cardioplegia group.¹⁶ In another clinical study it was proposed that optimal cardioplegia might actually be tepid (29°C).⁷

Cardioplegia was initially developed not only to protect the myocardium but also to create a quiet and bloodless surgical field. Continuous blood cardioplegia has a serious disadvantage because of limited visibility. This resulted in widespread use of the intermittent instead of continuous application of blood cardioplegia. However, it was shown¹⁷ that continuous cold blood cardioplegia results in fewer cardiac events, better left ventricular performance, and a marked improvement of right ventricular function in comparison with similar solutions of blood cardioplegia administered intermittently, independent of their means of delivery. In practice, uninterrupted delivery of blood cardioplegia is hardly possible, and therefore most procedures are done with intermittent cardioplegia delivery. This is also the case in our operations, although cardioplegia was never interrupted for longer than 10 minutes. In warm blood cardioplegia it is important that any single period of ischemia (ie, time off cardioplegia) is limited to less than 14 minutes because otherwise, adverse clinical events increase significantly.¹⁸

Basically, in coronary bypass surgery a significant lower mortality with the use of cold⁹ or warm^{3,5} blood cardioplegia than with the use of antegrade cold crystalloid cardioplegia could not be shown, in either historical⁹ or randomized clinical trials.^{3,5} In contrast, our study shows a clear influence of the type of cardioprotection on hospital mortality in valve procedures and combined valve and coronary bypass procedures. This was indicated by the findings of Chitwood and colleagues,¹⁹ who described, in an uncontrolled study of 194 patients undergoing complex cardiac procedures, a 30-day mortality rate of 3.1% with combined antegrade and retrograde cold blood cardioplegia.

In conclusion, we found that patients undergoing valvular cardiac surgery who received continuous retrograde blood cardioplegia had lower perioperative mortality than patients receiving single-dose antegrade crystalloid cardioplegia. However, the association between the use of blood cardioplegia and better results does not imply a causal relationship and certainly does not exclude the influence on hospital mortality of recent overall improvements in cardiac surgery, which cannot be traced by means of sophisticated statistical techniques.

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Appendix. Analysis of maximum likelihood estimate

Parameter	Model with propensity score quintiles				Model without propensity score quintiles			
	Estimate	SE	χ^2	$P > \chi^2$	Estimate	SE	χ^2	$P > \chi^2$
Intercept	-11.8038	1.9394	37.0435	<.001	-12.1844	1.8871	41.6879	<.001
Age	0.1071	0.0251	18.1871	<.001	0.1060	0.0246	18.5181	<.001
CPB	0.0148	0.0033	20.1666	<.001	0.0148	0.0032	22.0293	<.001
NYHA class + 1	0.8906	0.3881	5.2646	.022	1.0934	0.3697	8.7449	.003
Reoperation + 1	0.8693	0.3301	6.9349	.008	0.8343	0.3268	6.5187	.011
Blood cardioplegia	-0.8278	0.3546	5.4501	.020	-0.8508	0.3308	6.6154	.010
Quintile 5	-0.2618	0.6167	0.1802	.671				
Quintile 4	-0.5072	0.4991	1.0326	.310				
Quintile 3	-0.7925	0.4758	2.7745	.096				
Quintile 2	-0.8532	0.4676	3.3289	.068				
Renal failure	1.1400	0.5852	3.7947	.051	1.2532	0.5649	4.9217	.0265
Active endocarditis	2.4752	0.8377	8.7317	.003	2.2629	0.8434	7.1990	.007

For explanation of the used statistical methods and variables, please see "Statistical Methods" section and "Prediction of Hospital Mortality: Multivariate Analysis" section. CABG, Coronary artery bypass grafting.