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What is the role of coronary revascularization to recover the contractility of the dysfunctional heart?

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Coronary artery disease is the predominant aetiology of heart failure and left ventricular dysfunction in industrialized countries. The pathophysiological substrate of hibernating myocardium constitutes the conceptual target of coronary revascularization by coronary artery bypass graft (CABG) or coronary angioplasty or percutaneous coronary intervention (PCI). Studies, mainly observational, conducted in the past have demonstrated a prognostic benefit of CABG on survival. These findings were confirmed by the long-term follow-up of the STICH study in which, however, documentation of inducible ischaemia or myocardial viability was not predictive of a prognostic benefit of CABG. Revascularization via PCI in the recent REVIVED-BCIS2 study did not demonstrate a significant benefit in terms of death or heart failure hospitalization compared with optimal medical therapy. Pending the long-term follow-up of the REVIVED-BCIS2 study, optimized medical therapy, cardiac resynchronization therapy, and the implantable cardioverter defibrillator, where indicated, are the mainstay of treatment in patients with dilated ischaemic cardiomyopathy. The decision for coronary revascularization is made in the individual patient, possibly with a higher bias in patients with angina, three-vessel coronary artery disease, severe left ventricular dysfunction, and cardiac remodelling.

Introduction

In the last decades, heart failure has become responsible for a progressively increasing number of hospitalizations and mortality and coronary heart disease has become the main aetiopathogenetic factor in industrialized countries.

For over a century, it has been known that myocardial hypoperfusion, even if not such as to determine the death of myocytes, can cause a significant impairment of their contractility. In acute, after myocardial infarction, segments of viable myocardium adjacent to the necrotic area can show a contractility deficit that can transiently persist for hours or days even after normal coronary blood flow has been restored ('stunned' myocardium). This is the so-called myocardial 'hibernation', as defined by Rahimtoola in 1985,[1] where there is a persistent contractile dysfunction secondary to a chronic reduction of the coronary flow at rest, such as to keep the ischaemic cells alive but with a significant impairment of the contractile function.

The identification of dysfunctional but viable myocardial tissue, capable of improving its function after surgical or percutaneous revascularization, has been a source of considerable interest for its important managerial and prognostic implications in patients with coronary artery disease and significant left ventricular dysfunction.

Myocardial revascularization in the presence of ischaemic ventricular dysfunction

The Coronary Artery Surgery Study (CASS) study published in 1983[2] was one of the first to demonstrate a survival benefit obtained with coronary artery bypass graft (CABG) surgical revascularization in patients with left ventricular dysfunction. In this study, survival was evaluated in patients with an average age of 55 years and severe left ventricular dysfunction [left ventricular ejection fraction (LVEF) <35%] depending on whether they were

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treated with medical therapy alone (420 patients) or with CABG (231 patients). Coronary artery bypass graft was associated with improved survival, especially for patients with LVEF < 26%, in whom the 5 year survival was 43% with medical therapy alone vs. 63% with surgery.

These results were confirmed by a large meta-analysis of 21 studies conducted between 1983 and 2016 with over 16 000 patients with left ventricular dysfunction (LVEF < 40%) and coronary artery disease in which the prognostic benefit of surgical or percutaneous revascularization was evaluated [percutaneous coronary intervention (PCI)].[3] Compared with medical therapy alone, revascularization showed a significant reduction in total mortality [CABG hazard ratio (HR) 0.66; PCI HR 0.73], with a significant advantage for CABG intervention over PCI (HR 0.82, $P < 0.001$).

In a more recent large meta-analysis of 20 observational studies and only 4 randomized clinical trials, Gaudino *et al.*[4] compared the optimal therapeutic strategy (CABG, PCI, or medical therapy alone) in over 23 000 patients with ischaemic left ventricular dysfunction. Coronary artery bypass graft intervention in these patients was associated with the best survival data, followed by PCI and finally by medical therapy alone.

In 2011, the STICH study was published[5] which enrolled 1212 patients aged 60 years on average with severe left ventricular dysfunction (LVEF < 35%) of ischaemic genesis susceptible to CABG, randomizing them 1 : 1 to surgical revascularization vs. medical therapy alone. In the subsequent median follow-up of nearly 5 years, death from all causes (primary endpoint) did not show significant differences between the two groups (41% medical therapy vs. 36% CABG, $P = 0.12$), mainly due to greater intervention-related mortality in patients in the CABG group which offset the subsequent benefit, while there was a slight advantage with revascularization in cardiovascular mortality (33% medical therapy vs. 28% CABG, $P = 0.05$) and cumulative incidence of total mortality and hospitalization for cardiovascular causes (68% medical therapy vs. 58% CABG, $P < 0.001$).

Assuming a follow-up too short to highlight statistical differences, the same researchers continued the follow-up of the STICH study for a median of 9.8 years demonstrating a 16% reduction in total mortality in favour of the CABG (death from all causes 66% medical therapy vs. 59% CABG, $P = 0.02$).[6]

A sub-analysis of the STICH study evaluated the effect on prognosis of three anatomical variables consisting of three-vessel coronary artery disease, severe left ventricular dysfunction (LVEF < 27%), and high end-systolic left ventricular volume (>79 mL/m^2).[7] In the 636 patients with at least 2 of these prognostic factors, mortality was significantly reduced with CABG intervention compared to medical therapy alone (HR 0.71), while a benefit of CABG was not observed in the other patients (HR 1.08). In particular, a benefit of CABG on total mortality and cardiovascular mortality was not observed in patients without three-vessel coronary artery disease. This study demonstrates that the anatomical extent of coronary artery disease is an important predictor of the benefit of CABG in patients with ischaemic cardiomyopathy.

Based on these findings, in the presence of severe left ventricular dysfunction (LVEF < 35%), the current 2018 European Society of Cardiology guidelines on revascularization[8] recommend surgical revascularization in patients with multivessel coronary artery disease and acceptable operative risk (class 1, level of evidence B) or, alternatively, percutaneous revascularization (class 2A, level of evidence C) vs. medical therapy alone.

Inducible ischaemia and revascularization in patients with ischaemic ventricular dysfunction

The original protocol of the STICH study involved the use of ischaemia testing by radioisotope stress testing or echocardiography and myocardial viability testing by echocardiography, or single-photon emission computed tomography (SPECT) myocardial scintigraphy.

This assessment became optional during the course of the study and ischaemia and vitality data were obtained in only 33% and 50% of patients, respectively.

O'Fee *et al.*[9] evaluated the presence of inducible ischaemia in 402 patients (mean age 61 years and mean LVEF 26%) of the STICH study who underwent SPECT or stress echocardiography with dobutamine and its correlation with prognosis. The 255 patients with inducible ischaemia (63% of the total) did not show a significantly different 10 year mortality compared to patients without inducible ischaemia, neither on the basis of the presence nor on the basis of the extent of ischaemia. Similarly, there were no significant differences in mortality between patients with or without inducible ischaemia based on randomization to CABG intervention or medical therapy.

Rozanski *et al.*[10] retrospectively evaluated all patients undergoing SPECT since 1998 for almost 20 years, looking for a correlation between the extent of ischaemia, early myocardial revascularization, and mortality. In 39 883 patients with LVEF > 45%, early revascularization was beneficial only in the presence of severe ischaemia (HR 0.7), while in 3556 patients with more severe ventricular dysfunction (LVEF < 45%), early revascularization resulted in a reduction of mortality in the presence of both moderate (HR 0.67) and severe (HR 0.55) ischaemia.

Similarly, Rodenas-Alesina *et al.*[11] published a study of 747 consecutive patients with LVEF < 40% on an ischaemic basis who underwent SPECT, evaluating the correlation between the extent of ischaemia, early myocardial revascularization, and major adverse cardiovascular events (MACE) consisting of cardiovascular death, myocardial infarction, and hospitalization for heart failure. After a median follow-up of more than 4 years, early revascularization was significantly related to a reduction in MACE only in patients with significant ischaemia defined as ischaemic area > 10% (HR 0.59).

In patients with stable coronary artery disease in the absence of left ventricular dysfunction, coronary revascularization was not superior to medical therapy. The ISCHEMIA study[12] evaluated the prognosis in 5179 patients with at least moderate inducible myocardial ischaemia, randomized 1 : 1 to either an initially invasive strategy (coronary angiography followed by revascularization) or a conservative strategy (initial medical therapy and coronary angiography only in case of need). In the initially invasive group, revascularization was performed mainly by PCI (74%) and only in 26% by CABG. In the subsequent median follow-up of 3.2 years, the primary composite endpoint of cardiovascular death, myocardial infarction or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest did not show significant differences between the two groups.

A subsequent sub-analysis of the ISCHEMIA study[13] analysed the small subset of 398 patients with a history of heart failure or left ventricular dysfunction (LVEF between 35% and 45%) and compared them to other patients. The history of heart failure was correlated with a greater risk of cardiovascular events, and in these patients, the early invasive strategy showed a significant benefit compared to the conservative one (primary endpoint 17.2% vs. 29.3% at 4 years). On the contrary, in patients without a history of heart failure, even in the presence of left ventricular dysfunction, early revascularization did not show advantages over the initially conservative strategy (event incidence 13.0% vs. 14.6% at 4 years).

Myocardial viability and revascularization in patients with ischaemic ventricular dysfunction

The presence of viable but dysfunctional myocardium (hibernating myocardium) may represent a potentially reversible element of left ventricular dysfunction and could distinguish patients undergoing revascularization in the hope of functional recovery from those without myocardial viability in whom recovery will be unlikely.

Numerous retrospective observational studies have evaluated the effects on the prognosis of revascularization of areas of hibernating myocardium identified by viability search tests. In a meta-analysis of 24 observational studies, Allman *et al.*[14] evaluated the impact of revascularization compared with medical therapy alone in 3088 patients, mean age 61 years, with severe left ventricular dysfunction (mean LVEF 32%) who underwent search for vitality. In the follow-up of more than 2 years, in patients with viability (42%), revascularization was associated with an almost 80% reduction in annual mortality (revascularization: 3.2%/year—medical therapy 16%/year, $P < 0.0001$), while in the absence of myocardial viability, no difference was observed (revascularization: 7.7%/year—medical therapy 6.2%/year). The results of this meta-analysis underscore the utility of viability tests to identify patients with severe left ventricular dysfunction who may have a prognostic advantage with surgical revascularization. In the subgroup of 601 patients of the STICH study undergoing vitality research, the possible correlation between the presence of vitality and the benefit of BPAC on left ventricular function and prognosis at 5 and 10 years was evaluated.[15] The presence of viability, defined on SPECT as the presence of 11 or more viable segments and on dobutamine stress echocardiography as 5 or more segments with improvement in systolic function during testing, was documented in 487 patients (81%). In a 4 month follow-up, LVEF showed a slight but significant increase only in patients with vitality (+2.3%) but in any case comparable between patients undergoing CABG vs. medical therapy alone. During the 10 year follow-up, there were no differences in survival based on the presence or absence of viability (total mortality in patients with viability 64% and in patients without viability 68%, $P = 0.09$), nor overall nor within each of the two study arms (CABG vs. medical therapy alone, P 0.34). Similar results were obtained for the secondary endpoints (death from cardiovascular causes and the composite endpoint of death from any cause or hospitalization for cardiovascular causes). The authors conclude by stating the uselessness of vitality tests in predicting a long-term prognostic benefit of CAGB.

Overall, these studies show a probable advantage of revascularization in patients with left ventricular dysfunction and inducible myocardial ischaemia, the more marked, the more extensive the area of ischaemia and the more severe the left ventricular dysfunction. However, doubts remain about the prognostic benefit of revascularization in relation to the presence of vitality.

The REVIVED-BCIS2 study

The recent REVIVED-BCIS2 study was designed and conducted following the hypothesis that in patients with severe ischemic dilated heart disease and evidence of myocardial viability, percutaneous revascularization could produce benefit in terms of survival as well as improvement of the left ventricular function. These effects could be more evident than after surgical revascularization, as they are not burden by the post-operative mortality peak of surgery found in the STICH study.[16] This multicentre study randomized 1 : 1 700 patients, mean age 70 years, with severe left ventricular dysfunction (LVEF < 35%), coronary artery disease amenable to percutaneous revascularization, and the presence of viability, to PCI in addition to optimized medical therapy or alone. Viability (70% MRI, 26% DSE, and 4% SPECT/PET) had to be present in at least four segments that were dysfunctional and susceptible to revascularization. During the 3.4 year follow-up, the primary composite end point of all-cause death and heart failure hospitalization occurred equally in the two groups (PCI group 37.2% and medical therapy group 38%, HR 0.99). Similarly, the measurement of LVEF at 6 and 12 months did not document any differences (on average 27% in both groups). The only data in favour of PCI were the evaluation of the quality of life at 6 and 12 months, which however subsequently tends to diminish. The authors conclude that in the absence of coronary symptoms, there is no indication for percutaneous revascularization in patients with severe left ventricular dysfunction and viability.

The editorial accompanying the REVIVED-BCIS2 study[17] emphasizes the need for extended follow-up to be able to compare results with those of the STICH study. He then highlights some critical issues relating to the recruitment selection criteria which could have significantly influenced the result. In particular, it is possible that patients with more severe three-vessel coronary artery disease, who would have benefited more from revascularization, were referred for cardiac surgery, while patients with a relatively small extent of coronary artery disease were enrolled in the study. It is therefore conceivable that some of the left ventricular dysfunction may not have been totally dependent on coronary artery disease. If this were the case, revascularization via PCI would hardly allow recovery of systolic function.

The population of the REVIVED study was also largely asymptomatic for heart failure (in 70% NYHA I or II) and well treated, and perhaps for these reasons, the study did not reach the number of events expected to obtain statistical significance. Compared to the population of patients enrolled in the STICH study, patients in the REVIVED study received much more intense pharmacological treatment of heart failure. In particular, a non-negligible proportion of patients (about 50%) were treated with

aldosterone blockers and sacubitril/valsartan (16% in the PCI arm and 26% in the medical therapy arm), which at the time of the STICH study (2002–2007) were not available or not yet recommended by the guidelines. Cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillator (ICD) were also more frequently used in REVIVED than in STICH. Optimal pharmacological and electrical treatment of patients enrolled in REVIVED may explain the low rate of hospitalizations for heart failure (approximately 15%) observed in both arms of the trial. On the basis of these considerations, it is evident that, compared to the CABG of the STICH study, for the PCI of the REVIVED study, the bar to overcome was placed at a significantly higher level. We do not know whether an advantage of PCI over optimal medical therapy alone could have emerged with a larger series and longer follow-up (currently underway).

Conclusions

In conclusion, in patients with heart failure and/or left ventricular dysfunction, the main objective should be to optimize medical therapy with the use of ARNI and SGLT2 inhibitors, together with the use of electrical devices, which have demonstrated prognostic benefit and efficacy in improving LVEF. The decision regarding a possible coronary revascularization should be implemented in the individual patient by trying to understand whether the coronary artery disease has a causal role or is only coincidental with the cardiomyopathy. An increased propensity for revascularization should probably be legitimate in patients with angina, three-vessel coronary artery disease, particularly depressed LVEF, and left ventricular remodelling. Furthermore, the coexistence of significant functional mitral regurgitation should be evaluated, since its reduction through coronary revascularization by CABG or PCI could allow a favourable prognostic benefit.

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Data availability

No new data were generated or analysed in support of this research.

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