Does relief of outflow tract obstruction in patients with hypertrophic cardiomyopathy improve long-term survival? Implications for lowering the threshold for surgical myectomy and alcohol septal ablation

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Hypertrophic cardiomyopathy (HCM) is the most common cardiac genetic disease, with a high prevalence of 1 in 500 individuals, irrespective of gender or race (1). Rising awareness of this disease in recent decades, through first-of-their-kind societal guidelines both in the United States and Europe, the growth of national centers of excellence, improvements in advanced imaging and genetic testing, and the initiation of disease-specific pharmaceutical trials, has brought a bolus of patients to advanced clinical care. These patients are asking important questions with regards to quality of life, how best to live with this disease, the effects on their progeny and extended family, and importantly whether available therapies merely palliate disease or provide meaningful survival benefit.

Clinical manifestations of HCM are myriad and vary with the underlying substrate, both cellular and macroscopic, as modified by patient age and comorbidities. While young patients typically present with angina, exertional pre-syncope or syncope, subtle then progressive exercise intolerance or, most dramatically, sudden cardiac arrest, older patients more typically present with forward, followed by backward, heart failure symptoms over decades, similar to other diseases of the heart that impact cardiac output. Notable differences are that HCM is associated with an increased although ameliorated risk of primary cardiac arrest as patients age, and additionally that the obstructive form is marked by minute-to-minute dynamic perturbations of stroke volume and mitral regurgitation.

It has been known for some time now that symptomatic HCM patients have poorer long-term survival than asymptomatic patients, and that this mortality difference tracks both with maximal wall thickness and the presence of obstruction. Importantly, it is not the magnitude of obstruction that appears to matter, but simply its presence or absence—implying that obstruction precipitates declining function and/or an increase in pro-arrhythmia that impacts longevity (2-4). Late in the clinical course, patients not infrequently present with atrial fibrillation and full-blown congestive heart failure, including secondary pulmonary hypertension, biventricular failure and anasarca in some.

Historically, our treatments for HCM have been largely supportive—lifestyle modification to manage diet and exercise and thereby minimize risks of ventricular arrhythmia and congestion, and medications to improve the diastolic dysfunction and outflow tract obstruction (1). Studies on the effects of such maneuvers widely suggested palliation of symptoms. And so, the dogma to patients was that symptoms of heart failure, syncope, and angina can be controlled and mitigated by medications but that life expectancy is not affected. Although the threshold to place an ICD has always been disputed, high risk subsets are identifiable, with the presumption, albeit not proven prospectively, that population-based survival can be impacted favorably.

With regards to the invasive therapies, namely alcohol septal ablation and surgical myectomy, historically there has been little evidence that they affect survival, and accordingly patients that undergo these procedures are told specifically that there is an expectation only of improved function and quality of life. Elimination of obstruction leads to resolution of mitral regurgitation and unloading of both the left ventricle and atrium, with secondary regression of hypertrophy in both the region of resection (or ablation) and distant regions (5). Over time, up to 3–5 years at least, there is a continued and steady improvement in diastolic function, left sided and pulmonary pressures, and overall wall thicknesses, culminating in a more normally functioning heart (5-8). Consistent with this, studies support marked improvement in exercise tolerance, functional class, angina, and medication requirement in over 90% of patients, with no significant differences between the two invasive approaches (9,10).

What is intriguing now, however, is the recent suggestion that such anatomic regression and symptom improvement may effect a reduction in mortality—to an incidence that mirrors the general non-HCM population. For this to be true, it would imply that obstruction and its sequelae are critical to the reduced survival in adult patients with the obstructive form of HCM. Further, it would imply that such elimination of obstruction normalizes the heart failure state and overwhelms the known continued risk of sudden cardiac death in these patients, or that the elimination of obstruction normalizes both the heart failure state and pro-arrhythmia.

Data that invasive therapies improve survival are primarily observational. Looking at their experience with myectomy, Mayo Clinic published the first credible example of survival benefit compared to an age and gender matched non-HCM population. Specifically, survival to 8–10 years tracked with the general non-HCM population at roughly 80% (11). Since myectomy patients are young, however, averaging 48–50 years old, the obvious next question was whether alcohol septal ablation, typically performed in patients 10–15 years older, would follow suit. If not, then one might assume that there is a point in the heart failure progression beyond which elimination of obstruction will no longer confer a survival benefit, or that alcohol septal ablation provokes other mechanisms of death over time, such as declining systolic function or pro-arrhythmia. When superimposing the survival curves, however, again matching for age and gender, the exact same survival of roughly 80% at 8–10 years was seen, suggesting that (I) there may be no

realistic age limit to positively impact the natural history, (II) elimination of obstruction itself confers the survival benefit, and (III) scar development from ablation is not meaningfully pro-arrhythmic to outweigh this benefit (11). Since the publication of this paper, other series have also shown similar survival curves out to 10 years for both surgical myectomy and alcohol ablation, confirming these benefits (12).

Drilling down further, cardiac death from HCM must be related to either progressive heart failure or sudden cardiac arrest. Clearly, invasive procedures improve the heart failure state. But, what about SCD risk? Is this positively affected, negatively affected, unaffected, or differentially affected? Critics of alcohol septal ablation have theorized that while myectomy removes the myocardium in discrete fashion, without the production of a scar, while physically removing much of the patchy innate HCM scar itself, alcohol septal ablation potentially adds a second scar to an already high-risk substrate. If this were the case, then SCD risk might be differentially affected by the two invasive therapies, and perhaps the survival curves mentioned above simply do not extend long enough to see divergent survival. Inconsistent with this theory are the many studies looking at implantable cardioverter-defibrillator (ICD) shocks and sudden cardiac death in patients after either alcohol septal ablation or myectomy. Uniformly, these studies show a very low incidence of ventricular arrhythmias that not only mirror each other but are lower than expected for such a sick HCM population. Leonardi evaluated mortality and SCD risk after invasive therapies and found not only near identical outcomes but, if anything, a lower mortality rate after alcohol septal ablation once adjusted for age and comorbidities (13). More recently, a large meta-analysis of SCD and all-cause mortality after invasive therapies found low and similar rates between the two, with mortality 1.4% per year and SCD 0.4% per year (14).

Mechanistically, how would invasive therapies improve survival? Clearly, they alleviate heart failure and halt its progression, including potentially the development of so-called "burnt-out" HCM, so this must be a significant part of the benefit. But how might an improvement in SCD be explained? More research is needed here, in terms of whether these therapies modify the underlying substrate for automaticity or re-entry. Could it be that obstruction exacerbates microvascular ischemia that is a necessary trigger of the underlying arrhythmic substrate, and thus a more quiescent state ensues after relief of obstruction? Certainly, data does support that ischemia is present in

patients with HCM, even without epicardial coronary disease, and that such ischemia is a potent predictor of both progression and death (15). Alternatively, it could be that the overall propensity for arrhythmia is reduced with regression of cellular hypertrophy, or that a more normally-functioning heart can simply tolerate ventricular arrhythmias better. And, finally, it could it be a confluence or synergy of all of these positive mechanisms.

Our professional guidelines have not kept pace with these promising data, and even now HCM experts rarely suggest that invasive therapies may confer a survival advantage. After all, there is no prospective, randomized trial comparing invasive therapies to medical therapy. And, observational analyses are fraught with selection bias. Accordingly, the 2011 American College of Cardiology and American Heart Association guidelines recommend invasive therapies as a Class II for patients with severe heart failure symptoms (NYHA Class III–IV), but not a Class I—indicating that the data did not seem strong enough to mandate (1). By 2014, however, the European Society of Cardiology guidelines made invasive therapies a Class I for symptomatic patients with obstruction and suitable anatomy, and lowered the threshold to include NYHA Class II symptoms and obstruction-related syncope—indicating a stronger stance based on these favorable data for both improved function and survival (16). And, as practicing HCM specialists, it does appear that many of us in the field have mentally lowered our threshold for invasive therapies, armed with this data and the growing belief that elimination of obstruction may be a critical inflection point in this disease.

So, where does this leave us? Is there sufficient data to mandate invasive therapies as a Class I indication for all patients with obstructive HCM of sufficient magnitude, regardless of the presence, absence or magnitude of symptoms? And what about medications—what should their role be? While calcium channel blockers and beta-blockers rarely eliminate resting obstruction, disopyramide on rare occasion can eliminate both resting and provocable obstruction, and newer pharmaceuticals in development are being targeted to provide complete elimination of obstruction (1,17). Will we then have medications that remove obstruction with the same long-term survival advantage as invasive therapies?

These are indeed interesting times to be HCM specialists. Not only is there a renaissance of interest in the disease and a large number of patients coming to regional and national centers of excellence, but we now have the ability to offer them meaningful improvements in quality of life and potentially survival through invasive therapies that have been relatively perfected through decades of development. We suspect our threshold for such therapies may continue to lower and become a Class I indication for any patient with severe obstruction and acceptable anatomy, as it is in the pediatric population (1).

But that's just for the foreseeable landscape. What does the future hold beyond that? Will we see medications that can eliminate obstruction as well as invasive therapies, or prevent the development and progression of hypertrophy in genotype positive, phenotype negative patients? Perhaps yes—but for now it appears the data are at least sufficient to talk openly about invasive therapies as a modifier of both heart failure and SCD, with an aim to develop prospective data to prove these findings. And, for that matter, decisions regarding ICD implantations in patients with severe obstruction might best be deferred until relief of obstruction. New iterations of the guidelines will need to tackle these and other important questions, and provide some uniformity of opinion. Until then, a cautious attitude toward earlier institution of optimally-performed invasive therapies seems warranted.

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Footnote

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