EDITORIAL COMMENT

The Prognostic Impact of Septal Myectomy in Obstructive Hypertrophic Cardiomyopathy*

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A long-standing problem facing clinicians caring for patients with hypertrophic cardiomyopathy (HCM) is the scarcity of robust clinical evidence on which to base therapeutic decisions. For most interventions, there are no randomized controlled trial data. Rather, much of the literature consists of retrospective observational studies with historical controls. Individual referral centers with specialist interest have tended to develop their particular approaches to patient management and, even when more than one option is available for consideration, have tended to focus on a single choice. Once local experience convinces investigators that a particular treatment is warranted (albeit by way of comparison with historical controls), the opportunity to perform randomized studies has effectively been missed.

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In this setting, the particular problem that arises is that HCM is an unusually heterogeneous condition (1). The different underlying disease genes are associated with quantitative, and occasionally qualitative, differences in clinical features and natural history (2–4). Therefore, different selection biases arising from methods of patient ascertainment undoubtedly influence both the genetic makeup of a study population and the subsequent disease outcome. A clinical practice based on families referred after a sudden cardiac death will yield a quite different patient cohort from a referral practice of individuals selected for interventional procedures for outflow obstruction, and both will differ from patient populations ascertained through an echocardiography service. Unsurprisingly, conflicting findings on treatment outcomes ensue. Early enthusiasm for novel forms of treatment has not always been borne out, perhaps reflecting aspects of patient selection that were later negated by better controlled data. For example, the one instance in which practice has been informed by randomized trials was the demonstration that the apparent benefits of dual-chamber pacing in HCM were actually very modest and probably restricted to a small subset of patients (5).

SEPTAL REDUCTION FOR SYMPTOM CONTROL

Against this background of uncertainty, one area in which there have been clear data and a firm consensus is that patients with obstructive HCM who have persistent symptoms, or exercise limitation, despite maximum medical therapy benefit symptomatically from procedures to reduce the outflow gradient (6). In approximately 25% of patients with HCM, there is a dynamic obstruction of the left ventricular outflow tract caused by septal hypertrophy and systolic anterior motion of the mitral valve. In patients in whom such an outflow gradient can be demonstrated at rest, much more marked gradients are provoked during exercise. Surgical septal myectomy effectively abolishes systolic anterior motion of the mitral valve and the concomitant mitral regurgitation, improving left ventricular hemodynamics (particularly the key parameter of wall stress). Long-term experience from a number of centers convincingly shows that this approach is a proven one that provides lasting amelioration of symptoms (7). Moreover, surgical mortality in specialist centers is now <1% to 2%. Despite this, the uptake of surgical myectomy is relatively low, with <5% of patients with HCM being treated in this way in most case series. In contrast, there has been a marked proliferation of percutaneous, catheter-based, alcohol septal ablation, which achieves remodeling in the left ventricular outflow tract by causing a localized myocardial infarction in the proximal septum (8–10). Although significant controversy exists typically because individual centers strongly favor one or other technique and few offer significant experience of both, the general consensus is that operative risks, hemodynamic benefits, and initial symptomatic benefits are broadly comparable (in centers with appropriate expertise) with either technique. A critical difference is that long-term follow-up data are not yet available for alcohol septal ablation, and there are concerns that the intramyocardial scar may provide a long-term arrhythmogenic substrate and that the extent of myocardial damage may exceed the target area and lead to further, undesirable, remodeling. Furthermore, pacemaker implantation rates are still significantly higher with the percutaneous procedure (5% to 10%). While these long-term data are awaited, there is a valid concern that the threshold for intervention (now that it can be performed percutaneously) is becoming inappropriately low. There are no data to support use of alcohol septal ablation as “first-line” treatment, i.e., before trying maximum medical therapy, or in patients with obstruction but only minor symptoms; nevertheless, there may already be a trend toward these practices (11). In addition, the proliferation of alcohol septal ablation may lead to provision by low-volume oper-
ators without appropriate specialist expertise in HCM management and patient selection.

PROGNOSTIC IMPLICATIONS OF DYNAMIC OUTFLOW OBSTRUCTION

Recent findings regarding the natural history of patients with obstruction and the impact of surgical reduction on long-term death rates now polarize this debate further. The new findings potentially broaden the value of gradient reduction, which could have major clinical implications, emphasizing the importance of getting the facts right. Once again, the data only relate to surgical intervention. Early clinical studies had indicated that the presence of obstruction was not a clear, or clinically useful, predictor of the subsequent risk of sudden cardiac death. However, a recent large observational study (combining consecutive patients from three centers) suggested that outflow obstruction (>30 mm Hg at rest) was associated with a significantly greater risk of progressive heart failure, stroke, and overall disease-related death (12). Although this is a single study, and the effect size was not large, these observations could be interpreted to mandate a more aggressive approach to gradient reduction, at least in patients with refractory symptoms. The key question, of course, is whether procedures to reduce the outflow obstruction can be shown to improve prognosis. No randomized data exist with which to answer this question, but the report by Ommen et al. (13) in this issue of the Journal could be interpreted as evidence that surgical relief of obstruction improves long-term survival in adults.

CAN ANY ADVERSE PROGNOSIS BE REVERSED BY MYECTOMY?

Ommen et al. (13) report an observational study of 1,337 consecutive patients with HCM drawn from four U.S. and European specialist centers between 1983 and 2001. These patients were retrospectively grouped into three categories: patients with surgically treated outflow tract obstruction, patients with medically treated outflow tract obstruction, and patients without obstruction. Survival after myectomy was not different from survival in the nonobstructive group but was better than survival in the nonoperated obstructive group (for all-cause mortality, HCM-related mortality, and sudden cardiac death). The authors concluded that surgical myectomy appears to improve survival in patients with highly symptomatic obstructive HCM. Unfortunately, all of the surgical subjects came from one of the centers (Mayo Clinic) whereas the two nonsurgical groups were drawn from the three other centers (patients from these centers who were referred for surgery were not included). Thus, as usual in this field, concern exists regarding the biases inherent in comparing retrospective cohorts selected for different treatments. Referrals to the Mayo Clinic for myectomy will likely be selected for severity of symptoms in otherwise well, low-risk, patients, both in regard to HCM and general morbidity/mortality risk. Patients with equivalent gradients who do not get referred for surgery may be those with adverse factors that will generate a worse prognosis independent of procedure, which may be particularly the case for those described as having outflow tract obstruction with “severe functional limitation” who yet do not get referred. Some clues as to possible biases are apparent in the nonoperated obstructive group (older age, more atrial fibrillation, a greater proportion receiving amiodarone). Reasonable efforts have been made to measure and compare known confounders, and a “confirmatory analysis” focusing on patients <45 years of age is helpful, but unknown biases may remain. Of note, the comparison group of 228 patients with outflow obstruction who did not undergo surgery (and who showed the adverse prognosis) are the same patients that generated the initial adverse natural history data (12). If that group is somehow not representative, then the survival benefit ascribed to myectomy will have been exaggerated.

Survival analyses of this type also can be sensitive to decisions made in the statistical analysis. For example, appropriate discharges from an implantable cardioverter-defibrillator have been regarded as a sudden death (eight patients), where in fact many discharges are likely to be for nonfatal arrhythmias. Survival was censored for cardiac transplantation (nine patients) where, more conventionally (12), these would be considered as equivalent to deaths from heart failure. Patients who underwent surgical myectomy in association with other procedures (mitral valve surgery, coronary artery grafting; n = 64) were excluded from the analysis of myectomy outcome. This group will have contained high-risk patients with comorbidity, whereas such patients will not have been excluded from the medically managed obstruction group. Well-known problems also exist in comparing survival in surgical cohorts (in which mortality between diagnosis and operation is invisible) with medically managed cohorts followed from diagnosis in the same center. Reassuringly, the authors have (where possible) performed confirmatory analyses that suggest that their key findings are robust to these study design limitations.

TO WHAT EXTENT SHOULD THESE DATA ALTER PRACTICE?

For patients with refractory symptoms due to obstructive HCM, surgery can already be justified on symptomatic grounds; an added survival advantage increases the benefit but does not, in fact, change the existing indication. Specifically, it is not sound to extrapolate from these findings to conclude that prognosis would be improved by myectomy in asymptomatic obstructive HCM. Nevertheless, that is a plausible hypothesis that now needs proper testing (much of the apparent late benefit in the current series arose from a reduction in progressive left ventricular dysfunction, and this could plausibly be of prognostic value independent of symptoms earlier in life). Equally, it is not
sound to conclude that alcohol septal ablation will improve survival even in patients with refractory symptoms; this also needs formal evaluation. Thus, the relatively low uptake of surgical myectomy seems increasingly inappropriate, and strong arguments can be made for greater provision in specialist centers.

**THE NEXT STEP**

Although some uncertainty remains regarding the extent of survival benefit afforded by myectomy, this will never be resolved by a randomized study. Instead, because patients with refractory symptoms and obstruction will tend to be referred for an intervention anyway, the question to focus on is which of the two current approaches confers the greater lasting benefit. With the realization that gradient reduction may improve survival in patients with refractory symptoms, surely it is now time for a randomized controlled trial between surgical and percutaneous approaches.

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