Acute hemodynamic and functional effects of surgical ventricular restoration and heart transplantation in patients with ischemic dilated cardiomyopathy

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Objectives: Peak oxygen uptake (VO2) and ventilatory efficiency have prognostic implications in the population with congestive heart failure. This study evaluated quality-of-life functional capacity after the 2 treatment strategies of surgical ventricular restoration and transplantation for severe left ventricular dysfunction of ischemic cause.

Methods: The 75-patient study population (between 2004 and 2006) with severe heart failure included 35 patients undergoing surgical ventricular restoration (mean age, 62.6 ± 8.7 years), sometimes together with coronary artery bypass grafting or mitral surgery, and 40 cardiac transplant recipients (mean age, 55.6 ± 7.7 years). Preoperative and 6-month postoperative function (peak VO2, the anaerobic threshold, and the slope of minute ventilation/carbon dioxide uptake), cardiac catheterization parameters (left and right), and hospital and early outcomes were evaluated.

Results: The 2 groups had comparable baseline functional impairment and experienced similar hospital stay and early outcomes. They also showed similar improvements in left ventricular volume indexes and hemodynamic parameters and sustained significant improvements of median VO2, anaerobic threshold, and minute ventilation/carbon dioxide uptake values.

Conclusions: Both surgical strategies resulted in a significant and comparable improvement of functional capacity at the 6-month evaluation. These early studies must be repeated to determine the long-term benefits of surgical ventricular restoration because maximal VO2 and ventilatory efficiency lose their prognostic survival role after transplantation.

Ischemic left ventricular dysfunction continues to represent a major health care problem because it affects approximately two thirds of the patients referred for congestive heart failure. Limitations in organ procurement severely restrict the use of heart transplantation, make listing criteria increasingly selective, and strongly support the development of alternative surgical approaches. Dor’s pioneering experience1 has established the role of surgical ventricular restoration (SVR) to treat ischemic cardiomyopathy after the nidus of a large myocardial scar causes progressive cardiac dilation of remote muscle from adverse remodeling. SVR improves ventricular performance and functional class, with a gratifying 5-year survival and low rate of rehospitalization for heart failure,2,3 but the merits, indications, and long-term efficacy of this strategy remain under intense investigation.

Our prior study compared SVR and transplantation treatment of severe ischemic dilated cardiomyopathy4 and showed that ventricular reconstructive surgery provided a significant improvement in cardiac function, allowing for a better quality of life and a lower risk of rehospitalization than transplantation but higher hospital mortality. Absent from that analysis were measurements after cardiopulmonary exercise testing.
(CPET), which is a noninvasive way of evaluating patients with heart failure and is used consistently in the assessment for cardiac transplantation. Values gleaned from analyzing these test results have been a guide to treatment strategy choices used to determine long-term survival but have not yet been compared with values achieved after SVR for dilated ischemic cardiomyopathy. The goal of evaluating patients with end-stage ischemic cardiomyopathy is to determine how oxygen uptake (VO2) during exercise is changed after treatment with either ventricular restoration or heart transplantation at the 6-month postoperative interval.

Materials and Methods

Study Design

This is a single-center prospective study analyzing the experience over 18 months with surgical treatment of ischemic cardiomyopathy. From January 2004 through June 2006, 200 patients were operated on for ischemic cardiomyopathy at the Department of Cardiothoracic Sciences, Second University of Naples, “V. Monaldi” Hospital. Inclusion criteria for the present study were end-stage ischemic cardiomyopathy, defined according to Burch and colleagues; end-systolic volume index of 50 mL/m2 or greater; and an ejection fraction (EF) of 35% or less, excluding cases of isolated transplantation. Choice of surgical treatment was based on morphologic and functional cardiac parameters, but the SVR exclusion criteria, according to Dor, included (1) severely decreased right ventricular function, (2) lack of ischemic areas suitable for revascularization, and (3) lack of contraction improvement of basal segments during echo-dobutamine. Conversely, age greater than 65 years was a relative contraindication to heart transplantation because of the shortage of available donor organs and the high likelihood of waiting-time decompensation.

Surgical Procedures

All the restoration procedures were performed by means of a median sternotomy using mild hypothermic (28°C) cardiopulmonary bypass, aortic crossclamping, and myocardial protection with intermittent St Thomas I perfusion. The strategy included (1) endoventricular patch plasty according to the principles of Dor’s technique with our modifications, (2) repair of the regurgitant mitral valve (28.5%) with either Alfieri or Bolling techniques, and (3) coronary bypass grafting to provide complete revascularization (2.1 ± 0.9 grafts in 32 patients). Map-guided cryoablation was performed in 8.5% of patients with preoperative ventricular arrhythmias. Prophylactic intra-aortic balloon counterpulsation was instituted just before induction of anesthesia in 22.8% of patients with pronounced congestive heart failure to achieve intraoperative hemodynamic stability and prevent low postoperative cardiac output. Outpatient follow-up management included maintenance of an optimal heart failure regimen including β-blockers and angiotensin-converting enzyme inhibitors, which were administered by our clinic physicians.

During transplantation, the donor heart was procured by using standard techniques and was protected with 2 L of cold (4°C to 8°C) Celsior solution (Genzyme Corporation, Cambridge, MA) and topical saline slush. Excised grafts were then immersed in 1 L of cold Celsior solution and stored on ice in a closed cardiac storage container for transportation. All recipients underwent standard orthotopic transplantation by using the atrial anastomotic technique. Principles of posttransplantation care and immunosuppressive regimens have been described elsewhere.

Cardiac Rehabilitation Program

All patients in both groups enrolled in a comprehensive postoperative exercise rehabilitation program based on protocols designed by the European Heart Failure Training Group and the American Heart Association Committee on Exercise, Rehabilitation, and Prevention.

CPET and Heart Catheterization

Patients underwent exercise testing and heart catheterization during the preoperative evaluation and 6 months after the surgical procedure. Endomyocardial biopsy demonstrating the absence of acute rejection was required in patients undergoing heart transplantation before undergoing CPET postoperatively. All patients performed upright bicycle exercise to maximum tolerance with the use of a progressively increasing work rate at 10 to 20 W/min after a period of resting and unloaded pedaling, as recommended by Buchfuhrer and associates. Patients were encouraged to exercise until symptoms were intolerable. Investigator-determined exercise end points were severe ventricular tachycardia of 5 beats or greater, high degree of atrioventricular block, ST-segment depression of 3 mm or greater, systolic blood pressure of 250 mm Hg or greater, or progressive decrease in blood pressure. Breath-by-breath gas exchange measurements were performed with a Cosmed Quark (PFT Ergo, Rome, Italy) metabolic cart. VO2, carbon dioxide output, tidal volume, and breathing rate were measured. Blood gases (PaO2 and PaCO2) and pH were measured at rest and shortly before the end of exercise with the use of arterialized capillary blood samples.

From the above data, minute ventilation (V̇E), and the ventilatory equivalents for CO2 were calculated. Peak VO2 was determined as the highest VO2 achieved during exercise. The anaerobic threshold (V̇O2 anaerobic threshold) was measured by using the V-slope method. Typical changes in ventilatory equivalents and end-tidal gas concentrations were examined to search for agreement in cases that were questionable with regard to the precise V̇O2 anaerobic

Abbreviations and Acronyms

- CPET = cardiopulmonary exercise testing
- EF = ejection fraction
- NYHA = New York Heart Association
- SVR = surgical ventricular restoration
- VE = minute ventilation
- VO2 = oxygen uptake
threshold values. The $V_{E}$ versus $V_{CO2}$ slope was calculated by means of linear regression, excluding the nonlinear part of the data after the onset of ventilatory compensation for metabolic acido-
sis. The 6-minute walking distance, a test widely used for its ease of
administration and reproducibility, was not performed in the present
study. However, the CPET is noninvasive, more discriminating, and
above all more useful in comparing different treatment groups in
that it is more sensitive in detecting even small differences in exercise
capacity.13

The most recent right heart catheterization was used to measure
preoperative cardiac hemodynamic data: mean pulmonary artery
pressure, systolic pulmonary artery pressure, diastolic pulmonary
artery pressure, pulmonary capillary wedge pressure, cardiac index,
and pulmonary vascular resistance index. The same hemodynamic
parameters were obtained from the postoperative Swan–Ganz cath-
eter measurements. Coronary catheterization and left ventriculogra-
phy were contemporarily performed. Each angiogram was reviewed
in detail, independent of the clinical review. The angiograms were
reviewed by 2 observers familiar with the spectrum of allograft cor-
ony artery disease to arrive at a consensus regarding the subjective
grading of these films; the modified classification proposed by Gao
and coworkers14 was used. Abnormalities were classified to distin-
guish involvement of proximal epicardial large vessels and distal
small vessels (tertiary branches or greater), as well as the character
and extent of luminal encroachment (mild diffuse luminal irregular-
y, focal stenosis, or diffuse vascular obliteration), as defined by
Gao and coworkers.14 The finding of focal angiographic stenosis
of 70% or greater or evidence of diffuse large- or small-vessel oblit-
eration defined “severe” disease. The images of left cine ventriculo-
grams were digitized to obtain the left ventricular volume by means
of biplane analysis. The left ventricular end-systolic volume index,
left ventricular end-diastolic volume index, and EF were calculated.

Follow-up and Statistical Analysis
All preoperative, hospital, and follow-up data (total follow-up, 1182
months per patient; mean follow-up of group A, 16.9 ± 6.9 months;
mean follow-up of group B, 17.4 ± 8.5 months) were recorded in
a dedicated electronic database. Hospital mortality was defined as
death before the 30th postoperative day. SPSS software (version
10.1; SPSS, Inc, Chicago, Ill) was used for statistical analysis.
Data were expressed as means ± standard deviations for continuous
variables or counts and percentages for categorical variables. Anal-
ysis of variance and $\chi^2$ Pearson or Fisher exact tests were used for
statistical evaluation of the differences between groups. Two-tailed
paired $t$ tests were used for intragroup comparisons of hemodynamic
and functional data (before treatment vs after treatment). Nonpara-
metric tests were used in case of skewed distribution.

The authors had full access to the data and take responsibility for
its integrity. All authors have read and agree to the manuscript as
written.

Results
Preoperative Clinical Characteristics
Table 1 presents the preoperative clinical and demographic
features of the patient population. Those offered orthotopic
transplantation were younger because of the age restriction
of transplant candidacy and had more prior cardiac oper-
ations. Both groups had a similar sex distribution, incidence

| TABLE 1. Preoperative demographics and clinical features |
|-------------------|-------------------|-------------------|
| Group A (35 patient) | Group B (40 patients) | $P$ value |
| Age (y) | 62.6 ± 8.7 | 55.6 ± 7.7 | .001 |
| Female sex | 10 (28.6%) | 12 (30%) | NS |
| Diabetes | 13 (37.1%) | 15 (37.5%) | NS |
| Prior CABG | 10 (28.6%) | 22 (55%) | .013 |
| Preoperative NYHA | 3.2 ± 0.2; 9 | 3.3 ± 0.18; 29 | NS |
| Preoperative EF (%) | 27.1 ± 4.5 | 25.3 ± 7.5 | NS |
| Presence of MR | 37.1% | 47.5% | NS |
| MR = grade 2 | 28.5% | 42.5% | NS |
| Time to operation (mo) | 42.9 ± 56 | 40.2 ± 51.7 | NS |

$NS$, Not significant; $CABG$, coronary artery bypass grafting; $NYHA$, New York Heart Association; $EF$, ejection fraction; $MR$, mitral regurgitation.

Postoperative Data and Hospital and Postdischarge Outcomes
Hospital mortality was not different between the 2 treatments
(11.4% vs 7.5%). After SVR, mortality was from low cardiac
output in 3 patients and multiorgan failure in 1 patient. The 3
posttransplantation deaths were due to acute graft failure in 1
patient, pneumonia in 1 patient, and multiorgan failure in 1
patient. Global systolic function improved postoperatively in
survivors in both groups. The EF increased from 28.1% ±
7.3% preoperatively to 34.5% ± 9.3% postoperatively in
group A ($P < .001$) and from 27.3% ± 6% to 49.8% ±
7% in group B ($P < .001$). During follow-up, one sudden
death occurred after SVR, and 1 death from acute rejection
occurred after transplantation. Two patients in group A and
1 in group B experienced heart failure recurrence. Of these,
the patients undergoing SVR and experiencing heart failure recurrence had very severe preoperative ventricular enlargement
associated with mitral regurgitation, poor coronary
targets for revascularization, or both.

CPET and Cardiac Catheterization Analysis
Similar symptom improvement occurred in both groups
because mean postoperative NYHA class decreased from
3.3 ± 0.2 and 3.2 ± 0.18 to 1.7 ± 1.1 and 1.3 ± 0.3, respec-
tively. Left heart catheterization disclosed no evidence of
allograft coronary disease in heart transplant recipients. All
bypass grafts except 1 were patent in group A. Table 2 sum-
marizes cardiac catheterization data, CPET results, and
Weber–Janicki class assessment and medical therapy. In
comparison with preoperative status, surgical intervention
confirmed a significant and homogeneous functional benefit.
in both groups, as shown in Table 2. However, transplant recipients required significantly less cardiovascular therapy but needed an immunosuppressive regimen.

### Discussion

This prospective review, evaluating functional recovery of patients affected by ischemic cardiomyopathy treated either with heart transplantation or left ventricular restoration, showed similar improvement with both methods, thereby implying that absence of donor heart availability does not diminish the performance benefit gained from using the patients’ own tissues to surgically reconstitute cardiac size and shape. The most important findings show that both strategies (1) result in similar hospital and early outcomes and (2) confer a comparable functional parameter improvement after measurement by means of cardiopulmonary exercise and clinical assessment. In this perspective it should be noted that although patients undergoing transplantation were considered unsuitable for any other surgical therapy, many of the patients receiving SVR could have been offered heart transplantation based on their preoperative CPET parameters (mean maximal VO₂, 12 ± 1.3 mL · kg⁻¹ · min⁻¹). However, the degree of CPET performance observed after SVR might imply a significant prognostic benefit based on prior reports in patients undergoing transplantation.⁵,⁶

### Prognostic Role of CPET in Heart Failure

The value of CPET after heart failure is the capacity to place a numeric value on the ability to exercise and thereby convey a more realistic measure of efficiency of cardiac output to supply oxygen for body needs than is available from the more subjective NYHA classification. Of equal importance is that CPET is a pivotal modality in the initial evaluation of patients with advanced heart failure¹⁵ during evaluation for transplantation, yet is infrequently used in heart failure clinics for patients not considered for transplantation. For example, Mancini and associates¹⁶ found that peak VO₂ was the single best predictor of survival in patients considered for cardiac transplantation. Recent studies of ventilatory expired gas parameter show that a high VE/VCO₂ ratio at peak exercise or a high slope at submaximal exercise provides a powerful independent index of poor prognosis.¹⁷ Furthermore, the mortality rate of patients with a maximal VO₂ of 14.5 mL · kg⁻¹ · min⁻¹ or less was twice that of patients whose maximal VO₂ exceeded this value in the Veterans Administration Heart Failure Trial, and this functional test exerted a stronger predicting role than the type of drug treatment.¹⁸

### Effects of SVR and Heart Transplantation on Hemodynamic and CPET Performance

Previous studies have demonstrated that SVR significantly improves EF, left ventricular size, left ventricular shape,
hemodynamic parameters, and NYHA functional status in patients with congestive heart failure. Studies have also shown that SVR improves mechanical dyssynchrony, levels of neurohormones associated with congestive heart failure, cardiac function in high-risk surgical candidates, and myocardial performance in nonischemic areas remote from scars. Each of these factors improves tissue oxygen delivery and is the infrastructure of the reported CPET findings, which, to our knowledge, are the first evidence of significant improvements both in CPET and hemodynamic performance after ventricular restoration. The degree of postoperative dimensional and hemodynamic improvement presented in this series is consistent with prior data and is due to the following surgically induced changes: (1) complete revascularization that includes reperfusion of the upper part of the septum; (2) patient-tailored reduction of ventricular volume by means of exclusion of septal, anterior, and inferior components, together with lowering ventricular wall stress and improving remote zone mechanical efficiency; (3) restoration of the physiologically elliptical left ventricular shape to optimize mechanical efficiency while both avoiding incorrect positioning of the papillary muscles and worsening of diastolic dysfunction; and (4) correction of mitral regurgitation, as described by Menicanti and colleagues.

Despite improvement in survival and symptoms attributable to transplantation, exercise capacity, as assessed by means of CPET, remains markedly impaired when compared with that of healthy individuals and might not be different from that of medically stabilized patients with heart failure. Hence some cardiac transplant recipients, such as those included in the present work, have disappointing exercise performance that impairs quality of life, despite apparently normal resting cardiac function. Responsible mechanisms that limit normal return of peak exercise capacity in this transplant cohort include parasympathetic and sympathetic cardiac denervation that increases resting heart rate, attenuates heart rate response at peak exercise, and delays normalization of heart rate after exercise. Furthermore, diastolic dysfunction and limited cardiac contractile reserve allow contractile impairment to supplement these chronotropic changes, and these mechanical alterations occur simultaneously with altered peripheral circulatory mechanisms in transplant recipients and might be worsened in patients with higher NYHA status in ischemic transplant recipients. These data were determined only 6 months after transplantation and without evidence of secondary coronary disease but directly mirror the Registry of the International Society for Heart and Lung Transplantation, which shows that peak oxygen consumption might lose prognostic significance after transplantation.

Clinical Implications
The significant functional recovery observed in this study might indicate an improved long-term prognosis after SVR surgery because improved oxygen consumption is associated with lower mortality, as shown by Lund and coworkers, who studied the prognostic value of peak VO2 in 227 adults with heart failure who were reevaluated more than 60 days after initial evaluation. Patients whose values improved from a high- or medium-risk Heart Failure Survival Score or peak VO2 values (<10 mL · kg−1 · min−1 and 10–14 mL · kg−1 · min−1, respectively) to lower-risk values (>14 mL · kg−1 · min−1) had 1-year event-free survival rates of 89% and 83% after β-blocker therapy alone and were thereby removed from the transplant waiting list.

Furthermore, transplantation could be safely deferred in patients whose peak VO2 value was 14 mL · kg−1 · min−1 or greater, where their survival exceeded that of patients undergoing heart transplantation. Notably, the mean posttransplantation peak VO2 value of 16 ± 1.5 mL · kg−1 · min−1 was less than the normal value threshold of greater than 18 mL · kg−1 · min−1, which seemed to unfavorably compare with the reports of Leung and associates; however, in that study only one third of patients had ischemic causes, and they were remarkably younger (mean age, 48 years) and had higher preoperative functional capacity (preoperative peak VO2, 16 mL · kg−1 · min−1) than in the present experience.

In our study mean postoperative peak VO2 in patients undergoing SVR was 16 ± 1.5 mL · kg−1 · min−1, thus conferring a lower-risk prognosis to an initially high-risk cohort. Similar better prognosis considerations exist after VE/VCO2 slope analysis because the mean postoperative values in this report are lower than the greater than 34 cutoff known to imply a poor prognosis. The selection of a 6-month interval for the first measurement might provide an early assessment because neuroendocrine changes recover over 1 year, so that subsequent testing is needed to determine whether there is further improvement. SVR also avoids the aforementioned chronotropic and mechanical changes after transplantation, so that these observations suggest that the mortality of patients with ischemic cardiomyopathy can be significantly reduced by means of restoration surgery; remote muscle function might progressively improve, and the risk of secondary coronary disease after transplantation is avoided. Further testing is also essential to determine whether ventricular redilation is prevented because increased ventricular volume will counteract these positive results.

This study compared CPET results of SVR with those of heart transplantation. Another therapeutic option used for specific subsets of patients with dilated cardiomyopathy is resynchronization, and comparative studies could be performed, using VO2 as an end point. To date, in a randomized study, a slight improvement in peak VO2 value has been reported, and a recent study has claimed an increase of peak VO2 value from 13 to 14.8 mL · kg−1 · min−1 at 12 months, which is lower than our 6-month value, but no comparison with other treatment modalities has been carried out.
Study Limitations
This study analyzed the effect of SVR surgery on CPET performance in a small number of patients. Importantly, the improvement of left ventricular function in the patients studied is in close agreement with previous reports from our institution and from larger series, indicating that the patients enrolled in this study are indeed representative. SVR represents a surgical strategy aimed to correct all the anatomic and functional determinants of heart failure in ischemic cardiomyopathy. In doing so, our efforts are directed toward the vessel, valve, and ventricle, so that evaluation of the relative merits of each single operative step on functional and hemodynamic results is hampered, especially because continued medical therapy and the comprehensive rehabilitation program might have contributed to the improvement. The limited study sample prevented us from stratifying patients according to preoperative features (ie, mitral regurgitation, larger ventricles, and viability of remote areas), and the short 6-month follow-up analysis prevents any speculation on left ventricular redilation late after surgical intervention, even though the stability of SVR results is supported by the studies of Dor and colleagues. A longer follow-up (at least 1 year) is also needed to investigate the effects of late neuroendocrine rearrangements after ventricular volume change.

Conclusions
SVR is a comprehensive surgical approach tailored to address all pathophysiologic ventricular geometric factors contributing to heart failure development in ischemic patients, and application of this procedure provided a cohort of hospital survivors displaying the same significant CPET performance and hemodynamic improvement observed in a cohort of patients undergoing transplantation. These results support the hypothesis that direct improvement of cardiovascular function and optimization of ventricular geometry might improve functional capacity by acting on the intracardiac determinants of cardiac dysfunction, together with simultaneous correction of vessel and valve factors. Further studies are required to determine the durability of functional improvement because this favorable response after SVR might imply a long-term survival benefit that is associated with a better quality of life than currently available with either conventional treatments or after the use of cardiac transplantation. These results also need to investigate the effects of late neuroendocrine rearrangements after ventricular volume change.

References


