LETTERS TO THE EDITOR

Ventricular Reduction Therapy: Controlled Clinical Trials Overdue

Laks and Marelli’s article on left ventricular reduction therapy (1) is an excellent presentation of the state of the art. Although this is not to criticize the authors, their discussion raises an issue that should have been considered from the inception of this therapy and is embodied in the penultimate sentence of the report: “Ultimately, a randomized trial will be required to evaluate this procedure.” The case for randomized trials of all new therapies (2,3), including randomization from Patient no. 1 (4), has already been made on scientific, ethical and indeed behavioral (5) grounds. I will not belabor it. Unfortunately, this new radical though promising form of therapy has the disadvantage of a relapse to the “bad old days” when surgical therapies were considered immune to scientific trials (6). Originators of new therapies must realize that from Patient no. 1, they really do not know the results. Therefore, on ethical as well as scientific grounds, patients should be randomized immediately to give them a “50/50 chance” not to get the new therapy, which could always be no better or even worse than existing therapy (4). Therapeutic innovators cannot know the outcome when they begin to apply any objectively untested treatment. This also applies to the “learning curve” in which interventionists, including surgeons, become technically better with experience (4). Moreover, in any randomized trial, truly informed consent (versus advised consent) would let patients know that the trialists have reasonable hopes, but cannot promise results. (If they did know, a controlled trial would become unethical because it would deny half of the patients treatments the trialists consider to be successful). In randomizing the first patient, hopeful investigators would have half of the number of patients at any time, but if they are ethical (i.e., honest) they may be sparing the other half harmful procedures, particularly when it cannot be known for whom even an ultimately successful procedure might be contraindicated and could only be developed with appropriate denominators (2) (i.e., appropriate comparison groups). As with so many procedures in the past, “ultimately,” as stated by the authors (1), a trial may be forced, but with what explanations will patients be recruited? Finally, this is the day of “evidence-based-medicine”—mainly on a basis of randomized, controlled clinical trials. This was rejected ab initio by the originators of ventricular reduction. After all, “Science teaches us to doubt, and, in ignorance, to refrain.” In this admonition from Claude Bernard, the word “ethics” can be substituted for “science” (7). As always, the scientific case and the ethical case are the same (3).

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REPLY

We appreciate Dr. Spodick’s letter, which suggests an immediate need to initiate a controlled trial of partial left ventriculectomy (PLV). Although we do not wish to agree or disagree on the timing of such a trial, we would like to address several specific questions that designing such a study raises.

To justify a controlled clinical trial, one must first establish that there is uncertainty among experts as to treatment preference for a given group of patients. This is defined as “equipoise” (1). Effective equipoise has been described as the exact point when the most likely results of a proposed trial are thought to be an improvement sufficient to compensate for the disadvantage of the treatment with the greatest risk (2). Equipoise implies that we, as a group, have no rational preference for treatment arm A or B. This collective group has been further defined to include both physicians and the patients who are to be enrolled in such a study (3,4). This condition is essential to ensure an adequate informed consent protocol that protect patients from harmful therapies (5,6). To perfectly respect patient autonomy, it has been suggested that patients should be free to choose either arm of a trial, or the randomization alternative.

For the purpose of discussion, one can assume that PLV currently achieves 70% success rates at short-term follow-up in selected patients. With this as a valuable result, PLV could be among the available treatments for end-stage congestive heart failure, although not definitively. This implies a surgical procedure with its inherent risks, which may then require another operation (transplantation) later on for many patients. Indeed, this has been observed in the existing reported results.

Past experience with mechanical assist devices has taught us that a benefit may occur after surgical technique and technology evolve. In the early experience, some thought that it was not justified to bridge critically ill patients with an expensive treatment that would prolong waiting time for a scarce resource (7). We now know that implantable left ventricular assist devices (LVADs) can maintain patients’ physical condition (currently as outpatients in many cases) so that the few donor hearts that are available are not risked for patients too sick to tolerate transplant surgery (8). Implantable LVADs are now being studied as a destination therapy. The cardiomyoplasty trial, in contrast, demonstrated the difficulties in systematically offering an operation to patients who were relatively well treated with maximal outpatient medical treatment (unpublished data). The difference with implantable LVADs is that these were offered to critically ill status I patients receiving maximal intravenous therapy who were starting to show signs of end-organ...
dysfunction. Because such a cohort faced a very poor outcome, offering a procedure that potentially had a 20% mortality rate was (and still is) rational. Transplantation has a 5% mortality rate in optimized patients and a 70% five-year survival rate (9). Timing of surgical treatment is therefore based on specific knowledge of natural history reflected by the presence of factors that precisely define the prognosis.

Available current data do not point to equipoise between PLV and heart transplantation, particularly because long-term results are unknown. In addition, with ongoing refinements, medical treatment of congestive heart failure complemented by implantable LVADs has contributed to a plateau in the number of deaths of patients waiting for a heart transplant in the U.S. (http://www.unos.org). This has been true for the past several years, despite the increasing gap between the number of patients being listed for heart transplants and the number of heart transplants being performed.

This line of reasoning would indicate that with our present knowledge, which is limited by long-term follow-up, a controlled trial of PLV should be aimed at patients with congestive heart failure who are at greatest risk of dying while waiting for an available donor heart. Such patients stand to benefit the most from such a therapy. The alternative arm of such a trial would be maximal medical therapy, including inotropic agents, and implantable LVADs. One could then imagine a scenario in which the possibility of entering such a trial would be presented to class IV patients who are or about to reach status I and are also ideal selected candidates for PLV (e.g., dilated cardiomyopathy with left ventricular end-diastolic dimension >70 mm and preserved LV wall thickness). Because patients in both arms of the trial would remain listed for transplantation, follow-up would theoretically be equal for both the LVAD and PLV group. Such a trial would also provide the possibility for patients to cross over from the PLV group to the LVAD group. At the other end of the spectrum, another outcome of such a trial strategy would be for patients and treating physicians in the PLV group to choose to prolong the bridge period and avoid transplant surgery.

As long-term data regarding PLV become available, a more precise trial could separate class III and IV patients into two separate trials with different end points. Indeed, current knowledge may not be developed enough to design the most meaningful randomized trial possible.

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Is Electron Beam Computed Tomography the Sole Detection Method for Coronary Calcium?

Budoff et al. (1) emphasized the advantages of electron beam computed tomography (CT) over the currently used noninvasive imaging exercise techniques to distinguish between ischemic and nonischemic cardiomyopathy. However, other techniques that noninvasively detect coronary calcification, fluoroscopy and spiral CT have been used for the same purpose but were inexplicably omitted from their discussion. This omission mistakenly creates the impression to readers that electron beam CT is the sole available technique. Twenty years ago, Johnson et al. (2) used fluoroscopy for the diagnosis of the ischemic type of cardiomyopathy, a report that Hurst’s textbook of cardiology did not neglect to mention (3). Spiral CT is another widely available alternative for the detection of coronary calcium, which we have reported (4–8) and which has been published by others (9). The new generation of spiral techniques are based on the ability to scan the heart within a single breathhold, despite the lack of electrocardiographic triggering. The value of dual-slice spiral CT for the differentiation of ischemic from nonischemic dilated cardiomyopathy was reported 3 years ago (4). Budoff et al. confirmed the results of this study and reproduced them: The diagnosis of ischemic cardiomyopathy based on the presence of calcium by spiral CT (total score >0) yielded sensitivity, specificity and total accuracy rates of 100%, 92% and 97%, respectively, compared with 99%, 83% and 92%, respectively, in their study. The relatively reduced specificity found by Budoff et al. is probably attributable to their definition of dilated cardiomyopathy, which was based solely on a left ventricular end-diastolic volume. The main clinical relevance of both studies is the contribution of fast CT techniques to the noninvasive diagnosis of cardiomyopathy of unknown etiology. In these patients, the absence of coronary calcium indicates a nonischemic etiology and can rule out the necessity for coronary angiography.

One would expect the original reports to be highlighted by Budoff et al. to strengthen their findings. Instead, they mysteriously chose to ignore them. Was this a mere oversight?

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