Is There Evidence Supporting Coronary Revascularization in Patients With Left Ventricular Systolic Dysfunction?

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The mid- and long-term outcomes of revascularization procedures in patients with chronic left ventricular (LV) systolic dysfunction due to coronary artery disease (CAD) in the presence or absence of heart failure (HF) symptoms are still uncertain. The identification of dysfunctional myocardial segments with residual viability that can improve after revascularization is pivotal for further patient management. Hibernating myocardium (i.e., chronically dysfunctional but still viable tissue) can be identified by positron emission tomography (PET) and cardiac magnetic resonance (CMR) and its presence and extent can predict functional recovery after revascularization. Before β-blockers were introduced as routine care for HF, surgical revascularization appeared to improve survival in these patients. Nowadays, novel medical treatments and devices, such as cardiac-resynchronization therapy and implantable cardioverter–defibrillators, have improved the prognosis of HF patients and their use is supported by a number of clinical trials. To adequately address the unresolved issue of the prognostic benefits of coronary revascularization in CAD patients with chronic LV dysfunction on optimal medical therapy with/without devices a randomized trial is warranted. In such a trial the presence of viability will be assessed by either PET or CMR. This is an overview of the pathophysiological mechanisms, as well as of the main clinical studies and meta-analyses that have addressed this issue in the past 4 decades. (Circ J 2011; 75: 3–10)

Key Words: Coronary artery disease; Heart failure; Hibernation; Positron emission tomography; Revascularization

Pathophysiological Mechanisms Underlying Chronically Dysfunctional Myocardium in Patients With Coronary Artery Disease (CAD)

In the early 70s, 2 studies demonstrated that in patients with CAD testing wall-motion abnormalities were not necessarily due to irreversible scarring, but could improve upon administration of inotropic agents and that the improvement correlated with that observed following coronary artery bypass grafting (CABG).1,2 The transient amelioration of regional and global contractility in the dysfunctional myocardium induced by norepinephrine stimulation was also observed after CABG.3 In the 90s, at least 2 different mechanisms were hypothesized to underlie left ventricular (LV) systolic dysfunction in patients with CAD: (a) irreversible myocyte loss and replacement fibrosis after myocardial infarction (MI),4 and (b) chronically dysfunctional, but viable myocardium with preserved integrity of the myocyte membrane and contractile fibers, which can resume function following revascularization.5 The latter is also known as hibernating myocardium,6–8 a condition that is now believed to be the consequence of repeated episodes of ischemia. Transient contractile dysfunction (myocardial stunning) accompanies and follows episodes of ischemia during increases in myocardial metabolic demand in territories subtended by significant coronary stenoses and limited coronary flow reserve.9–11 Testing myocardial viability can help to detect areas of hibernation in patients with CAD and chronically dysfunctional myocardium, and identify those who might benefit from coronary revascularization (Figure 1).8

Identification of Hibernating Myocardium

18F-Fluorodeoxyglucose (18FDG) in combination with positron emission tomography (PET) is considered the gold standard for the assessment of myocardial viability, particularly in patients with severely impaired LV ejection fraction (LVEF).9 The perfusion/metabolism mismatch pattern is considered the hallmark of myocardial hibernation.10 Perfusion assessed with a flow tracer (13NH3) is reduced, whereas metabolism (18FDG uptake) is preserved.11

Alternatively, the use of a specific protocol (the hyperinsulinemic euglycemic clamp protocol) allows quantification of the metabolic rate of glucose uptake (μmol·g⁻¹·min⁻¹) under carefully controlled metabolic conditions and does not require a flow scan.12 18FDG-PET defines metabolic cell integrity and has the highest sensitivity compared with other methods for predicting LV functional recovery following revascularization, whereas techniques challenging the contractile reserve, such as dobutamine stress with echocardiogram (DSE), show...
the highest specificity.\textsuperscript{4,11}

**Revascularization in Patients With CAD**

In the Coronary Artery Surgery Study (CASS) trial, the 780 patients with ischemic heart disease assigned to receive either medical or surgical treatment had comparable survival rates at 5 years’ follow-up. These results led to the conclusion that bypass surgery can be safely deferred until “symptoms worsen to the point that surgical palliation is required”.\textsuperscript{13}

Over the decades, surgical revascularization has proven an effective therapy for the relief of angina.\textsuperscript{14}

Although coronary revascularization is performed frequently, its role in patients with moderate to severe LV dysfunction, but who do not have angina or reversible myocardial ischemia, remains uncertain.\textsuperscript{15} Recent European Guidelines on Heart Failure (HF) do not clearly recommend revascularization as a specific intervention in patients with chronic ischemic LV dysfunction, unless they suffer from angina, because of the uncertainty of balancing the benefit of revascularization with the increased periprocedural risks.\textsuperscript{16} This is due to the lack of specific randomized trials comparing the most recent optimal medical therapy (OMT), including cardiac-resynchronization therapy (CRT) and implantable cardioverter–defibrillators (ICD), with OMT plus revascularization, by either CABG or percutaneous coronary intervention (PCI).\textsuperscript{15} Furthermore, not infrequently in clinical practice the extent of myocardial viability is not measured before revascularization, and even in the Surgical Treatment for Ischemic Heart Failure (STICH) trial, viability is not assessed in all patients recruited nor is it used to direct therapy.\textsuperscript{17}

**Patients With Preserved LVEF**

A number of randomized trials (Table) have assessed the prognostic value of revascularization by either CABG or PCI in a large number of patients (>7,800 patients) with ischemic heart disease and preserved LVEF.\textsuperscript{18–22} In the 90s, the Atorvastatin vs. Revascularization Treatment study, was one of the first randomized trials comparing medical treatment inclusive of lipid-lowering drugs vs. PCI. Despite the relatively short follow-up (18 months), aggressive lipid-lowering therapy was at least as effective as PCI in reducing the incidence of ischemic events in low-risk patients with stable CAD.\textsuperscript{23} The more recent Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial confirmed these results in 2,287 patients randomized to OMT with and without PCI. The main results of COURAGE in patients with preserved LVEF (60±11\%) revealed no difference between treatments (P=0.62) in the primary endpoint of death or acute MI for a median follow-up of 4.6 years.\textsuperscript{18} The OMT arm of the COURAGE trial achieved a significant reduction in ischemia by using anti-anginal therapy combined with a strategy of optimal risk factor control and lifestyle modification. That trial included a nuclear substudy
using SPECT to measure the ischemic burden before and 6–18 months after treatment in a subset of 314 patients. The main findings of this prospective substudy were that: (a) at 18-month follow-up, the reduction in ischemic myocardium was greater with PCI + OMT (–2.7%) than with OMT alone (–0.5%); (b) patients treated with PCI + OMT exhibited significant ischemia reduction (33% vs. 19%); especially patients with moderate to severe ischemia (78% vs. 52%; P=0.007) affecting ≥10% of LV myocardium; (c) patients with reduction in ischemia had a lower unadjusted risk for death or MI, particularly if baseline ischemia was moderate to severe. The study was underpowered for estimation of prognosis; however, there was a trend indicating that ≥5% reduction in ischemia resulted in a reduced rate of death or MI in both treatment arms. However, no information is available to evaluate the agreement between anginal symptoms and the extent of myocardial ischemia or their relative prognostic importance.

Diabetic patients were recruited in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. The population of 2,368 patients with stable ischemic heart disease (mean duration of diabetes, 10 years; anginal symptoms, >82%) showed similar 5-year all-cause mortality rates in both the medical therapy and the revascularization by PCI or CABG groups. Only analysis of a secondary endpoint (composite of cardiac death and MI) revealed a benefit of CABG in patients with more extensive CAD compared with medical therapy or PCI, but there were no differences between PCI and medical treatment. Further evidence supporting the equivalence of modern OMT and revascularization is gained from the Occluded Artery Trial (OAT), which showed in 2,185 patients that PCI of an infarct-related artery went stress testing with SPECT or DES had better outcomes than those who did not, although there were important baseline differences (eg, age and LVEF) between the 2 groups. In the same study, mild–moderate inducible ischemia was not related to outcome in patients managed with OMT or PCI, and the lack of benefit of PCI compared with OMT alone was consistent regardless of the presence of inducible ischemia. These results could be explained by the following: (1) the extent of ischemia in the OAT substudy subjects was too small (in the COURAGE substudy the minimum extent of ischemia to observe a clinical benefit was 10% of LV); (2) ischemia alone is not a powerful enough determinant of prognosis in comparison with hibernation when treated by revascularization. On the other hand, a smaller randomized study, the Swiss Interventional Study on Silent Ischemia Type II (SWISSI II), showed that in patients with recent MI, PCI reduced the long-term (10 years) risk of major cardiac events (composite of cardiac death, nonfatal MI and/or symptom-driven revascularization) compared with OMT in patients with silent ischemia demonstrated by stress imaging (DES or SPECT). Furthermore, LVEF was preserved in PCI patients (54–57%), although decreased significantly in patients treated with OMT (from 60% to 49%, P<0.001).

**Patients With Reduced LVEF and/or HF**

Based on the results of some of the trials performed in patients with CAD and preserved LVEF (eg, BARI-2D), subgroups of patients in whom coronary revascularization confers prognostic benefit can be identified. So far there is no single randomized trial that has addressed this issue in patients with ischemic systolic dysfunction, except for the STICH trial, which is still ongoing.

A retrospective subgroup analysis of the randomized CASS trial suggested that patients with an LVEF of 35–50% had a mortality benefit from CABG in comparison with medical therapy at 10-year follow-up. The main limitations of that subanalysis are that: (1) medical therapy was not optimal according to today’s standards; (2) the total number of patients was only 160; and (3) patients with symptoms of HF had no obvious benefit from revascularization (Table).
Meta-Analyses and Retrospective Studies

In 2002, Allman et al\textsuperscript{27} published a comprehensive meta-analysis based on 24 retrospective studies published before 1999. The study evaluated a total of 3,088 patients with LVEF $\leq 32\%$ who underwent viability assessment as part of the workup before revascularization and were followed for 25±10 months. In patients with viable myocardium, revascularization was associated with a 79.6% reduction in annual mortality compared with medical treatment, whereas revascularization did not confer prognostic advantage in patients with minimal or absent viability. This meta-analysis demonstrated a strong association between the presence of myocardial viability by noninvasive testing and improved survival after revascularization in patients with chronic CAD and LV dysfunction. On the basis of this meta-analysis, which does not take into consideration more recent advances in the field, the 2010 European Guidelines for revascularization graded revascularization by CABG as an effective intervention in CAD patients with LVEF $\leq 35\%$, no significant angina and evidence of viable myocardium as level B evidence, class of recommendation IIa (whereas revascularization by PCI was graded as class IIb, evidence level C).\textsuperscript{14} The meta-analysis by Allman et al\textsuperscript{27}, however, suffers from a number of limitations: (1) all the studies were retrospective and not randomized; (2) the largest study included 353 patients, and 12 studies included less than 100 patients each;\textsuperscript{27} and finally, (3) it is unlikely that negative studies of comparable dimensions could be published. Another retrospective study by Tarakji et al\textsuperscript{28} in 306 patients with LVEF $\leq 35\%$ and HF (evaluated in a single center between 1997 and 2002) who underwent PET imaging before revascularization confirmed the results reported by Allman et al.\textsuperscript{27} Those authors went a step further, concluding that early revascularization might be associated with improved survival, regardless of the extent of viable myocardium.\textsuperscript{29} At the beginning of the year 2000, $\beta$-blockers were introduced for the management of patients with LV dysfunction because they had proven highly effective in reducing morbidity and mortality in patients with HF.\textsuperscript{29} Therefore, the effectiveness of revascularization should be re-evaluated in the more recent years in which adrenergic-blockers and implantable devices have been widely used to obtain a further significant reduction in mortality.

In 2008, Camici et al\textsuperscript{4} examined 14 studies carried out with established techniques to assess viability in patients with LVEF $\leq 45\%$ due to CAD and published between 1998 and 2006. Similarly to Allman et al,\textsuperscript{27} they found an absolute annual mortality reduction from approximately 12% in patients treated with medical treatment to 4% in patients who underwent revascularization in the presence of viable myocardium.\textsuperscript{4} On the other hand, the annual mortality rate observed in patients treated medically appears to be similar, independent of the presence of viability, which is at variance with the findings of Allman et al.\textsuperscript{27} The apparent discrepancy could be a reflection of the optimization of patient management according to more recent guidelines (Figure 2).\textsuperscript{14,16,30–32}

Indications Derived From Other Studies

The results of the substudy of the CASS registry were not supported by another OAT substudy that focused on patients with LVEF $\leq 44\%$ who were randomized to PCI or medical therapy.\textsuperscript{33} That analysis confirmed that low LVEF was a powerful predictor of increased risk after MI, and a comparison of 743 patients with LVEF $\leq 44\%$ vs. 1,442 patients with LVEF $>44\%$ found that there was no interaction between...
baseline LVEF and treatment effect (PCI or medical therapy) for the composite outcome of death, recurrent MI or New York Heart Association (NYHA) class IV HF. Furthermore, there was a trend towards a greater rate of re-infarction in the PCI subgroup reported in the primary OAT report, which appeared to be mainly attributable to patients with lower LVEF. The findings of the Total Occlusion Study of Canada (TOSCA)-2 trial in 381 patients randomized to PCI or medical therapy are also in line with these results. PCI with stenting of a persistently occluded infarct-related artery in the subacute phase after MI had no effect on LVEF, despite long-term patency. In fact, LVEF increased significantly in both groups, without a between-group difference: PCI 4.2±8.9 vs. medical therapy 3.5±8.2 (P=0.47). In a recent small prospective study, the effect of PCI on long-term myocardial function in patients with multivessel CAD was explored and quantified by CMR. Six months after successful revascularization, LVEF improved significantly from 46±12% to 51±13%. It is possible that in patients suitable for revascularization an advantage could be obtained by CABG in terms of more complete revascularization, and the need for complete revascularization can be another issue to consider in the final clinical decision. In a randomized trial, Cleland et al addressed the effects of carvedilol on LVEF in patients with hibernating myocardium and they concluded that carvedilol might improve the function of hibernating or ischemic myocardium or both; in fact, patients with more extensive hibernation/ischemia had a greater improvement of LVEF with carvedilol.

The PET And Recovery Following Revascularization-2 (PARR-2) Study

The PARR-2 study is the first prospective study to address the question of whether revascularization might be beneficial in patients with HF and whether clinical decisions assisted by PET alter patient outcome compared with standard care. The PARR-2 is a multicenter trial that randomized 428 patients with LVEF ≤35% due to suspected CAD who were considered for revascularization, HF or transplantation work-up. The extent and severity of scarring and mismatch on perfusion/18F-DG-PET were determined and considered in the context of a previously derived model for predicting LV recovery after revascularization. Using the results of this model and the interpretation of PET images, the physician and surgeon decided whether or not to proceed with revascularization. Although there was a trend for better outcomes using the PET strategy compared with standard care, the main results were inconclusive. After 1 year, the proportion of patients who had experienced one of the composite endpoints (cardiac death, MI and recurrent hospital stay for cardiac cause) was 30% in the “PET arm” vs. 36% in the “standard arm” (relative risk 0.82%, 95%CI 0.59–1.14; P=0.16). Interestingly, among the 206 patients without recent angiography, there was a significant reduction in cardiac death in the “PET arm”, but the absolute number of events was small. Patients who had not undergone recent angiography, as expected, represented a sicker population, with lower LVEF, worse renal function and more CABG. It should be stressed that in this study most patients (>70%) underwent revascularization by CABG, suggesting that the study population consisted of patients with more severe and extensive CAD. In such patients, the decision to revascularize becomes even more critical and PET imaging could help to optimize patient selection while reducing the need of coronary angiography in those without evidence of viability. However, it is worth noting that in the PARR-2 study there was approximately 25% non-adherence to the indications provided by PET. A post-hoc analysis in those that adhered to PET recommendations (“ADHERE” arm) showed a significant decrease in the hazard ratio for the primary endpoint compared with standard care. Further post-hoc analysis revealed that 18FDG-PET was more beneficial in experienced centers with ready access to and routine integration of 18FDG PET.

In a PARR-2 post hoc analysis that included 182 patients randomized to the PET arm, a minimum amount of viability of 7% of LV mass was necessary for an outcome benefit. Larger areas of preserved viability increased the benefit of revascularization. This threshold appears lower than that estimated from non-randomized studies (25%). Taken together, the findings of the PARR-2 trial support that 18FDG-PET viability imaging has clinical utility in identifying high-risk patients who may benefit from revascularization and is a valuable tool in improving patient outcomes only if 18FDG-based recommendations can be meaningfully incorporated into an overall management strategy.

The STICH Study: A New Trial Already Old

The concept that revascularization with CABG may improve the outcome of patients with ischemic LV dysfunction is being tested in the STICH trial, funded by the National Heart, Lung and Blood Institute. The first part of this study, focusing on the effectiveness of surgical ventricular reconstruction associated with CABG, has been published. In this first report, patients with LVEF ≤35% undergoing CABG without LV reconstruction had a perioperative mortality of 5% and a stroke rate of 3%. Patients were recruited and segregated in 3 different strata (medical arm, CABG arm or CABG+ventricular reconstruction arm). It should be noted that the allocation to the strata introduced a significant bias, because it was heavily dependent on the investigator’s decision. Furthermore, at variance with the CASS study, in the STICH trial there was no registry to follow eligible patients who were not randomized. In general, the concept underlying the STICH trial is to demonstrate that the surgical approach is superior to medical management of ischemic HF, rather than to demonstrate the benefit of revascularization in patients with ischemic LV dysfunction and residual myocardial viability. In STICH, PCI was considered as part of the medical stratum, although it has been recently demonstrated that PCI can effectively restore flow with a lower periprocedural morbidity and mortality than CABG. Additionally, in STICH, the management (repair or replacement or no intervention) of mitral regurgitation was left to the discretion of the study physician/surgeon. Finally, the original STICH protocol does not account for variables that may influence outcome and act as confounding elements, such as the use of CRT and ICD. Furthermore, viability was not assessed in all patients recruited, and in those in whom it was evaluated different methods were used, leading to a significant variability in the accuracy of its detection and determination of extent. The results of the viability tests did not guide the therapeutic intervention. The Trial suffers from the drawback of a design planned in the late 90s when mortality and morbidity due to HF in patients treated medically was higher, because some effective drugs and devices (CRT, ICD) were not routinely used and/or widely available. Additionally, the 35% 3-year mortality rate expected in the medical arm of STICH appears overestimated, considering that patients in NYHA class I were also recruited. However, the final judgment must await the publication of the results.
A New Study to Establish if Revascularization can Improve Prognosis in Patients With Ischemic LV Dysfunction

An unselective approach, such that in STICH, may expose patients to unnecessary risks: from impairment of renal function due to excessive use of contrast medium to potentially lethal events associated with CAGB and PCI. Clinical experience can play an important role in the final choice, but more objective criteria for assessing the potential benefit of revascularization in high-risk patients should be developed. It is our belief that residual myocardial viability is the key element in the management of these patients. We propose that this issue should be addressed in a specific clinical trial, as suggested in Figure 3.

Figure 3. Flowchart for a new study to assess the prognostic value of revascularization in patients with ischemic left ventricular (LV) systolic dysfunction. Proposal for a novel trial aimed at assessing the potential prognostic value of coronary revascularization by coronary artery bypass grafting (CAGB) or percutaneous coronary intervention (PCI) compared to optimal medical therapy when viable myocardium is demonstrated in the context of ischemic LV systolic dysfunction in patients with coronary artery disease (CAD) suitable for revascularization. EF, ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association.
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