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Institutional report - Cardiac general

Surgical ventricular reconstruction with different myocardial protection strategies. A propensity matched analysis☆

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Abstract

The aim of this study is to compare outcomes of patients undergoing surgical ventricular reconstruction (SVR) with normothermic cardiopulmonary bypass (CPB) and beating heart or hypothermic CPB and cardioplegic arrest. Between 2001 and 2008, 588 patients underwent SVR. A propensity score matching was performed and 91 matched pairs were created: group 1 (G1) operated with normothermic CPB and beating-heart technique, and group 2 (G2) operated with hypothermic CPB and cardioplegic arrest. Mean age was 62 ± 9 years in G1 and 63 ± 10 years in G2 [not significant (NS)]. Average follow-up was 42.7 ± 26 months (range 1–72). Major cardiac and cerebro-vascular events (MACCE) were assessed. Thirty-day mortality was 4% in G1 and 5% in G2 (NS). Kaplan–Meier survival at six years was 79 ± 4% and 72 ± 9% (NS) and freedom from MACCE was 82 ± 4% and 83 ± 7% in G1 and G2, respectively (NS). Left ventricular volume reduction, ejection fraction and New York Heart Association (NYHA) class improvement were significant in the overall population; no significant differences were found between groups. The following independent risk factors for cardiac death were identified: mitral valve regurgitation, surgery <3 months from myocardial infarction, NYHA class III–IV. This study showed that outcomes following SVR are not affected by myocardial protection strategies neither in cardiac function and clinical status nor in survival.

Keywords: Left ventricle; Myocardial remodeling/reshaping/ventriculectomy; Myocardial protection/cardioplegia

1. Introduction

Surgical ventricular reconstruction (SVR) for dilated ischemic cardiomyopathy has proved favorable in clinical and hemodynamic results [1]. This procedure is aimed at reducing left ventricular (LV) volumes and restore geometry. An important issue in this particular population of patients is represented by the techniques of myocardial protection adopted during surgery. In fact, it has been demonstrated that hearts affected by ischemic dilatation undergo a 'vascular remodeling phenomenon' characterized by narrowing of the vessel wall lumen, diminution in the number of vessels and lengthening of conductance vessels [2]; in such circumstances the normal myocardial and, in particular, endocardial flow distribution is severely impaired. Thus, myocardial protection becomes crucial in order to reduce the risk of low cardiac output syndrome that represents a major cause of perioperative mortality in these patients [3].

SVR can be carried out with different myocardial protection strategies: hypothermic cardiopulmonary bypass (CPB) and cardioplegic arrest of the heart or normothermic CPB and beating heart. It has not been established whether different myocardial protection strategies could affect patients' outcomes. The aim of this propensity-matched study was to compare early and long-term results of patients undergoing SVR with different myocardial protection strategies in terms of: survival, freedom from major cardiac and cerebrovascular adverse events (MACCE), cardiac function and clinical status.

2. Materials and methods

We reviewed all 588 consecutive patients who underwent SVR at two cardiac surgery divisions from January 2001 to December 2008. Of these, 115 (20%) underwent SVR with the beating heart and 473 (80%) underwent SVR with cardioplegic arrest. Informed consent was obtained prior to surgery for all patients. A propensity-score analysis was performed and 91 matched pairs were created; they represent the population of our study; group 1: SVR with beating heart; group 2: SVR with cardioplegic arrest. Data were prospectively collected in the institutional database of each center (based on the same dataset) and retrospectively analyzed.

Preoperative variables included in the propensity analysis were: age, sex, time from last acute myocardial infarction

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(AMI), body surface area (BSA), systemic arterial hypertension, hypercholesterolemia, diabetes, chronic kidney failure, reoperations, mitral regurgitation (MR), ejection fraction (EF), coronary artery bypass grafting (CABG) and left ventricle end-systolic volume index (LVESVI). (Propensity score c-index: 0.91.) Preoperative clinical and echocardiographic characteristics of each group are summarized in Table 1. Mean age was 61.9±9 years in group 1 and 63.2±10 years in group 2 [not significant (NS)]. The two groups appeared to have a similar preoperative profile, in particular EF, cardiovascular risk factors and LV dimensions were not statistically different. However, group 1 had a higher incidence of mitral valve regurgitation (55 patients, 60% vs. 22 patients, 24%; $P=0.02$) and a higher proportion of patients in New York Heart Association (NYHA) functional class III–IV (59 patients, 65% vs. 45 patients, 49%; $P=0.03$).

2.1. Surgery

Indications for surgery were ischemic dilated cardiomyopathy with the presence of large antero-septal akinetic or dyskinetic LV aneurysms, wall motion abnormalities together with symptoms of congestive heart failure (CHF), angina and ventricular arrhythmias.

SVR is a refinement of the Dor procedure and it has been extensively described previously [4]. All patients received a standard cannulation (ascending aorta, right atrium). Group 1 patients underwent normothermic CPB and beating heart surgery with a target mean perfusion pressure of 70 mmHg while in group 2 a moderately hypothermic CPB was performed and myocardial protection was achieved with intermittent doses (every 20 min) of cold blood cardioplegia. Mitral valve repair, when needed, was performed via the ventricular opening with a trigone-to-trigone stitch on the posterior annulus or with an annular ring implantation through the left atrium.

2.2. Follow-up

Patients who were discharged after surgery underwent clinical and echocardiographic assessment early after the operation and on a regular basis thereafter at our outpatient clinics. Echocardiography was performed at both institutions by the same physician with an iE 33 (Royal Philips Electronics, Amsterdam, The Netherlands) or with a GE Vivid 7 (General Electrics, USA) cardiac ultrasound scanner according to the American Society of Echocardiography guidelines. Those who were not able to reach our hospital (12 patients, 6 in each group) were followed-up by a telephonic interview with patients and with their referring cardiologist (or general practitioner) and a copy of the last available echocardiographic examination was obtained via email or fax. Mean follow-up was 42.7±26 months (range: 1–72) and was 100% complete.

2.3. Statistical analysis

Categorical variables are expressed as percentages and continuous variables are expressed as means±standard deviation (S.D.). All statistical analyses were performed with SPSS software (SPSS Inc, Chicago, IL, USA). The propensity score was estimated by a logistic regression model for each patient. Matching using caliper of width 0.2 the S.D. of the logit of the propensity score was performed according to Austin's suggestions [5]. The baseline characteristics and hospital outcomes for the two groups were compared by using χ^2 or Fisher exact tests for categoric data and Mann–Whitney *U*-test for continuous variables. Long-term survival and freedom from adverse events were analyzed by Kaplan–Meier survival curves. Comparison between group outcomes was carried out taking into consideration the matched nature of the propensity score-matched sample. In particular, Kaplan–Meier survival curves were compared by the Klein and Moeschberger test; paired *t*-test or Wilcoxon signed rank test were used for continuous variables and Mc Nemar test was used for binary (dichotomous) variables. Independent risk factors for hospital mortality were identified with a paired logistic regression analysis.

3. Results

Associated CABG was performed in 87 (96%) and 88 (97%) patients in group 1 and in group 2, respectively (NS). Mitral valve repair was performed more frequently in group 2 (10 patients, 11% vs. 3 patients, 3%; $P=0.04$) while periopera-

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Table 1
Preoperative clinical characteristics

	Beating ($n=91$)	Cardioplegia ($n=91$)	*P*-value
Age (years)	61.9±9	63.2±10	NS
Sex (Male)	70 (77%)	71 (78%)	NS
Arterial hypertension	47 (52%)	47 (52%)	NS
Diabetes	32 (35%)	33 (36%)	NS
BSA	1.85±0.18	1.83±0.18	NS
Previous cardiac surgery	2 (2%)	3 (3%)	NS
Hypercholesterolemia	41 (45%)	46 (51%)	NS
Time from AMI (months)	40.8±52.1	41.9±75.6	NS
LVEF	34.2±10.5%	34.9±8.4%	NS
LVESVI (ml/m^2)	74.5±37.7	69.8±29.6	NS
Chronic kidney failure	9 (10%)	6 (7%)	NS
Mitral valve regurgitation (3–4+)	55 (60%)	22 (24%)	0.02
Previous CVA	0	0	NS
NYHA III–IV	59 (65%)	45 (49%)	0.03

BSA, body surface area; AMI, acute myocardial infarction; LVEF, left ventricle ejection fraction; LVESI, left ventricle end-systolic volume index; CVA, cerebrovascular accident; NYHA, New York Heart Association; NS, not significant.

tive Intra-aortic balloon pump (IABP) implantation was higher in group 1 (27 patients, 30% vs. 10 patients, 11%; $P=0.002$). In particular, in group 1 IABP implantation was mainly preoperative due to the different policy adopted in one of the two centers, thus this difference does not reflect a higher incidence of post-cardiotomy failure in group 1. The incidence of postoperative major ventricular arrhythmias (2 patients, 2% vs. 4 patients, 4%; NS), acute kidney failure defined by the Risk-Injury-Failure-Loss of kidney function-End-stage kidney disease (RIFLE) [6] classification (11 patients, 13% vs. 4 patients, 5%; NS) and cerebrovascular accidents (CVA) (2 patients, 2% in each group, NS) was not different between groups. Early mortality occurred in four patients in group 1 (4%) and five patients in group 2 (5%) (NS). Causes of early mortality in group 1 were: low output syndrome in two patients, sepsis and mesenteric ischemia in one patient each; in group 2 were: low cardiac output in three patients, mesenteric ischemia and sepsis in one patient each.

Overall survival was 79%±4% and 72%±9% (NS) in group 1 and 2, respectively, 72 months after surgery (Fig. 1). Freedom from MACCE [all-cause death, CVA, documented MI, percutaneous coronary intervention (PCI)/CABG] was 82%±4% and 83%±7% (NS) in group 1 and 2, respectively, 72 months after the operation (Fig. 2). Echocardiographic results are shown in Table 2. All echocardiographic parameters showed a significant improvement in each group while the comparison between groups did not show significant differences apart from the incidence of postoperative MR. In particular, in the two groups the percentage of severe MR reduction is similar (group 1: from 55 to 11 patients, 80% reduction; group 2: from 22 to 4 patients, 82% reduction); group 1 had a higher incidence of preoperative severe MR and this proportion is maintained postoperatively (group 1: 11 patients, 12% vs. group 2: 4 patients, 5%, $P=0.02$). At follow-up, we observed a significant improvement of the following parameters compared to the preoperative measurements: LVESVI (group 1: from 74.5±37.7 to 51.6±23.7 ml/m², $P<0.001$; group 2: from 69.8±29.6 to 49.2±20 ml/m², $P=0.003$); EF (group 1: from 34.2%±10.5% to 39.4±10.4; $P=0.02$; group 2: from 34.9%±8.4% to 40.8%±8.8%; $P=0.01$).

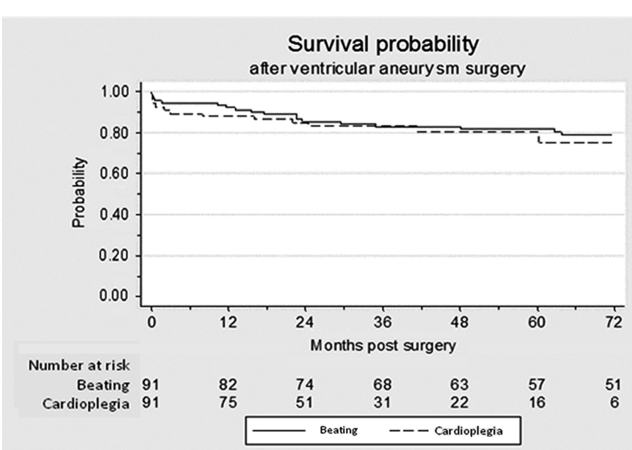

Fig. 1. Kaplan–Meier survival curve in group 1 (beating) and in group 2 (cardioplegia).

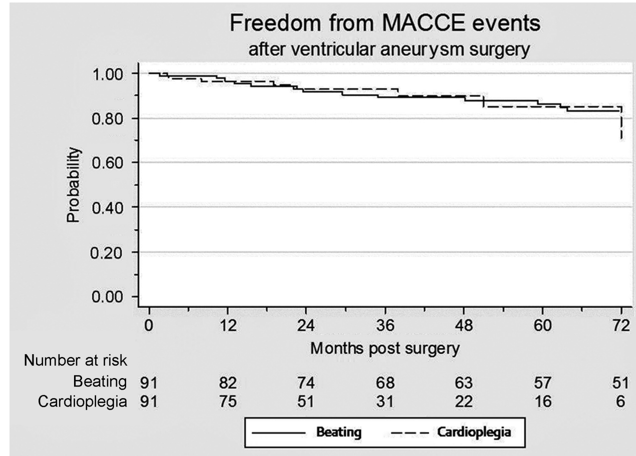

Fig. 2. Kaplan–Meier freedom from major adverse cardiac and cerebro-vascular events (MACCE) in group 1 (beating) and in group 2 (cardioplegia).

Patients experienced a significant improvement of their symptoms after surgery in both groups. In fact, preoperatively patients with NYHA class III–IV were 65% in group 1 and 49% in group 2 while at follow-up they were only 8% in both groups. Multiple regression analysis, performed on the entire population of 182 patients, identified the following variables as independent predictors for hospital mortality: preoperative mitral valve regurgitation [odds ratio (OR): 8.1, OR 95% confidence interval (CI): 2.7–24.1, $P=0.002$]; time from AMI <3 months (OR: 3.2, OR 95% CI: 1.2–8.8, $P=0.01$); preoperative NYHA class III–IV (OR: 3.9, OR 95% CI: 1.1–13.6, $P=0.04$).

4. Discussion

Surgical treatment of severe dilated ischemic cardiomyopathy is based on the so-called 3V approach: coronary revascularization (vessel), mitral valve repair (valve) and LV reconstruction (ventricle). This strategy has proved good results in terms of relief from symptoms of CHF, reduction of LV volumes and improvement in EF [1]. This surgical strategy, combined with optimal medical management of heart failure, represents the therapeutic option to heart failure [7]. The issue of myocardial protection during surgery for SVR has several implications related to the surgical technique itself and to the anatomic and functional modifications that occur in an ischemic dilated heart. In fact, SVR is performed in an open and non-vented left-ventricle where a traction on the edges is accomplished in order to have a good visualization of the LV cavity; this situation is different from the normal vented and collapsed heart. Kostelec and colleagues [8] developed an experimental pig model of heart failure and studied transmural and endocardial flows in normal and failing hearts both in vented and open conditions with continuous flow (beating heart) and with cardioplegic delivery in order to simulate a conventional heart operation and a procedure of SVR. They found that a vascular remodeling phenomenon occurs in dilated hearts mainly due to a narrowing of the vessel wall lumen, reduction of vessels number and lengthening of conductance vessels. These structural modifications lead

Table 2
Echocardiographic results

	Beating preoperative	Beating postoperative	*P*-value	Cardioplegia preoperative	Cardioplegia postoperative	*P*-value	Beating postoperative vs. cardioplegia postoperative
LVEDD (mm)	61±8.6	56±9.5	0.02	63.8±9	58.3±15	0.01	NS
LVEDV (ml)	200±79.1	146.7±46.4	0.009	191.4±61.2	140±57.3	0.007	NS
LVEDVI (ml/m²)	109.3±43.9	83.2±30.7	0.01	104.6±33.1	75.7±29.1	0.008	NS
LVESV (ml)	133.1±64.9	96.8±44	0.008	127.5±53.4	91.1±39.2	0.01	NS
LVESVI (ml/m²)	74.5±37.7	51.6±23.7	<0.001	69.8±29.6	49.2±20	0.003	NS
LVEF (%)	34.2±10.5	39.4±10.4	0.02	34.9±8.4	40.8±8.8	0.01	NS
SV (ml)	67.6±32.4	56.9±23.9	0.04	63.5±16.9	51.9±20.4	0.02	NS
SVI (ml/m²)	36.8±18.3	31.3±13.6	0.01	34.8±8.5	30±10.6	0.01	NS
MR (3–4+)	55 (61%)	11 (12%)	<0.001	22 (24%)	4 (5%)	<0.001	0.02

LVEDD, left ventricle end-diastolic diameter; LVEDV, left ventricle end-diastolic volume; LVEDVI, left ventricle end-diastolic volume index; LVESVI, left ventricle end-systolic volume index; LVEF, left ventricle ejection-fraction; SV, stroke volume; SVI, stroke volume index; MR, mitral regurgitation; NS, not significant.

to an alteration of flow distribution in open hearts during SVR, in particular cardioplegic delivery reduced flow by 64%. Furthermore, a lower flow at the same pressure of perfusion was observed in dilated ventricles meaning that higher pressures are needed during both cardioplegia delivery and beating heart with continuous perfusion of the coronary arteries. In our study, we did not observe significant differences in clinical and functional results with the beating heart and with the cardioplegic arrest. The propensity score, defined as the conditional probability of being treated given the covariates, can be used to balance the covariates in two groups, and therefore reduce the bias due to the retrospective observational nature of our data. This statistical method was introduced by Rosembaum and Rubin in 1983 [9] and is mainly aimed at estimating treatment effects when treatment assignment is not random. In our study, the propensity matching was performed using 13 preoperative variables and the c-index was 0.91 meaning that the two groups were substantially homogeneous. Athanasuleas and colleagues on behalf of the RESTORE group investigators [2] analyzed data of SVR performed with the beating heart and with cardioplegic arrest and, after matching for age, EF and NYHA class found no differences in survival rates between the two populations. Maxey and colleagues [10] retrospectively compared beating and cardioplegic SVR and concluded that the beating approach provides no additional advantage over aortic cross-clamp and cardioplegia. After these results coming from different centers and from these considerations it seems likely that, despite experimental data, the two myocardial protection strategies provide similar results. What we have to address now is the choice of the correct technique for each single patient and, in order to achieve this, we need to discuss the main advantages of each myocardial protection strategy. The main advantages of the open beating heart technique are: 1) a better definition of the myocardial scar, 2) better endocardial flow due to the vascular remodeling of the dilated heart, 3) less concerns related to aortic cross-clamp time that makes the learning curve easier. On the other hand, the main advantages of the cardioplegic technique are: bloodless surgical field and arrested heart. Further studies are needed to definitively identify which patients would benefit most either from one technique or from the other.

The finding that time elapsed from an AMI significantly affects surgical outcomes is not surprising since many studies have demonstrated that CABG performed in patients with recent or ongoing acute coronary syndromes carries a higher risk for short-term mortality [11–14]. Miyahara and colleagues found a significant reduction of surgical mortality in patients operated with on-pump beating heart CABG vs. the conventional technique [15].

Limitations are primarily related to the 'two-centers' design of this study. The open-beating technique was mainly performed at San Bortolo Hospital, Vicenza while the cardioplegic technique was mainly performed at San Donato Hospital, Milan. This was made in order to obtain a number of patients suitable for a good propensity matching. The propensity analysis was made to overcome this possible selection bias.

In conclusion, 3V (vessel-valve-ventricle) surgical approach to heart failure can be safely accomplished both with the beating heart technique and with the cardioplegic arrest of the heart; myocardial protection strategy does not seem to affect neither early nor late clinical results after SVR; SVR provides good hemodynamic results regardless of the myocardial protection strategy adopted; time elapsed from AMI seems to significantly affect postoperative outcomes.

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Conference discussion

Dr. J. Pepper (*London, UK*): This is a retrospective analysis of prospectively collected data from two separate units in Milan and Vicenza. The authors should be congratulated on their low operative mortality, as you saw, 4.3 and 5.3%, and excellent survival at six years, 72%, 79%. But we must recall that the comparison is not just between methods of myocardial protection or management but between different surgical teams in different hospitals. So I have several questions.

First of all, why was there a greater frequency of mitral regurgitation in Vicenza, the group that favoured the beating heart approach, which was 61%, compared to Milan, which favoured the cold blood cardioplegic approach where the incidence was 24%? I assume this mitral regurgitation was ischaemic, but I would just like to have confirmation of that. Do the authors think there are any predictors for mitral valve repair that emerged from their study? Thirdly, did they use a core lab for the echo assessment between the two hospitals? And finally, has this study caused either of the surgical teams to choose to alter their myocardial management in these patients?

Dr. D'Onofrio: I will try to answer all of your questions. First of all, you are right, the incidence of mitral valve regurgitation was different between the two groups. We repeatedly reviewed all echocardiographic examinations in order to identify the reasons for this difference. The beating group has a higher incidence of Type III aneurysms that caused a displacement of the papillary muscles. Unfortunately, we do not have a core lab but all echocardiographic examinations were performed by one physician at each institution. Mitral valve regurgitation and mitral valve surgery are one of the most important problems in these patients. We are calling back all our patients for a detailed echocardiographic examination because we would like to understand if there are specific factors able to predict whether a mitral valve should be repaired or not in this particular group of patients.

Actually we have observed that in the two groups there was an 80% reduction of incidence of moderate to severe mitral valve regurgitation after surgery independent of whether the mitral valve was repaired or not. Of course this depends on the reshaping of the left ventricle that brings papillary muscles into a more physiological position. So we would like to understand why and if there are predictors for this. We are currently analyzing these data, so maybe in the future we will be able to answer this question.

Your final question was about the different surgical management, right?

Dr. J. Pepper: Yes. Have you changed your method of management as a result of these studies?

Dr. D'Onofrio: Actually it is too early to answer this question. From this study we know that the results are similar with these two myocardial protection techniques. So what we have to assess now is who are the patients that would benefit most from one technique or from another technique. For example, patients suffering from acute myocardial infarction or acute coronary syndromes would benefit most from the beating procedure rather than the aortic cross-clamp with cardioplegic arrest because of the problems related to ischaemia-reperfusion injury.