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How can we Improve Non-surgical Septal Reduction for Hypertrophic Obstructive Cardiomyopathy?

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Abstract

The goal for treatment of medical refractory Hypertrophic Obstructive Cardiomyopathy (HCM) is reduction of the hypertrophied left ventricular septum which obstructs blood flow. A surgical approach consists of an open-heart myomectomy, while the less invasive percutaneous approach involves creating a myocardial infarction by injecting 95 to 100% ethanol through a septal artery, a procedure termed alcohol septal ablation (ASA). Although less invasive than myomectomy, there are several limitations of alcohol septal ablation. The most important appears to be full thickness infarction that is often complicated by heart block and ventricular tachycardia/fibrillation. The ideal therapy for septal hypertrophy would be to find an agent that induces a less severe injury and/or atrophy of the hypertrophied septum. We review several alternative techniques for selective injury of the septum and describe the ideal characteristics of such an ideal agent. Our central hypothesis is that the anthracycline antibiotic such as doxorubicin may be the perfect agent. Anthracycline-based chemotherapies have been used in the treatment of solid and hematological tumors for many years. These agents have known cardiotoxic side effects that are related to cumulative dose which can lead to heart failure. Although the mechanism of action of doxorubicin cardiotoxicity is controversial, it is very clear that these agents cause atrophy of the myocardium, induce apoptosis and necrosis, as well as anti-angiogenic effects. We propose that selectively treating the hypertrophied septum of HCM patients with injection of the anthracycline doxorubicin will lead to superior outcomes compared to ASA.

Keywords: Hypertrophic obstructive cardiomyopathy; Myectomy; Alcohol septal ablation; Doxorubicin

Introduction

It has been over three decades since Sigwart first described that brief occlusion of the septal artery with a balloon catheter leads to transient reductions in the outflow gradient across the aortic valve [1]. In 1995, Sigwart went on to describe the induction of localized infarction of the septum with infusion of ethanol in the septal coronary artery in three patients, all of whom continued to have symptomatic improvement 12 months later [2]. In the few years following this initial experience, the use of intracoronary infusion of alcohol down a septal artery to treat hypertrophic cardiomyopathy (HCM) was utilized by many others and showed an improvement in exercise capacity [3], has been shown to improve diastolic function [4,5] decrease left ventricular hypertrophy and mass [6], and cause changes at the cellular and molecular level that improve myocardial function. Cardiac magnetic resonance studies show a significant reduction in myocardial mass and improvement of intramural systolic function in the lateral (remote) wall, suggesting reversed left ventricular remodeling [7]. Immediately after this technique, there is an improvement and normalization in coronary flow reserve [8]. This, along with the percutaneous approach this offers as opposed to surgery, has lead to the widespread use of targeted delivery of ethanol termed alcohol septal ablation (ASA). Indeed, it has been estimated that more ASAs have been performed in the past

approximate 10 years than all myomectomies ever performed [9]. With overlapping but different indications, surgical myomectomy on cardiopulmonary bypass pump and the less invasive percutaneous alcoholic ablation through a septal artery provide the only two accepted modalities of therapy for severely symptomatic obstructive HCM, when medications have failed [10,11]. There is a difference of opinion in the scientific community on which approach is better, as well as a debate regarding the feasibility of and need for a randomized trial [12].

Limitations of ASA

Although less invasive than myomectomy, there are several major limitations of ASA. Large prospective registries, such as the German ASA registry, have shown major complications rates of 15.6%, a mortality rate of 1.2%, and a permanent pacemaker implantation rate of 9.6% [13]. 10-year data from this same registry showed 5.1% all-cause mortality and total in-hospital mortality at 1.2% in all patients [13]. Poor outcome was associated with old age [13,14] and lower alcohol dosage and the absence of atrial fibrillation as independent predictors of reduced cardiac mortality [13]. Furthermore, comparative nonrandomized studies show that myomectomy and alcohol ablation are similarly associated with subjective improvement in NYHA functional class, but surgery yields more favorable outcomes with fewer early complications, more complete relief of obstruction, and greater exercise capacity and oxygen consumption [15]. Moreover,

the risk for permanent complete heart block requiring pacing is up to 20 times greater with ablation (sometimes in young patients) than with myomectomy [15-16].

The injection of near absolute ethanol into the septal artery leads to a transmural scar compromising 10% of the LV mass (30% of septum) [17]. This strategy of intentional scarring myocardium contradicts a major tenet of preventive cardiology to minimize myocardial infarction and scarring [9]. The surgical approach of myectomy does not result in scarring of the myocardium only endocardial fibrosis. The presence versus absence of myocardial scarring is the major difference between the two treatments to reduce septal outflow obstruction [9] and the poorer outcomes in ASA may be related to the transmural scar. This increases the incidence for reentrant ventricular tachyarrhythmias and sudden death originating from the alcohol-induced myocardial necrosis and scarring in the patient with HCM, a patient who already has preexisting electrical instability and an unpredictable myocardial substrate [18]. Recent reports suggest that lethal arrhythmogenic events linked to ablation may not be uncommon [19,20]. In addition, alcohol septal ablation has also been associated with increased firing of implantable cardioverter defibrillators [13]. All these limitations suggest the need to think about other agents that might reduce septal hypertrophy via a percutaneous approach.

Alternative Techniques

The method of a percutaneous approach, whether that is intracoronary or otherwise, to the delivery of an agent to treat HCM is clearly less invasive than a surgical technique that requires a sternotomy. In contemplating alternative strategies for the non-surgical treatment of HCM, the best therapy would have specific effects at the cellular, myocardial, and clinical levels (Table 1).

Delivery	- Non-invasive (percutaneous)
	- Dose of therapy associates with a predictable effect
Clinically	- Has better or at least comparable mortality and morbidity to current therapy options
Electrophysiologically	- Does not result in damage to the AV node blood supply
	- Does not result in increased ICD firing
Effects on the myocardium	- Does not cause scarring (i.e. does not have an ischemic component)
	- Preserves local and global overall myocardial contractility
Effect at the cellular level	- Induces myocyte regression
	- Prevents myocyte hypertrophy

Table 1: Characteristics of the ideal modality of therapy for cardiac septal hypertrophy.

New approaches to treating septal hypertrophy have been attempted over the last several years, none of which have made it into widespread clinical practice. Table 2 summarizes these different alternative therapeutic strategies.

Promising animal studies have shown the potential of histotrispy, a novel ultrasonic technique that produces non-thermal, mechanical tissue fractionation through the use of high-intensity ultrasound pulses, in the non-invasive creation of atrial and ventricular septal defects [21,22]. Perhaps a measured delivery of such a therapy can result in the treatment of local or even global myocardial hypertrophy. Although this approach now requires a sternotomy, perhaps with further development of this technology, non-invasive methods can be developed, as in the case of advancement of intra-cardiac echocardiography from larger ultrasound probes [23,24].

Lessons from Oncology – Could Anthracyclines be used to Regress Septal Hypertrophy?

The effects of anthracycline on the heart have been well studied [25]. However, there is no generally accepted mechanism for how these drugs cause heart failure [26]. A general hypothesis for anthracycline-induced cardiac toxicity is that some form of cardiac injury occurs with every repeat exposure.

An additional finding of prior studies is that, at least in children, anthracyclines limit normal cardiac growth. This is supported by echocardiographic data of children exposed to anthracyclines showing that there is a reduction in ventricular wall thickness in comparison to age-matched children without anthracycline exposure resulting in increased end-systolic wall stress [27]. However, studies have shown that the young heart has a greater capacity for myocyte division and perhaps regenerative capacity [28]. Based on this, one would expect children to have enhanced regenerative capacity allowing for better recovery from anthracycline exposure.
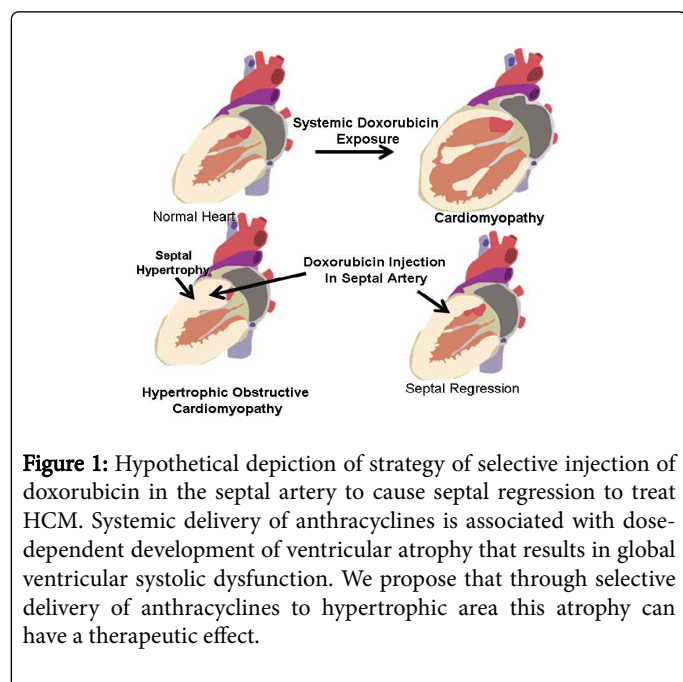
A possible explanation for this was provided by De Angelis, et al. [29] who showed that anthracyclines markedly diminish the number of cardiac progenitor cells in rodents. Huang et al. [30] demonstrated that anthracyclines induce a loss of cardiac progenitor cells in young mice at doses of anthracyclines that might be considered more in line with those used clinically. They exposed young "juvenile" mice to repeated low doses of doxorubicin and found that the number of cardiac progenitor cells decreased in hearts after exposure. They demonstrate that the hearts of these mice are left with permanently altered vascular architecture with a quantifiable rarefaction of arteriolar branching and reduced capillary density, all consistent with anti-angiogenesis. These observations led to the idea that anthracyclines may be leveraged to cause regression of septal hypertrophy in HCM [31].

Large animal studies have shown doxorubicin effects that support this concept. In a 2008 article, Christiansen et al. [32] performed doxorubicin injection in the left main artery in a pig model [32]. With the aim of developing a cardiomyopathy model, they were able to show macroscopic dilatation in various degrees throughout the left ventricle as a result of multifocal necroses. At a histological level, there was an advanced degree of tissue reorganization in the damaged myocardium

with only small areas of healthy appearing myocardium without an ischemic component. This would suggest that doxorubicin results in sparring of some healthy myocardial tissue.

Approach	Technique	Description	Advantages	Limitation
Intracoronary	Wire [33]	Performed by mechanically occluding the septal artery using thrombogenic floppy tips of used balloon wires instead of alcohol	Provides an option when the anatomy of the septal artery is not suitable for alcohol ablation	Foreign body remains in the septal artery
	Transluminally delivered polyvinyl alcohol [34]	Embolization of the septal artery with PVA foam particles		
Endomyocardial	Radiofrequency ablation [35,36]	A catheter is placed at the bundle of His. Radiofrequency ablation is performed with an irrigated-tip ablation catheter	Provides an option when the anatomy of the septal artery is not suitable for alcohol ablation	
	Ventricular pacing from the right ventricular apex [37,38]	Pacing the right side of the interventricular septum	Theoretically, creates paradoxical motion of the interventricular septum, pulling it away from the outflow tract during early systole, creating less systolic anterior motion of the mitral valve, and thereby decreasing outflow obstruction.	Randomized trials have shown less improvement in objective measurements and have shown a large placebo effect, with true improvement in only a small percentage of patients [39,40]
	MitraClip [41]	Catheter-based treatment of LVOT obstruction targeting primarily SAM using Mitraclip implantation	Non-surgical	Foreign body remains in mitral valve. Performed in only one patient with prior surgical myomectomy
Surgical	Histotripsy [21,22]	Nonthermal, mechanical tissue fractionation through the use of high-intensity ultrasound pulses, in the non-invasive creation of atrial and ventricular septal defects	Potential for further development allowing percutaneous approach	Studies tailoring therapy to reduction of septal thickness need to be conducted

Table 2: Novel approaches to treating septal hypertrophy.

Figure 1: Hypothetical depiction of strategy of selective injection of doxorubicin in the septal artery to cause septal regression to treat HCM. Systemic delivery of anthracyclines is associated with dose-dependent development of ventricular atrophy that results in global ventricular systolic dysfunction. We propose that through selective delivery of anthracyclines to hypertrophic area this atrophy can have a therapeutic effect.

With the widespread use of anthracycline-based chemotherapies in oncology, the adverse cardiovascular effects of these agents can be put to good use in a controlled, programmed manner to ablate cardiac myocytes. In the case of HCM, this can be in the form of septal artery delivery (Figure 1), or even more diffuse delivery in cases of inherited or acquired cardiomyopathy that result in global cardiac hypertrophy [32]. Because doxorubicin has potent antiangiogenic effects along with the well-established cardiotoxicity, this chemotherapeutic agent could provide another mechanism for the utility of such an approach.

Even though myomectomy and ASA provide good clinical outcomes, the quest should go on in the pursuit of novel modalities of treating severely symptomatic HCM when maximum medical therapy has failed. Further pre-clinical and clinical studies should be conducted to examine whether the myocytotoxicity of anthracyclines, or other chemotherapeutics, might provide an answer to this clinic problem.

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