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 interventionalists, 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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REFERENCES


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

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