

The Role of Surgical Ventricular Remodelling in Ischemic Cardiomyopathy: Implications of the Results of the STICH Trial

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INTRODUCTION

Representing approximately two-thirds of the burgeoning heart failure population [Gheorghiadis 1998], the prevalence of ischemic cardiomyopathy (ICM) continually grows as management of acute myocardial infarction and heart failure improves.

Recently published results of the Surgical Treatment for Ischemic Heart Failure (STICH) trial [Jones 2009] demonstrated no reduction in mortality or hospitalization for patients undergoing surgical ventricular restoration (SVR) in addition to coronary artery bypass grafting (CABG). Given the previously demonstrated improvements in left ventricular (LV) systolic function and volumes reported for SVR [Athanasuleas 2004], these results will be influential in the future management of ICM patients.

The LV dysfunction seen in these patients involves a varying combination of infarction with fibrous scarring, viable myocardium (stunned or hibernating), and the effects of ventricular remodelling. Medical management using a combination of beta blockers, angiotensin converting enzyme inhibitors, spironolactone, and cardiac resynchronization therapy has improved both symptoms and prognosis in multiple randomized controlled trials [Hunt 2005].

The role of CABG and its ability to improve LV function and prognosis was first documented in the 1970s [Yusuf 1994]. These initial studies failed to demonstrate prognostic benefits for revascularization in the absence of anginal symptoms. Although significant evidence exists that demonstrates that revascularization of patients with LV dysfunction is beneficial, particularly in the presence of demonstrable myocardial viability [Gunning 1997], its superiority to modern medical therapy has not been systematically demonstrated.

Surgery on the scarred left ventricle has evolved since Cooley reported LV aneurysmectomy in 1958 [Cooley 1958]. Multiple techniques have attempted to restore ventricular geometry, reduce ventricular volumes, restore systolic function, and reduce myocardial oxygen demand.

The ability of SVR to reduce LV volumes and improve ejection fraction has been clearly demonstrated [Athanasuleas 2004]. Translating these improvements to favorable clinical outcomes over and above either CABG or medical therapy has not before been addressed in a clinical trial. Furthermore, the evolution of the SVR procedure, to reconstruct the ventricle of patients with areas of akinesis rather than dyskinesis, has not been subjected to rigorous evaluation.

THE PATHOPHYSIOLOGY OF ISCHEMIC CARDIOMYOPATHY

LV dysfunction in ICM involves the combined insults of cardiac ischemia and pathological remodelling.

Coronary Ischemia

Myocardial ischemia results in a spectrum of injuries to the LV. Acute myocardial infarction causes regional muscle loss and collagenous scar formation. Early infarct borderzone changes can cause infarct expansion.

From observations that akinetic myocardial segments regained function after revascularization or catecholamine stimulation evolved the concept that ventricular akinesis does not always represent infarction [Braunwald 1982]. Up to 50% of patients with ICM have viable but noncontractile myocardial segments called hibernating myocardium [al-Mohammad 1998].

Demonstration of the presence of akinetic myocardial segments with metabolic activity or recruitable function on nuclear imaging, echocardiography, or cardiac magnetic resonance imaging (CMRI) can predict improvements in both LV function and clinical parameters with revascularization [Camici 2008]. Hibernating myocardial segments have near normal resting blood flow and are a result of repetitive acute ischemia. The spectrum of cellular ultrastructural changes, which in the extreme results in myocyte de-differentiation, explains the variable time course and completeness of response to revascularisation [Baz 2001].

LV Remodelling

Loss of myocyte function does not fully explain the inexorable decline in LV function and changes to LV architecture in patients with ICM. LV remodelling is a self-perpetuating process characterized by progressive ventricular dilatation and increases in wall stress, further perpetuating subendocardial ischemia and increasing myocardial oxygen demand. Ventricular dilatation changes the LV shape from elliptical

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Table 1. Summary of STICH Trial Hypothesis 2 Outcomes at 48-Month Follow-up

	Coronary artery bypass grafting (CABG) only	CABG + surgical ventricular restoration (SVR)	P
Death	28%	28%	.98
Hospitalization for cardiac causes	42%	41%	.73
Composite endpoint of death of hospitalization for cardiac causes	59%	58%	.90
Operative (30-day) mortality	5%	6%	.40
Acute myocardial infarct	4%	4%	.96
Stroke	6%	5%	.35
Left ventricular end-systolic volume index	-5 mL/m ² (6%)	-16 mL/m ² (19%)	<.001
Postoperative length of stay			
Intensive care unit, h	49.8	69.5	<.001
Hospital, d	8.0	9.0	<.001

to spherical, compromising the efficiency of systolic function [Athanasuleas 2004].

At a cellular level, myocyte hypertrophy represents a combined response to the local and system activation of the renin-angiotensin system, myocardial stretch, and systemic neuro-hormonal responses involving catecholamines and natriuretic peptides. Early remodelling post-myocardial infarction is mediated locally by a combination of serine proteases and tissue matrix metalloproteinases, which represent a component of the inflammatory response to tissue injury.

SURGICAL VENTRICULAR RESTORATION

Revascularization alone can improve regional wall motion in areas of myocardial viability; however, advanced remodeling changes, in particular increased LV volume, ameliorate the potential benefits of CABG and strongly predict poor long-term outcomes [Mandegar 2008].

The SVR operation has evolved from a simple linear aneurysm resection to an endoventricular infarct exclusion technique in a bid to restore the elliptical shape of the LV and reduce ventricular volume. The acronym SVR describes a family of operations, the prototype being the endoventricular patch plasty championed by Dor [Dor 2001], but includes operations tailored to inferior wall and global LV dysfunction. Conceptually, decreasing LV size reduces wall stress and subendocardial ischemia. Reinstating the left ventricle's elliptical shape improves LV systolic mechanics and mitral valve function.

Utilizing cardiopulmonary bypass and either cardioplegic arrest or induced ventricular fibrillation, an endoventricular patch is placed at the junction of the infarcted myocardium and the viable segments via an anterior ventriculotomy. A mannequin/inflatable balloon can be used to size the ventricle to 60 mL/m². Concomitant CABG is performed.

Perioperative mortality rates around 5% and 5-year survival rates of 70% have been reported [Athanasuleas 2004]. Advanced symptoms, age, concomitant mitral valve surgery, LV end-systolic volume index (ESVI) > 80 mL/m², and poor

LV function all predict worse long-term outcomes. The presence of remote asynergy predicts worse perioperative and long-term outcomes, highlighting the necessity for adequate basal segment myocardial function.

Despite the poorer outcomes of the patients with more advanced preoperative heart failure, it is probable that any additional benefit of ventricular restoration over CABG will be seen in these sicker patients with more advanced changes of LV remodelling, which are unlikely to be reversed by revascularization alone.

THE SURGICAL TREATMENT FOR ISCHEMIC HEART FAILURE (STICH) TRIAL

The absence of randomized trial evidence to support either the role of revascularization or LV reconstruction in patients with ICM led to the funding by the United States National Heart Lung and Blood Institute of a multicenter international randomized controlled trial in 2002 [Velazquez 2007].

The STICH trial recruited 2000 patients with coronary artery disease and a LV ejection fraction of 35% or less. Patients were subdivided into 3 groups: Stratum A, medical therapy or CABG; Stratum B, medical therapy, CABG, or CABG and SVR; and Stratum C, CABG or CABG and SVR, based on the presence of left main coronary disease, anginal symptoms, and anatomic suitability for the SVR procedure, defined as dominant anterior LV akinesia or dyskinesia. Patients in stratum A were randomized 1:1 either to medical therapy (MED) or CABG; Stratum B 1:1:1 to MED, CABG, or CABG and SVR; and Stratum C 1:1 to CABG or CABG and SVR.

Patients with recent myocardial infarction, need for aortic valve replacement, planned percutaneous coronary intervention, or coexisting non-cardiac disease resulting in a life expectancy of less than 3 years were excluded.

Optimal medical therapy included the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, beta blockers, spironolactone, antiplatelet agents, and resynchronization therapy where appropriate.

Surgical therapy was part protocol determined: internal mammary artery (IMA) grafting was required. Use of cardiopulmonary bypass, mitral valve repair, and the ventricular reconstruction technique were at the operating surgeon's discretion. The endoventricular patch plasty was the preferred LV reconstructive technique [Dor 2001].

The trial pre-specified 2 primary hypotheses and 10 secondary hypotheses.

Major Hypothesis 1

Coronary Revascularization. Improvement in myocardial perfusion by CABG combined with MED improves long-term survival compared with MED alone.

Major Hypothesis 2

LV Restoration. In patients with dominant anterior wall LV akinesia or dyskinesia, LV shape and size optimization by SVR combined with CABG and MED improves long-term survival free of cardiac hospitalization compared with CABG and MED without SVR.

Secondary Hypotheses

The secondary hypotheses pre-specified subgroups for analysis using CMRI, myocardial viability assessment, hemodynamic assessment with echocardiography, and genetic variables. Also included are assessments of the inflammatory parameters, cost effectiveness and quality of life measures.

Follow-up was performed at 4 monthly intervals. Echocardiography was performed at 4 months and 2 years, and 6 minute walk tests were performed at 4 months and annually thereafter.

RESULTS

The results of hypothesis 2, were published recently in the *New England Journal of Medicine* [Jones 2009]. Of the 1000 patients randomized to CABG or CABG and SVR, 499 underwent CABG, and 501 underwent CABG and SVR. Cost effectiveness analysis and quality of life were reported elsewhere [Mark 2009].

There were no significant differences in the 2 surgical groups in terms of age (mean 62 years): mean ejection fraction was 28%, 90% had multivessel coronary disease, and <10% had renal insufficiency. Moderate to severe mitral regurgitation was present in <20% of patients. Coronary risk factors were evenly distributed between groups.

Median follow-up was 48 months and was 99% complete.

Outcomes

Both groups showed similar symptomatic improvement. As assessed using the Canadian Cardiovascular Society (CCS) angina classification, 77% of patients in both groups had no angina, and 20% were CCS class I/II, with a mean improvement of 1.7 classes.

Symptoms of heart failure were classified according to the New York Heart Association (NYHA) criteria, with a mean improvement of 1 class in each group.

Outcome data are summarized in Table 1. The primary endpoint of death from any cause or hospitalization for

cardiac causes was reached in 59% of the CABG only group and 59% of the CABG and SVR group ($P = .90$).

Perioperative morbidity and mortality were similar in both groups.

Both groups showed similarly large, sustained improvements in quality of life and symptom scores. Perioperative costs were analyzed on the cohort treated in the United States only and showed higher costs in the CABG and SVR group, based on a median 4-day increased intensive care stay [Mark 2009].

Preoperative NYHA or CCS Class, non-insulin-dependent diabetes mellitus (NIDDM), LV ejection fraction (EF) <28%, number of disease coronary vessels, or presence of mitral regurgitation did not effect outcome.

IMPLICATIONS OF RESULTS OF THE STICH TRIAL

This randomized trial clearly defines the impaired outcomes of patients with ICM, with a 28% 4-year mortality in patients optimally medically treated and surgically revascularized. The results of hypothesis 1, comparing medical therapy to revascularization, due for publication in 2011, will help to define whether revascularization provides an additional benefit over medical therapy in patients with ICM. The addition of the SVR procedure increased health care costs and prolonged intensive care stay, but without a price in terms of perioperative mortality.

The equivalence of CABG with CABG and SVR may seem surprising given the prognostic importance of LVEF and LV volumes in patients with cardiomyopathy. The STICH authors provide 2 potential explanations for the trial's negative outcome: selection bias may have excluded enrollment of patients in whom a definite benefit of LV reconstruction was anticipated, and secondly, improvement in LV systolic function may have come at the cost of impaired diastolic function, which adversely affects survival of cardiac failure patients.

Many potential factors that could affect the applicability of the trial results were not addressed in the report. The improvement in LVESVI in the SVR group was 10 mL/m², less than was previously reported by the RESTORE group [Dor 2001; Athanasuleas 2004], and only 60% received an endoventricular patch. Changes in LVEF were not reported, nor were the changes in LVEF or LVESI stratified to initial ventricular size and function. It is possible that the patients in whom the perioperative risk is highest—those with LV volumes >80 mL/m²—present the subgroup in whom there is the maximal benefit over CABG alone.

Also not reported were subgroups based upon basal segment myocardial function, non-anterior wall asynergy, and the extent of anterior wall infarction—variables likely to affect any potential benefit of LV reconstruction. The extent of viable myocardium is likely to affect the benefit of CABG.

The perioperative assessment using CMRI to assess LV anatomy and viability will help to define these subgroups. The presence of anterior wall akinesia or dyskinesia—a reflection of the pattern of and extent of LV remodelling—may also define patients in whom CABG provides an equivalent outcome to CABG and SVR. The extension of LV reconstruction

to patients with non-transmurally infarcted akinetic anterior walls may prove to have overstepped the benefit of the operation.

The published results of the STICH trial leave many questions unanswered. ICM is a heterogeneous disease. Before the role of LV reconstruction is dismissed as a clinical option, an in-depth analysis is required of the subgroups of patients who fall within STICH trial's selection criteria. Different anatomic subsets of patients, the presence or absence of myocardial viability and its distribution, and ventricular size and volume are but a few of the variables that could potentially categorize patients in whom benefit for this operation over and above CABG may be demonstrable.

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