EDITORIAL COMMENT

Is It Time for a Randomized Trial of Surgical Treatment of Ischemic Heart Failure?*

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Should we take seriously the concluding paragraph of the article by Athanasuleas et al. (1), in this issue of the Journal, calling for a randomized comparison of the surgical anterior ventricular restoration (SAVER) operation with medical therapy or with coronary artery bypass grafting (CABG) in patients with postinfarction dilated cardiomyopathy? Do their uncontrolled observational data reported from a multicenter feasibility registry of outcomes indicate this new operation is sufficiently mature to deserve a randomized comparison with standard medical and surgical therapy? In any case, what is standard medical and surgical therapy for ischemic heart failure?

The authors trace the mechanistic heritage of the SAVER operation to early left ventricular (LV) aneurysmectomy that appeared to reverse heart failure by lowering LV wall stress. These linear amputations of dyskinetic scar commonly deformed the LV blood pool into a box-like shape. Cooley et al. (2) and Jatene (3) introduced intracavitary reconstruction techniques for repairing defects left by aneurysm resection that reduced LV cavity size while retaining a more elliptical shape. Dor et al. (4) further refined these operative techniques and applied them not only to patients with dyskinetic scar but also to those with only akinetic myocardial segments. To emphasize the operative objective of restoration of LV size and shape to normalize over any specific operative technique, the authors named their investigatory group RESTORE and the family of operations performed SAVER. More recently they have applied this technique to akinetic segments in the right coronary artery distribution and, therefore, suggest dropping anterior so that surgical ventricular restoration (SVR) becomes both the final operative objective and a name.

Operative illustrations in the Athanasuleas et al. (1) article will reassure cardiac surgeons that adoption of the SVR operation will pose no unusual technical challenge or learning phase cost measured by excessive patient mortality or morbidity. The familiar LV cross-sectional diagrams from the experimental work of Reimer and Jennings (5) depicting the influence of duration of ischemia on progression of the wave front of irreversible myocardial damage will aid cardiologists in understanding the objective of the SVR operation (Fig. 1). Aggressive early management of acute coronary syndromes in patients often arrests the ischemic process before it reaches the transmural stage. With later healing of infarcted myocardium, scarring is maximal in the subendocardial region and is interlaced with normal myocardium in diminishing amounts toward the epicardial surface. Ventricular wall or chamber imaging commonly shows an akinetic zone that gradually blends with myocardium with increasingly normal function in contrast to the dyskinetic region with a discreet neck typical of an LV aneurysm. At the time of cardiac operation, the epicardium of these zones may appear normal, and palpable thinning is often minimal in the arrested, decompressed heart. This appearance derives from preservation of a rim of normal myocardium covering the myocardial fibrosis and contrasts with the leather-like appearance and thinness typical of an LV aneurysm. Unlike the LV aneurysmectomy focused on removal of myocardial scar on the Batista operation designed to reduce LV size by indiscriminate removal of portions of the LV wall, the SVR operation attempts to decrease the circumference of the zone of endocardial scar through an incision in normal epicardium. The surgical repair using the intrinsic scar or an extrinsic patch to absorb excess linear tension in the zone relieves wall stress on the overlying residual viable epicardial myocardium that is closed over the repair, and thereby reduces the tendency for continued gradual expansion of the akinetic zone. Moreover, the purse-stringing effect of the endocardial repair acutely decreases chamber size and restores a more elliptical shape, thereby globally decreasing wall stress and enhancing function in myocardial regions remote from the repair.

Progression of LV enlargement typical of ischemic heart failure, known to be a marker of increased mortality, may be an unalterable consequence of irreversible myocardial injury or surgical therapies that relieve chronic myocardial ischemia and normalize LV size and shape and may reverse this progression and thereby enhance survival. Revascularization alone acutely restores contractility to myocardium previously dysfunctional from ischemia (6) and dramatically improves LV ejection fraction in some patients with ischemic cardiomyopathy (7). Moreover, improvement in ventricular dysfunction after CABG translates into survival benefit (8). Revascularization alone may be all that is needed to arrest gradual enlargement of akinetic myocardium. If so, the added operative time and the threat of air or particulate embolism associated with ventriculotomy to perform SVR would be unjustified. However, perhaps revascularization of chronically ischemic myocardium and failing to repair preexisting damage from the ischemia may be analogous to

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underwent CABG without internal mammary artery use have been eliminated. The million or more patients who (CASS), a decade of uncertainty about its proper role would value of internal mammary artery use in the CABG operation been addressed in the Coronary Artery Surgery Study; a second decade intervened before observational patient data gradually became sufficient to support its routine use. Had the added conduit to saphenous vein. A second decade intervened in 1975. This conduit had been first used for direct coronary bypass in 1964 (9) and during the subsequent operative results can be prospectively monitored by noninvasive imaging in a trial to ensure specific operative maneuvers needed to perform SVR are familiar to all cardiac surgeons. Moreover, the quality of operative results can be the wavefront of cell death moves from the subendocardial zone across the wall to involve progressively more of the transmural thickness of the ischemic zone. Typically a large zone of subepicardial myocardium in the ischemic bed is salvageable by early reperfusion. In contrast, the lateral margins in the subendocardial region of the infarct are established as early as 40 min after occlusion (10). This operation now stands at a point of information development analogous to that of optimal ventricular size and shape reconstruction. This new operation is sufficiently mature to justify a direct randomized comparison of CABG with SVR and CABG without SVR in appropriately selected patients.

Further direct observational comparison of these two surgical approaches without randomization will not define the value of SVR added to CABG. Encouraging widespread use to produce more data on SVR outcomes will only increase surgical bias that may preclude ever appropriately testing the procedure. The SVR operation now stands at a point of information development analogous to that of internal mammary artery use during coronary bypass grafting in 1975. This conduit had been first used for direct coronary bypass in 1964 and during the subsequent decade was championed by individual surgeons as a superior conduit to saphenous vein. A second decade intervened before observational patient data gradually became sufficiently convincing to support its routine use. Had the added value of internal mammary artery use in the CABG operation been addressed in the Coronary Artery Surgery Study (CASS), a decade of uncertainty about its proper role would have been eliminated. The million or more patients who underwent CABG without internal mammary artery use during this decade paid the price for needless delay with excess death and more repeat operations. Promising operations can be evaluated too soon or too late. The present time is ideal for objective assessment of the value SVR adds to CABG in patients with regional akinesia and subendocardial scar.

Since SVR is not a stand-alone operation for ischemic cardiomyopathy, it must be evaluated in the context of standard medical and surgical therapy. In any case, what is standard medical and surgical therapy for ischemic cardiomyopathy? Along the broad spectrum of severity of ischemic heart failure, specific clinical information, such as severe angina or left main coronary artery stenosis, may clearly indicate the need for surgical therapy in some patients. However, a large number of patients fall into a gray zone without clear evidence for benefit from either specific management strategy. Evidence supporting choice between therapies was never strong and has only been confused by recent studies showing improved outcomes with both therapies. Patients for whom equipoise of anticipated benefit now exists between modern medical and surgical therapy represent the broad population who are appropriate candidates for a randomized trial to provide the context for assessing the value SVR adds to CABG.

To my knowledge, no randomized trial has directly compared long-term benefits of surgical and medical treatment of patients with ischemic cardiomyopathy. In the 1969 to 1972 developmental era of surgical myocardial revascularization, high mortality rates were observed in patients with heart failure. Therefore, initial randomized trials comparing CABG to medical treatment conducted from 1972 to 1978 excluded most of these patients from participation. In a subgroup of 160 CASS patients with LV ventricular ejection fraction <0.50, the 10-year survival was 61% in the 82 medically-treated patients and 79% in the 78 patients who underwent CABG (p = 0.01) (10). This survival advantage of CABG was not related to the presence or severity of heart failure or angina symptoms. A meta-analysis by Yusuf et al. (11) analyzed individual patient data from CASS, and the six other early randomized trials. Only 191 (7.2%) of the 2,649 total patients had an ejection...
fraction <0.40, and only 106 (4.0%) of these patients had heart failure symptoms. Moreover, angina was a common symptom in the few patients with symptoms of heart failure. Coronary artery bypass grafting improved survival among all patients with proximal left anterior descending artery stenosis, three-vessel or left main coronary artery disease. In these patients with a survival benefit from CABG, a low ejection fraction increased the absolute benefit but did not change the relative benefit of CABG. A literature search of 326 published reports on results of CABG in patients with heart failure or LV dysfunction identified three well-designed cohort studies (12). Mortality benefit of CABG over medical therapy was 10 and 20 lives per 100 patients at three years in two of the three studies and 29 lives per 100 patients at five years in the third study.

The therapy then called medical treatment in all randomized trials and most observational comparisons with CABC was really only a reflection of coronary artery disease (CAD) natural history since it rarely included drugs now known to be lifesaving, such as angiotensin-converting enzyme inhibitors, beta-blockers, lipid-lowering drugs and antiplatelet agents. Refinement of operative and postoperative surgical management also has steadily improved CABC results over the past two decades. The paucity of modern data available to clinicians who must make daily high risk management decisions in patients with heart failure emphasizes the need for a properly designed randomized comparison of these therapies commonly used in clinical practice.

The RESTORE investigators recently have been joined by other cardiovascular specialists in planning a multicenter international randomized Surgical Treatment for IsChemic Heart failure (STICH) trial. If the STICH trial is approved for funding by the National Heart, Lung and Blood Institute, it will test two key hypotheses of surgical therapeutic strategy in patients with heart failure, LV dysfunction and CAD amenable to CABC:

1. Coronary revascularization hypothesis: Improvement in myocardial perfusion by CABC combined with aggressive medical therapy improves long-term survival compared to medical therapy alone.

2. Left ventricular reconstruction hypothesis: Optimal LV shape and size reconstruction by SVR combined with CABC and aggressive medical therapy improve long-term survival free of cardiac morbidity compared to medical therapy with CABC and medical therapy alone.

Patients with heart failure, LV ejection fraction ≤0.35, and CAD amenable to CABC first will be characterized by angina intensity or left main coronary stenosis as appropriate for only surgical therapy or for randomization to either medical or surgery therapy. All patients will be further evaluated for appropriateness of SVR indicated by dysfunction in a single LV region. Primary end points of survival and survival free of morbidity and secondary end points of morbidity, quality of life and cost will be compared among treatment groups. Registries of clinical information will be maintained for patients who are eligible but decline trial entry. Both randomized and registry patients will be monitored at regular intervals for a minimum of 3 years. Core laboratories for radionuclide, cardiac magnetic resonance, echocardiography, molecular biology and pVO2 studies will support studies to elucidate mechanisms responsible for the effectiveness demonstrated by randomized comparison of these therapeutic strategies.

The inclusive design of this proposed trial excludes only patients for whom medical treatment is the only reasonable therapeutic alternative, those with coronary anatomy best suited for revascularization by percutaneous coronary intervention and those who are heart transplant candidates. Therefore, results of the STICH trial will be generalizable to almost all of the large number of patients in this country with CAD, heart failure and LV dysfunction. If medical and surgical therapies result in equivalent survival, medical management without intensive evaluation for CAD will be the preferred strategy of care to be pursued in the more than 300,000 patients who first present with heart failure of unexplained etiology each year in this country. A more aggressive search for the 70% with CAD as the etiology can await demonstrated failure of this strategy indicated by development of overt ischemic symptoms. Conversely, if surgical therapy is shown to have a survival advantage over medical therapy in the STICH trial, early aggressive evaluation of CAD as a correctable etiology of new onset heart failure would be the preferred strategy.

Perhaps CABC alone will be found to be all that is necessary to achieve maximal surgical benefit. More exciting is the promise that surgical restoration of single zones of LV dysfunction to a more normal size and shape contributes survival advantage beyond CABC. This finding would make a new therapeutic option available to millions of patients who now suffer from ischemic heart failure.

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