

EDITORIAL COMMENT

The Role of Alcohol Septal Ablation in the Treatment of Left Ventricular Outflow Tract Obstruction in Hypertrophic Cardiomyopathy*

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More than 50 years after its first modern pathologic description, hypertrophic cardiomyopathy (HCM) continues to excite controversy in the medical literature. One of the most polarizing issues in this field has been the treatment of symptomatic left ventricular outflow tract obstruction, a common feature of the disease that causes limiting symptoms and increases the risk of heart failure, atrial fibrillation, and cardiovascular death (1,2). In this issue of the *Journal*, Nagueh et al. (3) report data from a North American registry of >800 symptomatic patients treated with alcohol septal ablation. The results are broadly consistent with recent meta-analyses in which alcohol septal ablation was associated with mortality rates and improvements in functional status similar to those reported for surgical treatment, albeit with a higher risk of permanent pacemaker implantation and greater post-intervention outflow tract gradient (4–6). The question remains, do the 2 techniques have equivalent safety and efficacy?

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Despite early debates about the hemodynamic significance of left ventricular outflow tract pressure gradients in patients with HCM, evidence from the past half century convincingly shows that their abolition by pharmacologic or other means improves symptoms. Current guidelines recommend that symptomatic outflow tract obstruction should be treated initially with negatively inotropic drugs (beta-blockers, verapamil, and disopyramide) and by correction of exacerbating factors such as vasodilator therapy, anemia,

excessive weight, and dehydration (7). Only when symptoms persist despite aggressive medical therapy or the side effects of medication are intolerable should a more invasive approach to gradient reduction be explored.

For largely historical reasons, surgical resection of the basal interventricular septum (septal myectomy) is generally regarded to be the gold standard against which other techniques are measured. Contemporary surgical series from high-volume experienced centers report substantial reductions in outflow tract obstruction in >90% of cases and long-term symptomatic improvement in as many as 70% (4–7). Operative mortality for myectomy alone is less than 1% to 2%, but as high as 5% when combined with other procedures such as mitral valve surgery (4–8). A long-standing limitation of the technique has been a lack of surgical expertise, which has confined the procedure to a small number of centers in North America and Europe. This, combined with the desire to develop less invasive and safer methods for achieving symptom relief, has led to the search for alternative nonsurgical approaches, of which alcohol septal ablation has emerged as the most promising, but also the most controversial.

Soon after its inception, a number of concerns were raised about the safety of the alcohol ablation procedure. The very idea of deliberately causing myocardial necrosis seemed to run counter to mainstream cardiology practice in which preservation of myocardium is the norm. This view was strengthened by histologic examination of hearts from individuals who died after septal ablation and later by noninvasive imaging, which suggested that the intramyocardial lesion produced by alcohol injection might be a potent substrate for ventricular arrhythmia (9,10). Alarm was also expressed at the dramatic increase in the number of patients undergoing invasive therapy after the introduction of alcohol septal ablation in the mid-1990s, the fear being that the apparent simplicity of the alcohol technique had led to its inappropriate use in patients with mild functional limitation. The patients in this registry all appeared to have significant symptoms, but it is striking that calcium channel blockers and disopyramide were administered to only 12% and 11% of patients, respectively. We can only speculate on the reasons why this might be so, but it does support the idea that the threshold for intervention has been lowered too far in some cases.

Until very recently, the only available data on long-term outcomes after alcohol septal ablation were derived from single-center studies. The survival rate at 5 years in the registry seems lower than that reported for surgery in some series (11,12), but a study that compared survival in patients undergoing alcohol septal ablation with that of a historical age- and sex-matched cohort of myectomy patients operated on at a major HCM center in the United States failed to demonstrate a statistically significant difference in 4-year mortality between the techniques (13). Several papers have used appropriate implantable cardioverter-defibrillator

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shocks as a surrogate marker for the risk of sudden cardiac death after intervention (14), but these data should be interpreted cautiously because periprocedural ventricular arrhythmias have decreased with the use of echocardiographic contrast guidance and smaller volumes of alcohol and because of the well-known uncertainty surrounding the use of implantable cardioverter-defibrillator shocks as a surrogate for sudden death.

Of course, the only way to determine whether alcohol septal ablation and surgery have equivalent safety is to perform a randomized, controlled trial, but the heterogeneity of the disease and the challenges of organizing and funding a large multicenter study in a relatively rare disease probably mean that this will never happen. At present, the next best sources of data are large meta-analyses that have compared some of the larger series and found no significant difference in survival between the techniques (4,5). Nevertheless, even if we accept that overall survival is similar, we still cannot assume that the 2 treatments are interchangeable.

Although outflow tract obstruction is frequent in patients with HCM, its mechanism is not the same in all cases. The essential feature is a misalignment of the mitral valve and submitral structures within the left ventricular cavity that permits contact between 1 or both mitral leaflets and the interventricular septum during ventricular ejection (15,16). In most patients, this geometric substrate for obstruction is caused by asymmetrical septal hypertrophy and anterior displacement of the papillary muscles, but in some individuals, the dominant mechanism is an abnormality of the mitral valve such as elongation of one or more scallops of either leaflet or annular calcification. When long redundant slack mitral valves are the dominant mechanism, patients should be preferentially referred to surgery, where specific procedures to address mitral slack can be performed along with myectomy. Changes in aortoventricular alignment, as may occur in elderly hypertensive patients, can also predispose to obstruction even when the basal septum is of normal thickness or only mildly hypertrophied. It is reassuring that the authors of this paper state that none of the patients who underwent alcohol septal ablation had anomalous insertion of the papillary muscle into the mitral valve or primary mitral valve disease, but the importance of defining the mechanism of obstruction before embarking on invasive treatment cannot be overstated.

Another problematic scenario is that of severe hypertrophy with obstruction in the midcavity as well as outflow tract. In this situation, it is often the small stroke volume and increased cavity pressure caused by the extensive hypertrophy that are the dominant mechanisms of symptoms. One therapeutic approach to this problem is to aggressively remodel the left ventricle with extensive resection of muscle (17) or by injection of alcohol into more distal myocardial segments (18). As the prevalence of midcavity obstruction is not reported in this study, its impact on symptoms and long-term survival after alcohol ablation is uncertain, but the risks of causing substantial myocardial necrosis mean

that the use of alcohol ablation to target more distal hypertrophy in the ventricle should be avoided.

The core principle of alcohol ablation is that the depot of injected alcohol should be localized to the basal interventricular septum and nowhere else. Because the volume of myocardium subtended by the epicardial and perforating coronary vessels is extremely variable, it is mandatory to inject echocardiographic contrast medium before alcohol injection to ensure that there is no risk of infarction elsewhere. Previous studies using careful intracoronary contrast echocardiography suggest that misplacement of contrast leads to a change in the initial target vessel in 11% of cases and a failure to identify a suitable vessel in 8% (19). It is, therefore, striking that only 4 patients in this registry were excluded because of the fear of remote infarction, and it is worrying that ethanol was injected in >2 vessels in >20% of cases. This practice is not peculiar to this registry and reflects the belief that gradient reduction in the catheter laboratory is the arbiter for further alcohol injections. The observation in the registry that a smaller number of septal arteries injected with alcohol and a greater post-procedural septal thickness were associated with a higher mortality could be used to support this approach, but a plausible alternative explanation is that failure to reduce the outflow gradient with a single injection means that myocardial necrosis has occurred in segments other than the basal septum. This is important not only as an explanation for why alcohol septal ablation often fails to reduce outflow gradients to the same extent as surgical intervention, but may also explain the higher mortality in patients who underwent injection into a single vessel. It is already known that in many patients with HCM, progressive loss of contractile function develops, which is associated with poorer outcomes (20), and it is noteworthy that the registry data show a negative correlation between the pre-procedural ejection fraction and long-term mortality. Because the registry does not report the cause of death, it is impossible to determine whether there was an excess of heart failure deaths after alcohol ablation, but it seems inconceivable that extensive loss of myocardium is conducive to preservation of systolic performance in the long term and once again suggests that the use of gradient reduction in the catheter laboratory as an index of success endangers patients.

Conclusions

Resolution of the adversarial debate about these 2 techniques is challenging because of the lack of randomized trial data and inevitable differences in the demographic and clinical characteristics of patients selected for each procedure. Nevertheless, it is possible to follow some key principles when managing left ventricular outflow tract obstruction in HCM. 1) All patients should be assessed by clinicians expert in the diagnosis and management of the disease before intervention. 2) Invasive treatment should be considered only when patients have received aggressive

medical therapy. 3) Invasive procedures should be performed only by cardiologists and surgeons with appropriate training and demonstrable expertise in the management of HCM. 4) The type of therapy should primarily be determined by myocardial and valvular morphology. 5) When either therapy is deemed appropriate, patients should be informed about the relative merits and risks of each and should be offered access to both techniques.

The take-home message from this registry is not that all patients with outflow tract obstruction should undergo alcohol septal ablation, but rather that there is no single treatment that suits all patients and that careful pre-assessment by teams with expertise in managing the complexity of HCM is essential.

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