INVITED COMMENTARY

Does CABG Improve Left Ventricular Ejection Fraction in Patients with Ischemic Cardiomyopathy, and Does It Matter?

The study of Bax et al. (*1*) that is reported in this issue of *The Journal of Nuclear Medicine* addresses an important clinical issue. Specifically, in the setting of left ventricular failure with markedly reduced ejection fraction (mean ± SD, 30 ± 6 in this study), selection of patients with ischemic heart disease who will benefit from coronary revascularization often is problematic. The authors correctly note that coronary artery bypass grafting (CABG) carries increased risk in this patient group. In the Coronary Artery Surgery Study registry, for instance, surgical mortality was as much as threefold greater and 5 y survival was one third less for patients with reduced left ventricular ejection fraction (LVEF) than for patients with normal LVEF (*2*). However, in a more recent series, operative mortality was only 3.8% and actuarial survival was 94%, 82%, and 68% at 1, 2, and 5 y, respectively, after surgery in 79 consecutive patients with a mean LVEF of 18% ± 5% (*3*). Nevertheless, physicians are understandably reluctant to recommend surgery for these patients if the prospects for benefit are limited.

The search for myocardial viability typically commences at this juncture. If substantial viable myocardium is present, the benefits logically outweigh the risks of CABG and are widely believed to do so. However, more precise framing of the question of benefit, and consideration of mortality versus symptomatic status, are important. Indeed, several authors have suggested that recruitable contractile reserve is an important determinant of improvement after CABG in ischemic heart disease patients who undergo surgery primarily for heart failure (*4*). Patients without such reserve are less likely to benefit symptomatically from CABG, whereas those with reserve are. Further, studies have shown that ischemic heart disease patients with a low LVEF who undergo surgery primarily for angina are more likely to obtain symptomatic benefit than are those who undergo surgery primarily for heart failure (*3,5*). Mortality data, however, generally focus on all comers with ischemic heart disease and low LVEF and typically show benefit relative to historic control subjects who are medically treated (*3,5*). Mickleborough et al. (*3*) reported no difference in long-term survival between patients who underwent surgery primarily for angina and patients who underwent surgery primarily for heart failure. A prospective, randomized clinical trial with endpoints of mortality and symptoms in this patient group, however, has not been performed and clearly is required to address these issues more definitively.

In the absence of such a trial, the study of Bax et al. (*1*) and related investigations (*6–12*) represent efforts at fine tuning the selection process to identify those patients most likely to benefit from CABG. Two approaches have been used. One relies on preoperative evaluation of contractile function, typically with dobutamine echocardiography (*9,13*), although radionuclide ventriculography would work equally well (*14*) and possibly better, especially in patients with difficult acoustic windows. The other approach, used by numerous investigators (*8,10,11,15–18*) including Bax et al. (*1*), involves a combination of myocardial perfusion imaging and assessment of some cellular metabolic function, be that retention of thallium, sestamibi, or ^{18}F-FDG. Bax et al. focus on myocardial perfusion–glucose metabolism mismatching as the criterion for viability and conclude that if at least 30% of the left ventricular myocardium remains viable, CABG will improve the LVEF and functional class of the patient. Bax et al. present no data on mortality. Although their conclusions have intuitive appeal and are in accord with the results of some (*8,11*) but not all (*14,19*) prior studies, it is worth considering why matters may be more complex than they appear at first glance.

First, a point or two is to made concerning data analysis in this study. Figure 2 of Bax et al. (*1*) and an associated multiple regression analysis provide the basis for their conclusion. Their figure, however, shows the expected amount of scatter and an r^2 of 0.62, meaning that only approximately 60% of the change in LVEF after CABG is explained by the number of viable dysfunctional segments present preoperatively. Moreover, as is well known, correlation cannot establish causation; thus, neither the simple nor the multiple regression analysis should be construed as proving a causal relationship between increased LVEF and the number of preoperatively viable segments. As shown in Figure 2 of Bax et al., many instances of three or fewer viable segments were associated with a decline in LVEF after CABG. There is

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little reason to suppose that successfully revascularizing one to three viable segments would actually result in a decline in LVEF. Further, some of the apparent strength of the correlation between the number of preoperatively viable segments and improvement in LVEF after CABG in fact reflects this aggregation of paradoxic data points in addition to a single, very high value at the opposite end of the spectrum (i.e., 10 viable segments).

Other lines of evidence support the view that the relationship between the number of viable dysfunctional myocardial segments and improvement in post-CABG functional status may not be simple. First, although a substantial body of data indicates that survival is improved by CABG in patients with ischemic heart disease and left ventricular dysfunction, especially triple-vessel disease (*3*,*5*), the evidence regarding improvement in functional capacity has been more variable. As the authors appropriately note, a recent study by Samady et al. (*19*) showed that symptoms of heart failure and angina were improved after CABG in patients with a low LVEF preoperatively (0.24 ± 0.05), independently of any improvement in global left ventricular systolic function. Also, no difference in survival was seen for 32 mo between the group without improvement in LVEF (from 0.24 ± 0.05 to 0.23 ± 0.06) and the group with improvement (from 0.24 ± 0.05 to 0.39 ± 0.10).

The correlation between exercise capacity and LVEF in patients with either idiopathic or ischemic dilated cardiomyopathy is known to be poor (*20*–*22*). A recent PET study also failed to show a correlation between the amount of viable but asynergic myocardium and a change in either post-CABG exercise capacity or symptomatic status, even though the number of viable, dysfunctional segments was predictive of improvement in LVEF (*14*). In the study of Bax et al. (*1*), sample size was small, especially in group C ($n = 8$), and the improvement in the LVEF of group B ($n = 17$) was minimal (from 28 ± 7 to 32 ± 9). In contrast, the sample size in the study of Samady et al. (*19*) was larger: 68 in the group with improved LVEF after CABG and 36 in the group without improvement. Further, although post-CABG LVEF was evaluated sooner in the study of Samady et al. ($\geq$90% of patients within 6 wk, versus 3–6 mo in the study of Bax et al.), the time difference cannot account for the absence of correlation between change in functional class and change in LVEF (*19*). Similarly, Pagano et al. (*14*) studied patients 6 mo after CABG and failed to show any correlation between the amount of viable, dysfunctional myocardium and improvement in symptomatic status or exercise capacity. Accordingly, the conclusion of Bax et al. that improvement in functional class in their groups B and C was related to improvement in LVEF should be regarded with caution.

Long-term follow-up was not performed in the study of Bax et al. (*1*), and the hypothesis that improvement in LVEF will translate into a survival benefit thus remains unproven. In the study of Samady et al. (*19*), the possibility exists that some group B patients who failed to show improvement in LVEF at approximately 4–6 wk after CABG may have shown improvement later, thereby causing an apparent lack of correlation between change in LVEF and survival. However, whether later improvement would have been found is unclear. It is always easy to argue that improvement will occur if only we wait long enough. Shivalkar et al. (*23*) studied patients at baseline and 3 mo after CABG and showed improved LVEF in a subset of patients with regional hypokinesis and a PET mismatch pattern. The authors speculated, however, that improvement in this subset might have been seen even sooner had they looked earlier. They reported another subgroup with a matched, moderate reduction in flow and FDG and evidence of myocyte injury on biopsy. This subgroup, as a whole, failed to show improvement in LVEF at 3 mo, although 7 of 15 individuals actually did improve. The authors speculated that LVEF might eventually improve in the others if myocytes, which showed excess glycogen on histologic examination, could regenerate the contractile apparatus, which appeared deficient or absent.

Although this hypothesis is plausible, no data were obtained to support or refute it. Also, in approximately 50% of the group, global contractile function clearly improved despite evidence of glycogen accumulation and a disruption of the contractile apparatus comparable with that in patients who failed to improve. Accordingly, the correlation even between histology and the return of contractile function is unclear, save for the extreme case of extensive transmural scarring (*24*). In the end, even with serial studies of regional and global ventricular function, one will always be able to argue that, whatever the time points sampled after CABG, they were not quite optimal (either too soon or too late, depending on the results and what was being sought). Finally, as noted by the authors and others (*25*), the adequacy and durability of revascularization remain issues that can potentially confound pre-CABG and post-CABG predictors of benefit for both symptoms and survival.

Where are we left, then, in terms of answering the questions posed by the title of this commentary? Prior data (*5*–*12*), along with the data of Bax et al. (*1*) and of a recent similar investigation (*14*), generally confirm the hypothesis that the greater the amount of dysfunctional but viable myocardium before CABG, the greater is the likelihood of improvement in LVEF after CABG. The minimum number of segments required to make the surgery worthwhile is unclear, although the authors of this study suggest that the amount is substantial, perhaps as much as one third of the left ventricle. Others have suggested an even higher threshold of 50% (*14*). Also to be remembered is that the augmentation of LVEF after CABG generally is modest: seven points in this study (weighted average, groups B and C) and in a prior report from this group (*6*), and

nine points in the report of Pagano et al. (*14*). More important, the significance of the improvement in LVEF for outcomes that really matter—namely, mortality and functional status—is unknown and will be determined only by the outcome of a prospective, randomized clinical trial.

Such a trial would be helpful in, for instance, establishing whether CABG effects a survival benefit in all patients with low LVEF and ischemic cardiomyopathy or only in those who have substantial residual viable myocardium and in whom LVEF improves, even by as few as 7–10 points. The data of Samady et al. (*19*), as well as previously noted investigations concerning the poor relationship between exercise capacity and LVEF (*20–22*), indicate that the small likely gain in LVEF from CABG is unlikely to greatly affect the patient's functional status. Furthermore, whether the symptoms of patients with ischemic cardiomyopathy who undergo surgery primarily for relief of heart failure will improve more from surgery than from medical treatment remains to be proven, although nonrandomized, observational studies suggest the symptoms do improve (*14,19*). Although one can define a subset of ischemic cardiomyopathy patients who are likely to have an increase in LVEF with CABG, this information often has not proven useful in predicting improvement in functional class. Moreover, improvement in mortality after revascularization of viable myocardium may have little to do with change in either ejection fraction or functional class. Instead, improvement may be a result of other factors, such as electric stabilization or reduction of ischemic events (*26,27*). Indeed, existing data from observational studies indicate no difference in survival after CABG between patients with LVEF improvement and patients without (*19*), again suggesting that changes in contractile function may not be the most helpful surrogate endpoint.

In light of these considerations, one might ask what the usefulness of assessing pre-CABG viability may be and what tests are most appropriate. One answer will not fit all. A younger patient with known multivessel coronary disease, a history of myocardial infarction, and typical angina on maximal medical therapy either may not require viability assessment (angina generally indicates viable myocardium) or may be best served with a high-sensitivity test combining assessment of both myocardial perfusion and metabolism. When PET or FDG is not available, rest–redistribution thallium (*11,28*) is an excellent alternative. However, if the patient is older and the primary indication for CABG is relief of heart failure symptoms, then an examination that has higher specificity for recovery of contractile function (e.g., dobutamine radionuclide ventriculography or echocardiography) may be preferred, although the limitations must be considered. A positive result (i.e., demonstration of substantial contractile reserve) would be a good indication to proceed, but a negative result should not necessarily exclude the patient from CABG, especially if regional ischemia was evident during the test and was sufficient to account for failed augmentation of global LVEF with low-dose dobutamine. Other clinical scenarios in patients with chronic ischemic cardiomyopathy can be readily imagined and suggest the general principle that the diagnostic approach should be tailored to the CABG indication. Finally, until the results of a randomized clinical trails become available, the connection between predicting a return of global or regional contractile function and patient outcome, be it mortality or symptomatic status, will remain murky.

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