JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 5, NO. 10, 2020

EDITORIAL COMMENT

Cerclage Septal Ablation for Hypertrophic Cardiomyopathy

Will a Backdoor Attack on the Septum Be Better?*

Richard G. Bach, MD

Obstruction to left ventricular (LV) outflow by an asymmetrically thickened interventricular septum has been recognized as a common physiological feature and as a cause of disabling symptoms among patients with hypertrophic cardiomyopathy (HCM) since the earliest recognition of the disease. Reducing the thickness of the septum as a therapeutic intervention was first conceived of by Andrew Morrow in 1960, when he performed the first septal myectomy on a severely symptomatic 10-year-old boy with HCM (1). Over the next 35 years, the only available method of therapeutic septal reduction remained surgical septal myectomy via a median sternotomy. Although this procedure was largely effective, at that time, it was associated with relatively high operative risk, and not all patients were candidates for surgical intervention.

In 1995, an innovative interventional cardiologist, Ulrich Sigwart, reported the first nonsurgical approach to septal reduction, the selective transcatheter delivery of alcohol into a septal artery (2). Since then, thousands of patients with HCM and severe LV outflow tract obstruction have been successfully treated by alcohol septal ablation (ASA) enhanced by contrast echocardiographic guidance, with excellent short- and long-term results (3). However, despite well-proven efficacy and safety, the use of ASA is limited by septal artery anatomy. In some patients, the target septal artery may be small or inaccessible, may perfuse a segment that misses the site of septum–mitral leaflet contact, or may also perfuse other myocardial regions, making it unsafe for alcohol infusion. As a result, it has been estimated that 5% to 15% of patients are not suitable candidates for ASA.

In response to the limitations of myectomy and ASA, other approaches to septal reduction have been proposed and performed, including covered stent implantation; septal artery embolization using coils, microspheres, or cyanoacrylate glue; MitraClip (Abbott, Abbott Park, Illinois) restriction of systolic anterior motion of the mitral valve; and endocardial radiofrequency ablation. Although these might have been intended to allow intervention for patients with features unsuitable for myectomy or ASA, each of these has its own limitations, and none have supplanted ASA as a preferred method of nonsurgical septal reduction. Among them, endocardial ablation using a radiofrequency catheter or needle applied to the right or left side of the interventricular septum has emerged as arguably the most promising alternative method that overcomes some of the limitations of ASA. This modality has shown efficacy in limited case series, but it notably does not thin the septum significantly and can be associated with a high rate of atrioventricular conduction block. Long-term outcomes are not available (4).

In this issue of *JACC: Basic to Translational Science*, Shin et al. (5) reported on a series of proof-of-concept experiments in explanted hearts and in a swine model of a novel transvenous approach to septal reduction that they called "cerclage radiofrequency ablation." In this approach, a radiofrequency catheter, which they newly designed for this purpose, was

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

From the Cardiovascular Division, Washington University School of Medicine, St. Louis, Missouri.

The author attests he is in compliance with human studies committees and animal welfare regulations of the author's institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Basic to Translational Science* author instructions page.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2020.09.002

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 5, NO. 10, 2020
OCTOBER 2020:999-1001

inserted over a guidewire via the coronary sinus into a septal vein, and ablation performed by application of radiofrequency energy. They performed dose-finding experiments in ex vivo hearts to determine the optimal energy and temperature level for adequate tissue injury, reporting the ablation of a 5- to 13-mm diameter zone of myocardium in tissue sections. The in vivo application of cerclage ablation in a swine survival model showed feasibility for inducing a defined region of necrosis within the septum, with documented reduced wall motion and a variable degree of thinning in the targeted septal segment at 8-week follow-up.

This is an interesting technique. It capitalizes on methods, such as accessing and traversing the coronary sinus using fluoroscopy, that have become routine for electrophysiologists. Approaching septal reduction from the venous circulation may obviate some of the common risks inherent in left heart catheterization and arterial access (e.g., stroke and serious access site bleeding). Nevertheless, the swine in the model did not have basal septal hypertrophy or LV outflow tract gradients to assess, the amount of late septal thinning beyond 8 weeks was not investigated, and the model failed to inform the effectiveness of this technique for addressing those fundamental aspects of the abnormal physiology of HCM. The true efficacy and safety of this technique will only be proven by experience in patients. Furthermore, despite the advantages proposed by the investigators for cerclage ablation over ASA and endocardial radiofrequency ablation, new and potentially greater risks could be encountered when manipulating radiofrequency catheters deep in the coronary venous circulation, as is required by this technique. The coronary sinus and veins are relatively thin-walled structures. The risk of dissection and perforation, reported for coronary venous LV pacemaker lead implantation for cardiac resynchronization therapy, seems inescapable when negotiating the coronary venous anatomy with guidewires and stiff catheters for cerclage ablation. The angulation of segments of the venous anatomy has also been recognized as a challenge to coronary venous lead implantation and may represent a greater challenge to guidewire and catheter advancement into relatively small septal veins. Although unsuitable septal artery anatomy is a recognized limitation of ASA, the potentially greater variability in the number and distribution of septal veins may likewise limit applicability of this technique. Finally, the investigators reported they observed remote damage to septal perforator arteries up to 2.5 cm away from the ablation zone in their model. Because of the potential close proximity of a target septal vein to the left anterior descending artery in patients undergoing this procedure, this observation raises concern about bystander coronary artery injury, a dreaded and potentially catastrophic complication already described for catheter-based radiofrequency ablation in other settings.

It has also been recognized that the injury to the hypertrophied septum produced by endocardial radiofrequency ablation differs from the injury induced by alcohol infusion. In some patients, this could induce tissue edema that can result in a transient increase in wall thickness and an increase in the pressure gradient across the LV outflow tract (4). In the animals subjected to cerclage ablation, local edema led to an early increase in wall thickness in all hearts studied, with 2 of 6 animals showing a >50% increase. Because immediate reduction of the systolic intraventricular gradient has been helpful to guide and predict the success of ASA, a paradoxical increase in the pressure gradient could impede the operator's ability to judge the success of the procedure. An increase in wall thickness and LV outflow obstruction might be associated with serious clinical consequences among patients with severe degrees of resting obstruction. Among the 108 cases of endocardial radiofrequency ablation for HCM reported to date, 1 death was attributed to this complication (4).

Techniques that overcome the limitations of standard therapies have the potential to meet an unmet need and expand the application of an effective treatment to previously untreatable patients in need. However, proof of their effectiveness and safety requires carefully conducted clinical trials. Septal myectomy and ASA have a long track record of success and are applicable for most patients with HCM and indications for septal reduction therapy. For the uncommon individuals who are not suitable for either technique, having a safe and effective alternative approach would be attractive. None of the recently described alternative methods have emerged as ideal in that regard. Nevertheless, further study will be needed to determine if cerclage ablation can fulfill that promise. Meanwhile, the demand for and the future of septal reduction therapy as a mainstay of treatment for obstructive HCM is uncertain because of the promising results for reducing LV outflow

obstruction medically by the oral myosin inhibitor, mavacamten, in current clinical testing. A successful medical therapy that relieves LV outflow obstruction and symptoms may limit the need for anatomic septal reduction, although the long-term safety and tolerability of mavacamten or agents like it likewise remain to be proven. Having multiple tools in our clinical toolbox to reduce the burden of disabling symptoms for patients with HCM will be welcome, but each will require rigorous clinical testing before acceptance into clinical practice.

AUTHOR RELATIONSHIP WITH INDUSTRY

Dr. Bach has received institutional research funding for Washington University School of Medicine, but no personal compensation, from MyoKardia and Cytokinetics.

ADDRESS FOR CORRESPONDENCE: Dr. Richard G. Bach, Cardiovascular Division, Washington University School of Medicine, Campus Box 8086, 660 South Euclid Avenue, St. Louis, Missouri 63110. E-mail: rgbach@wustl.edu.

REFERENCES

1. Morrow AG, Brockenbrough EC. Surgical treatment of idiopathic hypertrophic subaortic stenosis - technic and hemodynamic results of subaortic ventriculomyotomy. Ann Surg 1961;154:181–9.

2. Sigwart U. Nonsurgical myocardial reduction for hypertrophic obstructive cardiomyopathy. Lancet 1995;346:211–4.

3. Nagueh SF, Groves BM, Schwartz L, et al. Alcohol septal ablation for the treatment of hypertrophic obstructive cardiomyopathy a multicenter North American Registry. J Am Coll Cardiol 2011;58:2322–8.

4. Yang HN, Yang Y, Xue YH, Luo SX. Efficacy and safety of radiofrequency ablation for hypertrophic obstructive cardiomyopathy: a systematic review and meta-analysis. Clin Cardiol 2020;43:450–8.

5. Shin E-S, Chon M-K, Jun EJ, et al. Septal reduction using transvenous intramyocardial cerclage radiofrequency ablation: preclinical feasibility. J Am Coll Cardiol Basic Trans Science 2020;5:988–98.

KEY WORDS hypertrophic cardiomyopathy, radiofrequency ablation, septal ablation, septal reduction therapy