The heart failure challenge: Optimizing medical and surgical management

Normand Racine MD, Jean-Lucien Rouleau MD

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The treatment of patients with coronary artery disease and left ventricular dysfunction has improved markedly over the past two decades. Nevertheless, the morbidity and mortality rates remain high in this population. In addition to pharmacological therapies to attenuate neurohumoral overactivation, the present challenge is to find additional therapeutic avenues. Percutaneous coronary intervention, although widely used in patients with coronary artery disease, is more challenging with multivessel disease and associated left ventricular dysfunction, and its optimal use in heart failure remains in question. Cardiac surgical revascularization and surgical ventricular restoration have also been advocated. To date, there are no prospective, randomized clinical studies to prove a benefit from these invasive interventions and to identify which patients may derive the most benefit compared with optimal medical therapy alone. The current management of patients with ischemic heart failure needs to be challenged and requires an objective evaluation of these invasive interventions. The ongoing Surgical Treatment for Ischemic Heart Failure (STICH) trial is the first randomized trial designed to determine the long-term benefits of surgical revascularization and surgical ventricular restoration compared with optimal medical therapy alone. The results of this study will provide additional evidence-based information to guide physicians in the rational allocation of health care resources. The role of percutaneous angioplasty in patients with ischemic heart failure also needs to be addressed objectively.

Key Words: *Cardiopulmonary bypass; Congestive heart failure; Remodelling; Revascularization*

Over the past two decades, progress in pharmacological and interventional therapies has significantly enhanced survival rates in patients with coronary artery disease (CAD), particularly in the setting of an acute myocardial infarction. Survival of patients after a myocardial infarction is, however, commonly accompanied by some degree of left ventricular (LV) dysfunction. Indeed, CAD is the most common cause of dilated cardiomyopathy in North America (1,2). However, despite recent advances in our management of patients with asymptomatic and symptomatic LV dysfunction, morbidity and mortality rates remain high in this population, particularly when LV dysfunction is accompanied by CAD (3-5). Thus, we continue to be challenged to find ways of further improving

Le défi de l'insuffisance cardiaque : En améliorer la prise en charge médicale et chirurgicale

Le traitement des patients qui souffrent de coronaropathie et de dysfonction ventriculaire gauche s'est nettement amélioré depuis une vingtaine d'années. Néanmoins, les taux de morbidité et de mortalité demeurent élevés dans cette population. En plus des traitements pharmacologiques visant à atténuer la suractivation neuro-humorale, le défi actuel consiste à trouver de nouvelles avenues thérapeutiques. L'intervention coronarienne percutanée, bien que couramment utilisée chez les patients coronariens est plus complexe en présence de maladie affectant plusieurs vaisseaux et associée à une dysfonction ventriculaire gauche; c'est pourquoi son utilisation à grande échelle reste controversée dans l'insuffisance cardiaque. La revascularisation coronarienne et la correction ventriculaire chirurgicales ont également été proposées. À ce jour, aucune étude clinique prospective randomisée n'a par contre confirmé les avantages de ces interventions efficaces ni permis d'identifier les patients les plus susceptibles d'en tirer plus d'avantages que du traitement médicamenteux optimum seul. La prise en charge actuelle des patients qui souffrent d'insuffisance cardiaque ischémique doit être revue et requiert une évaluation objective des interventions efficaces potentielles. L'essai STICH (pour *Surgical Treatment for Ischemic Heart Failure*) est le premier essai randomisé conçu pour déterminer quels sont les avantages à long terme d'une revascularisation et d'une correction ventriculaire chirurgicales comparativement au traitement médicamenteux maximum seul. Les résultats de cette étude fourniront des renseignements additionnels fondés sur des preuves pour aider les médecins à utiliser rationnellement les ressources en soins de santé. Le rôle de l'angioplastie percutanée chez les patients qui souffrent d'insuffisance cardiaque ischémique mérite également d'être étudié de manière objective.

the medical and surgical management of patients with heart failure and CAD.

The role of cardiac surgery in patients with LV dysfunction is continuously evolving and involves not only coronary artery bypass grafting (CABG), but also therapy for mitral regurgitation, surgical ventricular restoration (SVR), ventricular assist devices and cardiac transplantation (6-13). Although all of these surgical interventions have a definitive role in the therapy of patients with LV dysfunction, particularly surgical therapy for ischemic mitral regurgitation (a common complication of significant ischemic cardiomyopathy and an independent risk factor for excess mortality in patients with LV dysfunction [14]), the present article focuses on the roles of CABG and SVR.

Department of Medicine, University of Montreal and Research Centre, Montreal Heart Institute, Montreal, Quebec

Correspondence: Dr Normand Racine, Research Centre, Montreal Heart Institute, 5000 Belanger Street East, Montreal, Quebec H1T 1C8.

Telephone 514-376-3330, fax 514-593-2575, e-mail normand.racine@icm-mhi.org

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THE ROLE OF CABG

Observational studies have shown that patients with LV dysfunction who are undergoing CABG have a higher perioperative and long-term mortality than patients with normal LV function (15-18). The presence of comorbid conditions also contributes significantly to higher perioperative mortality. Nevertheless, despite a higher perioperative mortality, the available evidence suggests that in patients with extensive CAD and LV dysfunction, surgical revascularization is associated with a better survival rate than that of patients treated only with medical therapy (16,17,19-22).

At this time, the most important evidence supporting the use of CABG in patients with LV dysfunction and CAD is the Coronary Artery Surgery Study (CASS) (20). CASS was designed to compare medical treatment with surgical treatment of patients with stable CAD. Of these patients, a subset of 160 had a baseline LV ejection fraction (LVEF) between 35% and 49%. The seven-year survival rate of this subset of patients with LV dysfunction was significantly higher in the surgical group than in the medical group (84% versus 70%, respectively, $P=0.01$). The patients who appeared to benefit the most from CABG were those with three-vessel disease associated with impaired LV function (20). Similarly, an analysis of the CASS registry for patients presenting with angina and an LVEF of less than 35% demonstrated a better three-year survival rate in patients treated with CABG (84%) compared with those treated medically (68%) ($P=0.0007$). Improvement appeared to occur only in patients limited by angina, whereas patients whose primary limitation was dyspnea or fatigue had no improvement in three-year survival rates (19). Evidence from cardiac imaging studies suggesting that CABG is particularly beneficial for patients with extensive myocardial viability or hibernating myocardium in coronary territories amenable to surgery supports the results from the CASS registry (23-25).

Early results from the Duke University Cardiovascular Database (21) support the superiority of CABG in patients with LV dysfunction and extensive CAD. This comprehensive registry showed that patients with an LVEF of less than 35% had a higher 10-year survival rate with surgical revascularization than that of medically treated patients (46% versus 27%, respectively, $P=0.0005$).

In patients with unstable angina, the Veterans Affairs Cooperative Study, which compared medical therapy with CABG in this setting, showed improved survival rates with CABG in the subgroup of patients with impaired LV function (26,27). After five years of follow-up, surgically treated patients had less angina, improved exercise tolerance and required fewer antianginal medications than did the medically treated patients (28).

Unfortunately, there are no large randomized trials comparing current medical therapy alone with current CABG and related interventions. In the CASS and Veterans Affairs Cooperative Study (20,27), medically treated patients did not receive current nonsurgical therapy that is shown to improve survival rates, such as acetylsalicylic acid, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, aldosterone receptor blockers or statins. Interventions such as the implantation of internal cardiac defibrillators and cardiac resynchronization did not exist at the time. Similarly, surgical interventions did not yet include as effective perioperative myocardial preservation, surgical repair of the mitral valve or enhancement of reverse ventricular

TABLE 1

Indications for surgical revascularization in patients with poor left ventricular (LV) function based on the American College of Cardiology/American Heart Association 2004 clinical guidelines update for coronary artery bypass grafting (CABG) (32)

Class I indication

CABG should be performed in patients with poor LV function who have significant left main coronary artery disease (50% or greater stenosis) or left main equivalent coronary artery disease (defined as 70% or greater stenosis of the proximal left anterior descending coronary artery and proximal left circumflex artery) or proximal left anterior descending coronary artery stenosis with two- or three-vessel disease

Class IIa indication

CABG may be performed in patients with poor LV function with significant viable, noncontracting, revascularizable myocardium and without any of the above anatomical abnormalities

Class III indication

CABG should not be performed in patients with poor LV function without evidence of intermittent ischemia and without evidence of significant revascularizable, viable myocardium

remodelling via surgical restoration of LV geometry (29). Indeed, over the past decade, although patients presenting for CABG are older, have more comorbid conditions, have a higher prevalence of prior percutaneous coronary intervention (PCI) and/or CABG, and have a higher predicted risk of mortality than their historical predecessors, clinical outcomes after CABG have continued to improve (29-31).

Publications since 1994 comparing medical therapy alone with CABG in patients with LV dysfunction all suffer from several important limitations. These studies are either observational, highly selective or involve a relatively small number of patients. Most of the patients in these studies manifested with angina, few had overt symptoms of heart failure and the great majority had only mild documented LV dysfunction. Also, many of these publications were derived from selective databases, such as imaging laboratories, rather than from population-based registries.

Therefore, the recently published 2004 report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines for CABG for patients with poor LV function is principally derived from remote observational publications (Table 1) (32). Despite this important limitation, the available data suggest that patients most likely to benefit from surgical revascularization are those with left main, three-vessel or two-vessel disease involving the proximal left anterior descending artery with concomitant LV dysfunction.

THE ROLE OF EVALUATION OF MYOCARDIAL VIABILITY

Myocardial revascularization of patients with LV dysfunction can result in significant functional and clinical outcome benefits. The presence of myocardial viability appears to help to predict those patients most likely to manifest improved symptoms and reversibility of chronic LV dysfunction (33-40). The assessment of myocardial viability is therefore important to identify patients with a significant amount of viable, dysfunctional myocardium that is likely to recover function if revascularized with adequate blood flow. A variety of imaging techniques have

helped to characterize the presence of viable but dysfunctional myocardial tissue, for example, myocardial perfusion imaging with radionuclide flow tracers, positron emission tomography (PET) imaging with ^{18}F -fluorodeoxyglucose, and assessment of inotropic reserve through echocardiographic or nuclear imaging under catecholamine stimulation (33-40).

The assessment of myocardial viability may also help to identify patients for whom CABG is most likely to improve chances of survival. Prior studies have shown that more than 50% of patients with CAD and severe LV impairment have functionally significant myocardial viability, as assessed by a PET mismatch pattern (ie, enhanced ^{18}F -fluorodeoxyglucose uptake relative to perfusion) suggesting viability (41-43). These patients with PET mismatches appear to have a worse prognosis than those without mismatches. Long-term follow-up studies suggest that patients with CAD and LV dysfunction with PET mismatch images are associated with a poor annual survival rate if treated medically, whereas revascularization appears to improve their chances of survival to a level similar to those without mismatches (34,35).

A recent meta-analysis of 24 published studies, using various imaging techniques and protocols, and involving 3088 patients with a mean LVEF of 32% who were followed for a mean of 25 months, suggested that patients with significant dysfunctional but viable myocardium who subsequently underwent a revascularization procedure had a reduced mortality of 79% compared with those not revascularized (3% per year versus 16% per year, respectively, $P < 0.0001$) (44). Although suggestive of CABG benefiting patients with significant myocardial viability, this meta-analysis had significant limitations in its applicability to current clinical practice. The studies were observational, nonrandomized and nonblinded, and therefore, subject to selection bias. The use of different techniques and protocols, different definitions of viable myocardium, inter-technique variability and limited information on the background medical therapies administered are all important limitations. Nevertheless, the concordance of results suggests that the assessment of the extent of myocardial ischemia and viability using these imaging techniques can play an important role in guiding clinicians in the selection of appropriate patients for revascularization.

CABG VERSUS PCI

The use of percutaneous revascularization with stenting (ie, PCI) has become the predominant form of cardiac revascularization. Although numerous clinical trials have compared PCI with CABG in the therapy of patients with CAD, precious little evidence exists comparing current PCI with current cardiac revascularization techniques. Two recently published studies used cardiac registries to compare surgical therapy with PCI. The first was the New York State cardiac registry, which compared death rates and subsequent revascularization within three years of either CABG or PCI in 59,314 patients (45). After adjusting for the severity of illness before revascularization, patients with two or more diseased coronary arteries who underwent CABG had significantly better survival rates than those who underwent PCI. Those patients with an LVEF of less than 40% particularly benefitted from CABG.

The second registry, the Duke University Cardiovascular Databank, was used in a nonrandomized, prospective study of 18,481 patients with significant CAD who underwent coronary angiographic evaluation. This study, presented at the ACC 2002 (46), also supported the use of CABG over PCI in

patients with multivessel disease. Again, as in the New York State cardiac registry, patients with proximal left anterior descending coronary artery stenosis or with three-vessel disease were most likely to benefit from CABG.

In the absence of current randomized studies to guide clinicians, the equipoise of determining which patients with LV dysfunction should have medical therapy versus CABG versus PCI often remains an important enigma. The decision is generally the result of the convergence of a number of patient characteristics, including patient preference, age, the presence of angina or congestive heart failure, the severity of LV dysfunction, coronary anatomy, prior CABG, the presence and severity of ischemia and/or viability, and the presence of comorbidities. Sometimes what needs to be done is clear, while at other times, the decision is difficult and subjective (47). Clearly, more data from current, prospective, randomized trials comparing various therapies are required to improve our decision making. The role of medical therapy in comparison with CABG in a large category of patients with CAD is presently being evaluated in the Surgical Treatment for Ischemic Heart Failure (STICH) trial (48), and we await the results of this trial with great anticipation. The STICH trial will also evaluate the role of cardiac imaging for viable myocardium in identifying patients suitable for CABG.

THE ROLE OF SVR

LV end-systolic dilation after a myocardial infarction is associated with increased wall stress in the failing ventricle and loss of the normal helical heart structure, and it is a major determinant of a worse prognosis (49,50). SVR implies making an incision into the scarred and dilated myocardium, the placement of a suture inside the LV to exclude the scarred segment and the repair of the abnormal area with an endocardial patch. Athanasuleas et al (51), as well as other authors, have demonstrated that SVR benefits patients with ischemic cardiomyopathy and an anterior scar by improving LV volumes, LVEF and the New York Heart Association functional class (14,50-53). The Reconstructive Endoventricular Surgery returning Torsion Original Radius Elliptical shape to the left ventricle (RESTORE) group (51) have also reported that in selected patients, SVR with CABG alone is associated with a better prognosis than is generally associated with LV dysfunction and heart failure, and with an acceptably low operative mortality (7.7%), particularly when ventricular end-systolic dilation is not markedly increased (5.5%).

However, new data from the Society of Thoracic Surgeons' National Cardiac Database (54) suggest that in the community at large, overall procedural morbidity and mortality rates for the SVR procedure are somewhat higher than previously reported by the RESTORE group (9.3% versus 5.3%, respectively). Indeed, SVR is an emerging surgical therapy for heart failure and is associated with a learning curve, such that appropriate training is required before initiation in a given centre. Also, the Society of Thoracic Surgeons' National Cardiac Database suggests that SVR is associated with a particularly poor prognosis when performed as an emergency procedure.

Clearly, aneurysm resection is the treatment of choice for some patients. However, for others, when no clear aneurysm exists, the therapeutic option of choice remains unclear. Overall, the data available on the SVR procedure suggest that it may be of benefit for some patients, but more information from prospective randomized studies is necessary before its

place in the therapy of patients with LV dysfunction is understood. The STICH trial is presently comparing CABG with and without the use of SVR in patients with LV dysfunction, and when available, data from this trial should answer most of the questions related to the place of this surgical technique in current practice.

THE STICH TRIAL

The absence of convincing evidence in favour of either surgical revascularization or medical therapy alone in a large subgroup of patients with heart failure has directed the scientific community to objectively compare these different therapeutic modalities. The STICH trial is the first randomized prospective study to evaluate the potential benefit of surgical revascularization in patients ($n=2425$) with ischemic cardiomyopathy and LV dysfunction (an LVEF of less than 35%). This study is evaluating two hypotheses: whether CABG improves long-term survival rates compared with medical therapy alone in patients without a clear indication for CABG, and whether CABG with SVR improves survival free of hospitalization compared with CABG without SVR in patients requiring CABG who have LV dilation and an anterior scar. All patients are to be treated with intensive current medical therapy.

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CONCLUSIONS

Over the past two decades, the therapeutic options for patients with heart failure have progressed tremendously. However, the best current therapeutic modality for the treatment of the large number of patients with ischemic cardiomyopathy and LV dysfunction remains unclear. One area where this is particularly true is the role of CABG with and without SVR in patients with LV dysfunction and CAD. Clinicians need more data to make better evidence-based decisions. The presently ongoing STICH trial was designed to answer these fundamental questions in the current era of optimal medical and surgical therapy. Another important question that remains to be answered is that of the role of percutaneous coronary angioplasty in patients with ischemic heart failure.

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