Myocardial protection during surgical ventricular restoration

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Abstract

Objective: Ventricular restoration is a novel procedure for treating congestive heart failure (CHF). The two important features include a technically correct procedure and adequate myocardial protection. The two protective techniques include conventional cardioplegia and the beating heart.

Methods: This report reviews a RESTORE clinical registry and summarizes background experimental work related to myocardial protection in failing dilated hearts.

Results: The RESTORE registry is reported, where protection is 55% with cardioplegia and 45% with beating heart. The beating method was used more frequently in patients with ejection fraction <30%, end systolic volume 80 ml/m^2, NYHA class >III/IV. Overall survival results favored cardioplegia except for the first 30 days, but after matching patients on age, ejection fraction (EF) and NYHA the beating results and cardioplegic results were comparable. Experimental work evaluated the safety of the beating method in failing diluted ventricles under acute conditions. Supplemental coronary perfusion studies in chronically dilated hearts after tachycardia induced cardiomyopathy were analyzed to show that (a) there was vascular remodeling (less flow at the same pressure in failing hearts with cardioplegic, but not beating delivery; (b) in the open state (used during restoration) subendocardial flow increased in the beating heart, and fell after cardioplegia. These studies were done without ischemia. Conclusions: Cardioplegic delivery for protection is ‘time dependent’ (needing ischemic intervals) while beating nourishment is ‘procedure dependent,’ as continuous perfusion is provided throughout the procedure is suggested. The importance of maintaining high perfusion pressure is emphasized.

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1. Introduction

The two basic considerations that are fundamental to the outcome of all cardiac surgical procedures are technical competence, and avoidance of iatrogenic damage by use of adequate principles of myocardial protection. Yardsticks relating to conventional blood cardioplegic protective methods are well established during surgical correction of adult diseases in the bypassed, decompressed, ventricle that undergoes coronary bypass procedures or valve repair and/or replacement. However, a fresh look is needed during ventricular restoration in patients with congestive heart failure (CHF), because cavity reconstruction must be accomplished in the open ventricle, rather than the collapsed, vented chamber that is commonplace during operations that do not rebuild cardiac form. An alternate option is the beating method of continuous perfusion, rather than intermittent cardioplegic solution delivery.

The evolution for clinical use of protective methods typically follows guidelines established during prior experimental studies that become tested in patients. An important question relates to the safety of reliance upon established cardioplegic methods in the collapsed heart, when restoration is done in the different geometry of a dilated open ventricular chamber. This analysis is especially important because the restoration procedure extends operative time to address the 'triple V' of CHF involving the 'vessel, valve and ventricle.' Until now, there is no background information to support abandonment of currently recognized 'safe' cardioplegic strategies, since the new open beating method of protection had not yet been tested in acutely of chronically dilated hearts.

Without this knowledge, different world wide centers within the RESTORE team used either the cardioplegic or beating method for restoration during ventricular rebuilding in ~1200 patients. This report will have two phases that
involve the early registry experience with either the beating or cardioplegic method, to be followed by recent studies that test these methods experimentally.

The summary the registry results in RESTORE patients will focus upon differences related to high risk factors, like age, ejection fraction, extent of stretch by left ventricular end systolic volume index (LVEF) rise, severity of heart failure by NYHA classification. Second, recent experimental studies on acute and chronically dilated hearts shall be described that employ the conventional cardioplegia and beating methods in dilated hearts to evaluate their effects on function and flow distribution. This nutritive element is essential during restoration because the vulnerable left ventricular endocardium may undergo subendocardial necrosis and produce low output syndrome, a predominant cause of perioperative mortality [1].

2. RESTORE registry

The influence of protection strategies on survival is especially important in patients undergoing SVR, because 67% of patients in the RESTORE registry were NYHA class III or IV, and this cohort is highly vulnerable to intraoperative injury. During the ventricular portion of the SVR procedure, cardioplegia was applied in 55%, and the open-beating method (B) in 45% but without uniformity as many used both methods. Overall, early mortality was 5.3% for 1198 patients, and rose to 8.7% when mitral procedures were added to CABG in patients with very dilated hearts [2,3].

Employment of the open-beating method (B) versus cardioplegic arrest (C) occurred more commonly in patients with ejection fraction ≤30% (73% vs 27%, p < .05), larger ventricles with LV end systolic volume index ≥80 ml/m² (50% vs 37%, p < .05), more advanced clinical symptoms of heart failure NYHA III and IV heart failure (81% vs 57%, p < .05; Fig. 1), as well as poorer hemodynamic status. Intra-aortic balloon pumping (IABP) used in 13.7% versus 7.3% in beating or blood cardioplegia patients (p < 0.02).

Comparison of the B and C methods results was difficult because the patients undergoing the B method were not matched to those using the C method. A risk factor was derived from logistic regression of ejection fraction (EF), NYHA index and age on the survival censor (1 for dead and 0 for alive at last follow-up). The B and C patients were evenly divided into low and high preoperative risk. While 60.6% of the B patients were high risk, only 41.5% of the C patients were high risk (p < 0.0001).

Despite greater risk factor, the B patients fared slightly better than the C patients in 30-day hospital survival (Fig. 2), although not significantly so (B 95.1% vs C 94.5%, p = 0.68). However, on a day-to-day comparison, the B patients had significantly better survival (p < 0.0001). The direct 5-year mortality analysis on the basis of protection method (B vs C) is strongly biased in favor of the cardioplegia group (Fig. 3a), but this difference was not statistically significant.

To compare 5-year survival for B and C patients on a comparable basis, they were matched on NYHA index, ejection fraction and age. The 5-year survival curve for these matched patients is shown in Fig. 3b. There was no significant difference between the B and C groups (p < 0.87).

The unavailability of concrete clinical or prior experimental data about protection capacities accounts for differences in opinions of the preferred strategy amongst RESTORE members, whose patient experience is reflected in this registry. For example, Dor advocates cardioplegic arrest as a method of protection, based upon his analysis of 1150 cases (1984 and 2004) where hospital mortality related to preoperative ejection fractions: 1.3% if ≥40%, 6.9% if 30–40%, and 13% if <30%. More importantly, 19% mortality occurred in a subgroup of 62 patients with severely depressed ventricular function (mean EF 17% and mean LVEF 125 ml/m²) [4]. However, a recent report in patients with EF ≤30%, showed reduction to 7.5% mortality when an intraventricular balloon was used to avoid chamber restriction. Restriction is less likely in this cohort, since patients with very low ejection fraction usually have larger chamber volume [4].

Menicanti, whose experienced institution used crystalloid cardioplegic arrest during CABG, mitral repair and restoration in their first 88 patients with ∼20% EF and ∼109 ml/m² LVEF, reports (a) substantial isotropic support (epinephrine) in 25% after >50 min aortic occlusion duration, and (b) 40% require intra-aortic balloon pumping if aortic occlusion averaged 100 min [2].
Conversely Kron, at another RESTORE center [5], compared the open-beating method to cardioplegic arrest [5] and found no difference between the two methods in 53 consecutive patients undergoing SVR with EF ≤ 25% and end-diastolic diameter ≥ 6.0 cm that were non-randomly divided between techniques. Their results differ from Dor and Menicanti, since there was no mortality in either group, thereby leading to the conclusion that the open-beating method is not necessary for successful early outcomes.

The RESTORE database of 11 centers doing 1198 patients became the infrastructure of the Surgical Treatment of Icshemic Heart Failure (STICH) Trial. Each of the participating surgeons had broad experience. In contrast, only 500 SVR procedures will be done in 117 centers involved in this new operation in this NIH sponsored STICH trial. Less experienced surgeons will take a longer time to rebuild the ventricle so that reducing ischemic time with novel use of the open-beating method of protection may be particularly appealing to early adopters of the procedure.

Restoration is an evolving technology in the CHF population, where there is reduced survival if CABG and mitral valve repair alone are done [8]. Decisions to add ventricular repair to conventional CABG and mitral valve repair in ischemic cardiomyopathy are supported by the 5-year survival of 69% reported in the RESTORE experience [6]. The aforementioned data implies that added intraoperative time should not dissuade surgeons from adding ventricular restoration. This clinical observation of safety will be further supported by the following experimental data that is harvested from studies of dilated failing acute and chronic ventricles that investigated the safety of the open-beating method in simulated high-risk conditions.

3. Acute dilated cardiomyopathy

Tradition has been the guidepost as surgeons consider options toward changing current operative and protection methods. Conversely, a paradigm shift in thinking must exist when there is progression toward alteration of conventional techniques. I carried this concept to Brazil, when I first began to learn about left ventricular restoration. This visit to Batista showed me three very important things. First, this experience offset any prior concept about my operating on the sickest patients, as the CHF patients in this clinic presented with marginal medical care, were often in extremis, and thus defined the apex of the high risk category. Postoperative monitoring included an arterial blood pressure, a Foley tube for urine volume measurement, and watching chest tube drainage volume to determine bleeding. Second, these patients received only protection by the beating empty heart, had pink warm hands and feet and full pulses, rarely needed any inotropic support, were awake within 1 h in the ICU, and frequently ingested a late lunch on the day of operation.

I realized that such immediate superb clinical myocardial performance in these terminal patients exceeded my expectations about function that could result from the blood cardioplegic methods that I spent my career developing [9]. Recognition of this limitation initiated the third step of testing of the beating method in my laboratory, a

![Overall 5-year survival](image)

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(a) Five-year overall survival, showing advantage for cardioplegic protection. (b) Matched patient analysis including age, ejection fraction and NYHA in 80 patients showing comparable (no significant differences) in survival with beating and cardioplegia methods.
fundamental requirement before introduction of this method into clinical practice. These observations launched my study of the beating heart in acute and chronic heart failure that will be summarized below, and presents findings that underlie my current conclusions about optimal methods of myocardial protection during restoration.

Intraoperative ischemia results from a discrepancy between how the adequacy of oxygen supply meets demands. The dilated working heart (Fig. 4) has the highest requirement, which falls to 10 ml/(100 gm min) in the normal working ventricle, diminishes during decompression to ~3 ml/100 gm in the vented state on bypass, and is lowest at 1 ml/100 gm during normothermic cardioplegia [10]. No change of demands exists during bypass in the beating empty heart, since it remains decompressed whether it is collapsed during venting or is open during traction for simulated restoration. Continuous perfusion of the beating state may avoid ischemia, whereas intermittent cardioplegia introduces an iatrogenic mismatching of supply and demand. For this reason, hypothermia is used to lower demand and offset the extent of the ischemic insult.

Complete recovery of myocardial performance is the most important immediate goal, and confirmation of the protective qualities of any method designed to prevent intraoperative damage requires achievement of this task. Testing in a model of the disease process requiring this protection is an important part of how each method is evaluated. Simulation of the partial left ventriculoplasty (PLV), performed by Batista seemed the easiest acute method, since the obtuse marginal coronary vessel is always interrupted during the ventriculotomy [11]. This iatrogenic damage provided a standard degree of injury from circumflex branch occlusion during the incision, thereby establishing a control finding of injury that sets the stage to determine (a) baseline function, (b) how such function is changed by inserting a lateral pericardial patch to create a spherical failing ventricle, and (c) evaluate the protection effects used during repair of this dilated failing chamber. All procedures were done on the same subject, allowing an intrinsic baseline measurement for subsequent comparisons. Furthermore, no ischemia was imposed by aortic clamping, so that the resultant left ventricular hemodynamic performance identified how continuous perfusion of the beating heart influenced outcome.

Lateral ventriculotomy and closure established the control values of baseline functional performance of the damaged heart, a comparison point for subsequent interventions; stroke work index was reduced 30% at 10 mmHg left atrial pressure during volume loading Starling function curves, LV elastance (EES) was lowered 25% by pressure volume loop measurement, and echo related ejection fraction fell from 65 to 47% when bypass was discontinued. Superimposed chamber dilation by patch placement produced severe left ventricular failure, as Starling curves fell 42 ± 6%, EES was reduced 55 ± 8%, and ejection fraction was lowered 43 ± 4% below baseline levels. Conversely, patch removal and reapproximation of the LV incision (Table 1) restored Starling curves, EES and ejection to the same baseline levels observed after re-closure of the LV incision.

The beating ventricle was continually nourished by perfusion, so that the surgical procedures of ventriculotomy, patch placement and then patch removal became the only variables. Profound failure was caused by the ventricular distention following patch placement, yet each heart was protected in the beating state and resumed control performance following patch removal. Conversely, inadequate protective methods would impair functional recovery, and decompensation would be expected to worsen after patch removal. These experimental findings parallel clinical events, whereby functional deterioration follows inadequate protection, despite successful surgical repair of lesions that cause heart failure.

4. Chronic dilated cardiomyopathy

Chronic experimental models that reflect the clinical state are the keynote seminal studies required to analyze differences between the beating and blood cardioplegic methods of protection. A model of pacer induced cardiomyopathy was developed to achieve this goal, and analysis at 4–5 weeks showed the CHF characteristics of raising end diastolic dimension 34%, doubling of pulmonary artery pressure (from 19–42 mmHg), reducing fractional shortening declined an average of 50–22% (falling to 14 and 17% in two studies), ascites, and a dilated, thin-walled heart. Simultaneously, a parallel study in normal hearts of the beating and cardioplegic methods was done to permit failure
heart comparisons to non-failing ventricles with unaltered size and shape.

Total and subendocardial perfusion were studied with colored microspheres, and comparisons were made in (a) the closed vented state (simulating prebypass, as well as the collapsed heart that is present during CABG and mitral procedures), (b) the anterior open ventricle (using the same incision employed during restoration) with the wall radius widened by holding the edges apart to mirror exposure (Fig. 5) during patch placement for clinical CHF in dilated hearts. Creation of stretched ventricular architecture by traction reproduced the normal radial contour that exists in the working heart. This normal spatial configuration differs from wall/myocyte distortion that accompanies ventricular collapse during venting and can explain why flow may become impaired in hypertrophied hearts [12].

Perfusion pressure was kept at 80 mmHg, and the effects of ventricular shape (differences between collapsed vented hearts vs open ventricles under wall traction), flow and distribution during perfusion were examined in normal and failing hearts. Without failure (Fig. 6a) subendocardial flow was lower during beating versus cardioplegia in the normal heart. Ventricular shape did not affect perfusion in non-failing hearts, since lower flow in the vented and open state was maintained in the beating state, whereas a higher flow in the vented and open positions persisted with cardioplegia. Conversely, failure hearts received the same perfusion pressure, yet showed several differences that include (a) lower overall flow than non-failure hearts in either the vented or open geometry conditions (Fig. 6b), (b) maintenance of higher flow during cardioplegia versus beating in the vented collapsed state, and (c) preferential 95% augmentation of subendocardial flow (0.40–0.78 ml/(min gm)) during the beating open state, so that flow now exceeded cardioplegic flow, and (d) cardioplegic delivery reduced flow by 64% (0.97–0.59 ml/(min gm)) during the open state.

No ischemia was introduced in these failing heart studies in the open ventricle studies, but there was a disparity between methods of delivery. The beating open state supplied preferential subendocardial nutrition, whereas cardioplegic delivery caused diminution of subendocardial flow. These observations imply that worsening of nutritive subendocardial perfusion will occur in failing hearts if flow is interrupted; the usual circumstance with clinical cardioplegic delivery.

The influence of perfusion pressure on nutritive endocardial flow distribution is shown in Fig. 6a and b, where (a) marked subendocardial under perfusion occurred during cardioplegic delivery in failing versus normal hearts, and (b) perfusion improved to the subendocardium with the beating state, and nutritive perfusion now exceeded flow during cardioplegic delivery. The keynote observation is that there was persistence of lower flow for the same perfusion pressure in dilated versus normal chambers, a finding that introduces a phenomenon that may be termed ‘vascular remodeling.’

Several mechanistic factors can explain vascular remodeling, and include narrowing of the vessel wall lumen, diminution in the number of vessels, or lengthening of conductance vessels. Coronary vascular resistance increases by these factors and the impact of this observation is threefold. First, a higher perfusion pressure is essential when nourishing failing hearts. Second, ischemia may occur in failing hearts despite continuous perfusion with either
continuous cardioplegia of the beating state (Fig. 7). Third, reperfusion may be inadequate following ischemic episodes by maintenance of the initially low perfusion pressure beyond the first 2–3 min.

Insight into the importance of this experimental observation is drawn from the visible increase in the vigor of contraction during clinical restoration when perfusion pressure is raised, as suggested earlier. Furthermore, these findings imply the potential of improving perfusion with intra aortic balloon counterpulsation, but subsequent studies are needed to evaluate this concept.

Paradigm shifts exist only when the truth becomes evident by biological studies. My work over the past 30 years has emphasized the need to understand methods of cardioplegic delivery, and to develop strategies to use these methods clinically. The experimental and clinical information presented herein allowed me understand the importance of blending different methods, whereby cardioplegic strategies are useful in the collapsed heart where intermittent ischemic intervals are needed. However, the beating state supplies better and uninterrupted subendocardial perfusion during restoration, especially at high perfusion pressures. Of key importance is that these salutary events during the beating state exist under operative conditions where visualization is excellent, so that there is no need to introduce periods of ischemia.

5. Clinical implications of experimental studies

These observations on flow dynamics in the failing heart carry several implications. First, differences exist between cardioplegia and beating delivery. Intermittent delivery occurs with cardioplegia, so that potential damage becomes time dependent upon the ischemic episodes between doses. Second, continuous perfusion exists during the beating state, creating the concept of procedure dependency, since there is no obvious ischemia. The learning process for new surgeons may become enhanced by the reducing concern about extending damage when restoration is added to a prior ischemia interval during CABG or valve repair.

Third, all coronary grafting (proximal and distal connections) should be done before restoration if the beating method is used, since higher perfusion pressure via the connected conduits insures improved nutrition to all previously ischemic regions. Fourth, aortic incompetence must be evaluated by intraoperative echocardiography, since only minor insufficiency (500 ml/min) will alter visualization, and requires a planning change when the beating method is used. A strategy designed to only place distal grafts before ventriculotomy will offset this impairment of visualization. The aorta is left clamped during restoration, and the heart is kept beating by perfusing each grafted vessel via a multi-armed cannula, while simultaneously leaving the internal mammary artery graft opened, and also delivering retrograde perfusion. This technique was as described recently [13], and proximal grafting delayed until after restoration.

The experimental findings indicate the importance of flexibility in selection of myocardial protection techniques. Methods may vary, since cardioplegia is used during the vented aspects of CABG and mitral repair procedures to compensate for the intermittent ischemia periods that necessary for visualization. Conversely, the beating heart has advantages during restoration, because provision of continuous subendocardial nourishment avoids superimposing unnecessary ischemic intervals during ventricular rebuilding. Finally, implementation of knowledge of vascular remodeling introduces the importance of keeping a higher perfusion pressure to improve subendocardial muscle nourishment, a collaborative surgical/perfusionist effort to benefit failing heart patients.

6. Conclusions

Review of myocardial protection during restoration in the 1198 patient the RESTORE registry showed a relatively even distribution between intermittent blood cardioplegia and continuous perfusion in the beating open state. The beating method was used more frequently in older patient, and those with lower ejection fraction, larger volume and more advanced heart failure, and a not significant tendency toward higher 5-year survival occurred in this subset.

The safety of the beating method was shown in acute studies. Preferential subendocardial nutrition occurred during perfusion of the open-beating state in chronically dilated hearts with heart failure, whereas cardioplegia caused diminished subendocardial perfusion. Intermittent ischemia would accentuate this supply demand discrepancy during cardioplegia administration. Higher perfusion pressures are needed during blood cardioplogic or beating flow delivery in failing hearts, because vascular remodeling exists in the coronary bed of failing versus to normal hearts.

Flexibility is a critical factor in planning protection strategies in failing hearts. Cardioplegia for CABG and mitral repair may nicely blend with continuous perfusion of the beating state during ventricular restoration, in order to insure adequate nutrition to the vulnerable subendocardial region.
References


