Lung volume reduction surgery: Tempest in a teapot

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Lung volume reduction surgery (LVRS) has resulted in perhaps the most dynamic controversy within cardiothoracic surgery in recent years. Initial publications reported compelling improvements in pulmonary function and resulted in rapid dissemination of the procedure throughout the United States and the world. The rationale for the enthusiasm was legitimate given the lack of alternative therapies for patients with severe end-stage emphysema. No medical therapy was able to improve pulmonary function or reverse the inexorable decline of breathless patients with emphysema. Only a very small subset of these patients were candidates for the surgical interventions of bullectomy or lung transplantation. Therefore, the opportunity to improve function and quality of life with a new surgical procedure inspired the hopes of desperate patients and their physicians. LVRS was easily the most exciting and innovative addition to general thoracic surgery since the first successful lung transplant procedure 20 years ago.

Parallel to the rapid clinical dissemination of LVRS, controversy emerged regarding the procedure's efficacy, long-term outcomes, selection criteria, and costs. Many clinicians raised legitimate questions regarding the validity of the early clinical reports, citing small patient numbers, incomplete follow-up, selection bias, and survivorship or follow-up bias as multiple factors confounding the interpretation of clinical outcomes from LVRS. Critics pointed at early publications that documented a high surgical mortality, prolonged mechanical ventilation, and prolonged hospital stays in some patients.¹ Medicare claims data revealed a 1-year mortality after LVRS of 23%, with uncertainty of whether this denoted the expected mortality of a progressive natural history of emphysema, or whether poor results were under-represented because of centers that performed LVRS but did not publish their outcomes.² These criticisms reflected the normal debate and evolution that are a natural order of dynamic and evolving medical care. Until LVRS, new procedures and interventions have primarily been evaluated by an evolutionary process of procedure refinement, observational studies, and occasionally randomized controlled trials. Randomized trials have generally been performed late within the process of procedure development, well after most interested clinicians believed that the majority of indications and outcomes were fairly well known.

LVRS has been developed in a new era—a time when evidence-based medicine is emphasized over the trial and error inherent in the development of new medical therapies. Insurers, and particularly Medicare, have become increasingly involved with medical decisions as well. Some of this is justifiable to prevent health care dollars from being squandered on frivolous therapies. However, since no clear criteria for Medicare coverage exist, decisions regarding reimbursement for a new procedure such as LVRS can easily appear arbitrary. Critics of the Medicare decision to withdraw reimbursement for LVRS believe that this decision moves uncomfortably close to government decisions of appropriate medical therapy for individual patients at best, or the unethical withholding of a promising therapy in an effort to control medical expenditures at worst. Bowing to public and legislative pressure, Medicare agreed to fund the historic National Emphysema Treatment Trial (NETT) as a pioneering collaboration between the National Institutes of Health (NIH) and Medicare in evaluating a new surgical procedure. The NETT developed as a large multi-institutional prospective randomized trial, comparing LVRS to maximal medical therapy in patients with severe emphysema.

Debate has continued to swirl around the NETT. Many LVRS proponents believe

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that sufficient case-control evidence exists to allow coverage in highly selected patients. In fact, some argued that requiring Medicare patients to enroll within the NETT to have a 50% chance of being randomized to LVRS consisted of coercion to participate in a randomized controlled trial. On the other hand, many applauded the innovative collaboration between Medicare and the NIH. The NETT assured rigorous evaluation of LVRS before it became widely applied and clinical biases limited the ability to conduct a randomized controlled trial. The NETT hoped to protect potential patients who may have experienced unnecessary morbidity or mortality as indications and outcomes gradually evolved in the fragmented process of single-institution observational studies.

It appears that both of these arguments have significant validity. As our patients' advocates, physicians bristle at the notion of a potentially beneficial treatment being denied for one of their patients. On the other hand, as clinical scientists, we wish to scientifically validate new treatment with as much precision as possible in an effort to avoid the possible harm of inappropriate use. This dilemma between individual patient advocacy and scientific validation of efficacy is not easily resolved and has led to a huge debate about the appropriateness of Medicare's coverage policy and support of a randomized trial. Clearly, LVRS is being subjected to a higher standard of validation than virtually any other medical or surgical treatment in the past. It is possible that political and economic considerations may be driving the heightened attention to LVRS. However, this cynical view rejects the notion that early and rigorous scrutiny of a new medical therapy may actually allow us to apply or discard that therapy more quickly and with more confidence, maximizing the benefit and minimizing the morbidity for the largest number of patients.

No matter how one views the political or economic events surrounding LVRS, the work and beliefs of the individual investigators and the NETT investigators are remarkably consistent, with less variation than might be expected between proponents of LVRS or proponents of the recently completed randomized trial of LVRS (NETT). When the polemic is set aside, it is easy to see that both groups of clinicians and investigators are complementary, working in the same direction, and both refining the role of LVRS in clinical practice. In this month's issue of the *Journal*, the article by Ciccone and her colleagues³ at Washington University is the most important article to date in refining long-term outcomes after LVRS. Each of the successive publications from Cooper's group at Washington University has substantially increased our understanding of LVRS—outlining the pilot experience,⁴ examining intermediate-term outcomes in a larger cohort,⁵ and comparing outcomes between matched patients receiving or denied LVRS.⁶ Ciccone's article adds substantially to these previ-

ous reports, now with 250 patients followed up for a mean interval of almost 5 years and a minimal follow-up of 18 months. Although most other reports have been flawed by missing data, which can easily obscure negative outcomes, the Washington University group has achieved remarkable and complete follow-up that tempers criticism about the validity of their outstanding results. This article, as well as the consistent scientific and rigorous evaluation of the Washington University clinical outcomes, displays the highest quality of single-institution case-controlled or observational studies. The authors have done everything right—prospective collection of data, consistent indications and techniques, sizable patient cohort, objective outcome variables, and rigorous efforts to maintain complete follow-up. Despite these strengths, this experience is still limited by its study design—problems with selection bias, survivorship bias, and statistical bias, as well as the difficulty of predicting reproducibility in other surgeons and other centers.

Selection bias is a confounding factor in any nonrandomized clinical trial, with known or unanticipated variables influencing the outcome in unpredictable and unsuspected ways. Selection of patients for LVRS has been based on vague criteria that limit reproducibility between centers. The Washington University group has learned to apply their selection criteria wisely, with good results. However, it is not clear whether this should define the selection of future patients considering LVRS. Perhaps with more stringent criteria, results could be further improved and morbidity lessened. Or perhaps the criteria should be broader, providing access to LVRS for more patients who would be excluded from LVRS benefits by immature selection definitions.

Survivorship bias is a corollary of follow-up bias. Incomplete follow-up in nonrandomized studies confounds interpretation of the outcomes because lack of follow-up is rarely random—poor follow-up usually over-represented by patients with poor outcomes. However, survivorship bias occurs when patient death prevents the continued consideration of that patient's outcome after surgery. In the case of LVRS, it is highly likely that death occurs most commonly in those patients with a poor result after surgery and that subsequent data are measured only in those patients who are more robust or who have benefited from surgery. This can significantly influence the interpretation of results when a large percentage of patients have died over the follow-up interval. Although it is likely that this mortality rate may be due to the natural history of emphysema, it is hard to know the detrimental or beneficial impact of LVRS on mortality in the absence of a randomized study. Unfortunately, the progressive distortion of long-term functional results by mortality tempers the enthusiasm we can have for long-term results in a nonrandomized study.

Statistical bias occurs when mean data are presented for

case-controlled studies that compare individual patient data before and after treatment. In the case of LVRS, patients consent to surgery with the hope for a clinically significant improvement in lung function and/or symptoms. Most data after LVRS provide the mean improvement in forced expiratory volume in 1 second (FEV₁), 6-minute walk, or dyspnea score and may also give a percentage of patients “improved” after LVRS. However, it is impossible to calculate from these data how many patients actually achieved a clinically significant improvement after surgery. Numerical or subjective, but negligible, improvement is calculated as a benefit but may be clinically insignificant to the individual patient. A minority of patients having a very large benefit can also skew the mean. Given the expectation of LVRS for patients with emphysema, a more precise measurement of benefit would probably be to set a clinically meaningful threshold that could then be objectively measured, such as a defined improvement in FEV₁, 6-minute walk, dyspnea scale, or maximum work. The percentage of patients achieving this outcome would then be defined as improved after LVRS and provide a better measure of how many patients are truly benefiting within our current selection criteria and surgical technique.

Finally, although single-institution studies provide a necessary pilot experience for a new surgical procedure, the true value of the procedure cannot be extrapolated from a single-institution experience. A number of institutional, selection, and individual factors may allow a hospital to achieve exceptional results in an area where they have experience, interests, and specialization. These results are needed to consider broader application of the surgical procedure. However, for LVRS to make a meaningful impact on patients with emphysema, multi-institutional studies are necessary to confirm the applicability of the operation and the results within definable selection criteria and across a spectrum of institutions and surgeons.

The results reported in this issue of the *Journal* by Ciccone and her colleagues are an important advance in our knowledge of LVRS. They confirm the apparent benefit of

LVRS over several years in a select group of patients at a center with a high level of expertise in pulmonary medicine and thoracic surgery. This experience does not obviate the need for a randomized trial. Indeed, the single-institution case-controlled trial and a randomized trial are complementary: the first providing the experience on which to base a randomized trial; the latter providing the most precise and unbiased evidence of efficacy and allowing broader selection criteria to be examined and refined. Single-institution studies will then be an important follow-up to a randomized trial to confirm, refine, or repudiate randomized trial findings. The NETT will publish its results this spring and will complement the work that Cooper and his colleagues have started with their LVRS experience. The individual contributions by the large number of investigators pioneering LVRS development, along with the collective contributions of the NETT investigators, have propelled the knowledge surrounding LVRS far beyond that of any similar new technology or procedure in its adolescence.

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