Obstruction in Hypertrophic Cardiomyopathy:
How Often Does It Occur? Should It Be Treated? If So, How?

Running title: Braunwald; Obstruction in HCM

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Hypertrophic cardiomyopathy (HCM) is the most common monogenic cardiac disorder and has been estimated to occur in one of every 500 persons in the general population, amounting to a total of about 600,000 persons in the United States. Its pathophysiology and optimal management have been the subject of conjecture and debate for more than a century. The issues surrounding left ventricular outflow tract (LVOT) obstruction in HCM have evoked the most discussion.

In 1907, a German pathologist, A. Schminke, described two hearts from women in their mid fifties. Decades before the development of left heart catheterization, and before any pressure gradients had ever been measured in humans, he wrote: “…Diffuse muscular hypertrophy of the left ventricular outflow tract causes an obstruction. The left ventricle has to work harder to overcome the obstruction. So, the primary hypertrophy will be accompanied by a secondary hypertrophy, causing an incremental (further) narrowing of the outflow tract…” Thus, Schminke presciently understood the vicious circle of left hypertrophy → obstruction → more hypertrophy, etc. A half century later, Morrow and I, despite having access to left heart catheterization, (but not being aware of Schmincke’s insight) struggled to explain our findings in two patients who had subaortic pressure gradients but no evidence of obstruction in the potassium citrate-arrested heart, a condition which we initially (and awkwardly) termed “Functional aortic stenosis”. However, we did conclude “…that the obstruction can only be explained by muscular hypertrophy of the left ventricular outflow tract…”

As open-heart surgery exploded in the early 1960s, patients with this condition (the name HCM had not yet been agreed upon) were encountered with increasing frequency by cardiologists and cardiac surgeons around the world; Sir Russell Brock provided especially useful insights. Indeed, HCM soon became the poster child for the hemodynamic era. Although,
by definition, all patients had left ventricular hypertrophy, left ventricular outflow tract (LVOT) obstruction was variable; in some it was always present\textsuperscript{5}; in a second group LVOT obstruction occurred only on provocation\textsuperscript{6}; and a third group had forms of left ventricular hypertrophy similar to those in the first two groups, but did they not exhibit LVOT obstruction even with provocation.\textsuperscript{5}

Since LVOT obstruction could be provoked or intensified by beta adrenergic stimulation\textsuperscript{6}, it was logical to try to prevent it with beta adrenergic blockers, which had just been developed and which proved helpful to many patients with HCM, perhaps less so to patients with severe LVOT obstruction in the basal state.\textsuperscript{7} Morrow at the NIH\textsuperscript{8} and Kirklin and Ellis at the Mayo Clinic\textsuperscript{9} turned their attention to the development of a corrective operation, surgical septal myectomy (SSM). However, in those early years, the operation was found to be technically challenging, the risk was substantial and it was carried out in only a small number of centers. Some observers even doubted that obstruction ever occurred in HCM and that the pressure differences between the left ventricle and the aorta, on which we based our recommendations about surgery, were artifacts\textsuperscript{10,11}.

Now to fast forward to 2006 when the Marons and their colleagues showed by echocardiography that LVOT gradients at rest and/or during exercise occur in 70\% of patients with HCM\textsuperscript{12}, are frequently associated with symptoms and adverse clinical outcomes\textsuperscript{13}, and concluded that when these obstructions are not responsive to pharmacologic therapy, they require mechanical relief. Two approaches to accomplish this are available today; the first is SSM, sometimes referred to as the “Morrow procedure”, which has gradually become both more extensive and safer over the years. In 1995, alcohol septal ablation (ASA) was introduced\textsuperscript{14}, and because it relieved obstruction without requiring open-heart surgery, quickly became the more
frequently employed procedure. However, SSM has continued to be carried out, mostly at specialized centers, and it is still considered to be the “gold standard”. The question most frequently asked today is which of these procedures is preferable and for whom?

Three major comparisons are available. Argawal et al performed a comparison of the results in eight institutions in which both procedures were employed; 326 patients received SSM and 380 ASA. Leonardi et al compared the results on 1887 patients who received SSM with those on 2153 patients who received ASA, usually in different hospitals. Several studies found their way into both comparisons. Both analyses concluded that the mortality rates were similarly low with both procedures. However, Agarwal et al pointed out that ASA increased the need for implantation of a permanent pacemaker, and left patients with low, but significantly higher, LVOT pressure gradients than did SSM.

The excellent paper by Sorajja et al from the Mayo Clinic, Rochester in this issue of Circulation provides the largest single center comparison of 177 patients who underwent ASA with an equal number of age and gender-matched patients who underwent SSM. These two groups were not randomized and the time that these procedures were carried out differed, from 1998 to 2010 for ASA and from 1983 to 2001 for SSM. At baseline, when compared to the SSM patients, the ASA patients had a significantly greater incidence of NYHA class III/ IV, and more frequently had a history of coronary artery disease, and of treatment with a beta blocker. Quite remarkably, the 8 year survival estimates were identical at 79% in both groups. However, the ASA patients had a residual gradient averaging 11 mm Hg and early pacemaker dependency of 20% compared to 5 mm Hg and 2% respectively for SSM patients. During prolonged follow-up of ASA patients, 5.6% required subsequent SSM and 2.8% repeat SA. The post ablation LVOT gradient in ASA patients was an independent predictor of both all-cause mortality and
subsequent need for these re-interventions.

The ACC/AHA Guidelines for the Treatment of HCM published in 2011 recommended, with a Class I indication, that “septal reduction therapy should be performed only by experienced operators… and only for the treatment of patients with severe drug-refractory symptoms and LVOT obstruction”. They also provided a IIa recommendation that SSM “is the first consideration for the majority of eligible patients with HCM” and that “when surgery is contraindicated, or the risk is considered unacceptable because of serious co-morbidity or advanced age, ASA… can be beneficial in … patients with HCM with LVOT obstruction and severe drug-refractory symptoms”.19 The paper by Sorajja et al18 provides further support for these recommendations.

Ordinarily, when there is a question regarding the choice between two competing therapeutic approaches, a randomized clinical trial is used to provide the answer. However, Olivotto et al have made the case20, and I believe quite convincingly, that such a trial presents logistical hurdles that cannot be surmounted in the foreseeable future.

So, where do go from here? The available comparisons between the two approaches to septal reduction therapy are largely retrospective and the risks for bias, both in patient selection and publication, creep in. A prospective multicenter registry which provides detailed baseline characteristics and descriptions of the procedure, as well as careful and systematic follow-up, could be very helpful. Much of the early work on HCM was conducted at the NHLBI, which has had extensive favorable experience with prospective registries – on cardiac transplantation, pulmonary hypertension and assisted circulation, to name a few. It would now be quite appropriate for the institute to organize a comparison of these two techniques of septal reduction which would be relatively inexpensive and cost-effective at a time of fiscal stringency.
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References:


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