Commentary

Has moderate ischemic mitral regurgitation to be corrected?—Analysis of a randomized trial

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The correct treatment of ischemic mitral regurgitation (IMR) is still not well established. Even if the benefit of revascularization in patients with depressed LV function is well known, patients with a substantial amount of dysfunctional but viable myocardium may not improve EF or prognosis after revascularization alone. Lack of recovery in patients with a considerable amount of viable tissue may be related to increased LV volume due to ventricular remodeling. The onset of secondary MR is the main factor that may induce progressive LV dilatation, affecting survival and functional status. The vicious circle related to the appearance of MR results in further LV remodeling with subsequent increase in MR grade. Nevertheless, there is still no clear evidence that correction of IMR could have a benefit in terms of survival, even if there are many evidences that IMR correction improves symptoms of heart failure if compared with patients with same IMR grade, but uncorrected (1,2). Moreover the natural history of uncorrected IMR are related only to MR secondary to an acute myocardial infarction (AMI), where revascularization is not expected to have any benefit (3,4).

Whereas there is general agreement to correct severe IMR, the problem of correction of moderate IMR has been recently addressed by a randomized study (5,6) including 301 patients with moderate IMR who needed coronary artery bypass grafting (CABG). Two groups were randomized, one CABG alone and one CABG + mitral valve repair (MVr). Results showed that, after 1 year, adding MVr to CABG was not beneficial with the exception of fewer patients with moderate or severe IMR at follow up. However, this study, which could provide answers, added only confusion.

First of all, the definition of IMR is unclear. The term "ischemic" includes a huge anatomic pictures, from the MR purely ischemic, then reversible with revascularization only, to the MR secondary to AMI, then non reversible with myocardial revascularization. It is preferable, as suggested by the guidelines (7), to add the term "chronic" to emphasize the post-infarction origin of the regurgitation. It is evident that MR if purely ischemic or if consequence of an AMI have different prognostic value and surgical indication.

In this trial IMR was defined as "functional valve incompetence due to myocardial injury and adverse left ventricular remodeling" (5). However, 35.8% of patients in the CABG only group and 31.3% in the CABG + MVr had no AMI, mixing patients with myocardial ischemia and with myocardial infarction. This aspect made results inconsistent.

The ejection fraction (EF) of the patients was on the high side. The mean was 41.2%±11.6% in CABG alone and 39.3%±10.9% in CABG + MVr, but the standard deviation (SD) was such that about 50% of the patient had an EF of 41.2% or more, identifying patients where indication to CIMR correction, in prospective, is doubtful: our group demonstrated that correction of less than severe CIMR does not influence 10-year outcome in treated or untreated patients when EF is >40% (8). Furthermore, due to the SD properties, EF was >52.8% in about 16% of the patients who had CABG alone and >50.2% in about 16% of the patients who had CABG + MVr. Evaluating left ventricular end-systolic volume index (LVESi) (54.8±24.9 in CABG alone group and 59.6±25.7 in CABG + MVr), about 16% of the patients had a LVESVi of 33.5 or less and 33.9 or less,

respectively.

Practically, this study includes a reasonable number of patients with normal EF and normal or mildly increased LVESVi. Moreover, overall about 60% of the patients had no or mild sign of heart failure. It is noteworthy that the diagnosis of IMR was confirmed perioperatively by transesophageal echocardiography on negative basis "to confirm the absence of a mitral-valve structural abnormality" and not because of presence of subvalvular abnormalities specific of IMR, as chordal tethering and so on. All these considerations cast shadow on the way the study was built and on its conclusions.

The conclusions of the first paper of this trial (5) focus on the higher early hazard of neurologic complications. In the CABG + MVr group a case of dural-based mass (not better specified, but most likely a meningioma, not related to the procedure) and 3 cases of metabolic toxic encephalopathy (related to the procedure in general and not specifically to the MVr added to these patients) were included. Moreover a case of stroke was counted twice (very likely a patient had 2 episodes of stroke). If, correctly, these neurological complications would be excluded, P value would become not significant (from 0.03 to 0.23). It seems that there is trend to include more complications possible in the CABG + MVr group.

In the follow up paper by Michler *et al*. (6) the conclusions were that "the addition of mitral-valve repair to CABG had no incremental effect on reverse left ventricular remodeling at 2 years". Data about LV volumes were not provided, but we know from the text that patients who never had moderate or severe persistent mitral regurgitation had more reverse LV remodeling that those who did. The prevalence of moderate or severe mitral regurgitation was higher in the CABG alone group than in the CABG + MVr group (32.3% *vs*. 11.2%, P<0.001). Then the prevalence of patients who had an improvement in LV volumes was at least 3 times higher in CABG + MVr than in CABG alone group. Quality of life was as well similar in both groups. However, the Duke Activity Status Index, which focuses on cardiac physical function, showed better scores in CABG + MVr patients, suggesting that adding MVr provided an increased ability to undertake tasks with higher metabolic demands quality of life. Again, the conclusions emphasized the negative aspects (early neurologic hazard), but failed to report the possible benefits in adding MVr to CABG (better cardiac physical function, less IMR grade which translates in higher reverse LV remodeling).

What did we learn from this randomized study? Not a lot. Twenty-six centers recruited 301 patients in 4 years, 2.9 patients per year. High EF and lack of AMI in a consistent number of patients puzzle about the generalization of the results which surely will follow. Another issue is making the problem more complicated, if possible. In this study the definition of CIMR severity was coherent with the previous guidelines (9). Moderate secondary MR included ERO 0.20–0.39 cm², vena contracta 0.3–0.69 cm and color doppler jet area from 20% to 40% of the left atrial (LA) area (5). Severe secondary MR included ERO ≥0.4 cm² or other criteria, as vena contracta, jet area/LA ratio and others (10). However, recently the gradation of severity for CIMR changed. What was called moderate (EROA ≥0.20 cm²), now became severe (7,11) and moderate CIMR is defined as progressive MR (grade B), with EROA <0.20 cm², regurgitant volume <30 mL or regurgitant fraction <50% (7). Some of the previous criteria disappeared, making difficult to draw any valid conclusion.

Another important point remains unexplained. Mean ERO was 0.2±0.1 cm² in both groups. According to SD properties, 50% of the patients had ERO <0.2 cm². How the core laboratory was able to confirm that 93% of the patients had moderate and severe IMR remains difficult to understand.

Randomized studies have been considered always the gold standard, as they are able to isolate the effects from the confounding factors and to assure the homogeneity of the samples. However, often we forget that randomized studies have intrinsic limitations. Selection of patients depends on inclusion criteria, which are restrictive, leading often to a small recruitment. In the study on moderate IMR (5), 6,676 patients were screened but only 301 (4.5%) were randomized. Results, however, are extrapolated to the entire population.

Having lost the opportunity to learn from this randomized study, how can we logically move in this complex and not well established field? We have to start from what we surely know: the presence of secondary MR worsens survival and symptoms in patients who had an AMI (3,4). It then seems logic that, if we are able to correct IMR without increasing in-hospital mortality, patients can have a benefit or, at worse, remained unchanged. Even in this randomized study results in patients who had MVr were similar, but not worse than in patients who had not. Remaining practical, it is evident that it is better, at the same EF, to be discharged from the Hospital, after surgical revascularization, with no or mild residual IMR rather than with moderate IMR.

In this scenario experiences coming from single or multi centers observational studies, summarized by meta-analyses, are by far more important, for decision making, than this randomized study, the results of which are questionable and inconclusive.

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Footnote

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