

# Role of endocardial septal ablation in the treatment of hypertrophic obstructive cardiomyopathy

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## ABSTRACT

Septal reduction therapy is accepted as a first therapeutic option for symptomatic drug-resistant hypertrophic obstructive cardiomyopathy (HOCM). Although, surgical septal myectomy is the gold standard method, alcohol septal ablation is a well-studied alternative approach in the patients with suitable anatomy. Endocardial septal ablation (ESA) therapy was relatively new defined modality and outcomes of the procedure were not clearly elucidated yet. We aimed to review the clinical aspects of ESA procedure and provide some historical background. (*Anatol J Cardiol* 2016; 16: 707-12)

**Keywords:** Ablation, hypertrophic obstructive cardiomyopathy, septal myectomy, alcohol septal ablation, radiofrequency

## Introduction

Hypertrophic obstructive cardiomyopathy (HOCM) is an inherited disease which presents with increased left ventricular outflow tract (LVOT) gradients. It is usually transmitted in an autosomal dominant pattern with variable penetrance. The estimated prevalence of hypertrophic cardiomyopathy is one in 500 and 20–30% of these patients presented as HOCM due to LVOT obstruction (1, 2). The prevalence of obstruction may be up to 70% with provocation maneuvers (3, 4). In most cases, basal septal hypertrophy and systolic anterior motion (SAM) of the mitral valve are the key components to LVOT obstruction.

The obstruction of LVOT, caused by systolic anterior motion (SAM) of anterior mitral leaflet with elevated intracavitary LV pressures, can produce disabling symptoms of heart failure and excess cardiovascular mortality (4–6). Septal reduction therapy (SRT) is the accepted treatment modality in patients with hypertrophic obstructive cardiomyopathy (HOCM). As a first successful application, Cleland (7) undertook and reported the results of transaortic resection in 1958. Then, the technique was developed and re-defined by Morrow (8). Although, myectomy is a well-established, effective surgical technique for drug resistant HOCM patients with decades of experience in its use, transcatheter alcohol septal ablation (TASA) is an alternative option in patients who refused surgery or high risk for surgery (9–12). However, a

significant limitation of TASA is reliance on coronary anatomy to provide access to target for ablation. Up to 15% of patients have no septal vessel suitable for TASA procedure (13, 14).

In theory, interrupting of the anterior MV leaflet contact with the septum, which cause a positive amplifying feedback loop further increasing LV pressures, may be achieved by endocardial septal ablation (ESA) of this SAM-septal contact area as a SRT. However, precise targeting of the SAM-septal contact area is imperative for success of the procedure. The existing literature includes different approaches to localize or to ablate target points in this relatively new and little known procedure. To discuss the potential role of ESA in HOCM therapy, after a cumulative literature search, we reviewed 59 cases previously published in 8 reports in which septal reduction was achieved by ESA (15–22).

## The pathophysiology of left ventricular outflow tract obstruction

It is well known that basal septal hypertrophy and SAM of the anterior mitral leaflet are the key components to LVOT obstruction in HOCM. In the majority of HOCM cases, the asymmetric septal hypertrophy leads to an obstruction of LVOT; this causes rapid acceleration of blood flow to apical of the mitral valve which is called as Venturi effect. It is thought that the narrowed LVOT contribute to pulling the mitral valve apparatus towards the

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septum. However, this is not the sole pathophysiological factor of LVOT obstruction. In some of the patients, obstruction may occur despite low velocities on LVOT. Abnormal posteriorly directed flow due to the septal hypertrophy may circulate around the mitral valve and back towards the LVOT. If there is a structural anomaly on anterior mitral leaflet like as redundancy, the leaflet may be caught by this flow. Then, the anterior leaflet may move towards to the hypertrophied septum. Once the anterior mitral leaflet interventricular septal contact occurs, the LVOT orifice is narrowed further and greater obstruction to flow develops, resulting in a higher pressure difference. This may cause positive amplifying feedback loop throughout ventricular systole.

If the contact duration of the anterior mitral leaflet and interventricular septum increases, the gradient of the LVOT will get higher (23). Main deleterious effects of LVOT obstruction are reduction of forward cardiac output, mitral regurgitation due to SAM, diastolic dysfunction and coronary flow abnormalities. The symptoms consisting of dyspnea, chest pain, pre-syncope and syncope result from LVOT obstruction.

#### Historical background of septal reduction therapy

Increased LVOT gradients (usually defined as peak gradient  $\geq 30$  mm Hg) are present in 20–30% and in up to 70% of hypertrophic cardiomyopathy cases at rest and with exercise provocation, respectively (5) and are associated with a higher mortality than matched hypertrophic cardiomyopathy patients without a gradient (5). Recent case series have suggested that removing the gradient may have a beneficial effect on survival (24, 25).

In most cases, the narrow of LVOT by asymmetric septal hypertrophy is exacerbated by contact of the anterior mitral valve leaflet with the interventricular septum due to SAM of the anterior mitral leaflet. The contact of the anterior mitral valve leaflet and interventricular septum cause a positive amplifying effect on LVOT gradient. Interrupting of this SAM-septal contact area is the potential target of septal reduction modalities.

According to the 2014 ESC guideline, surgical myectomy is the first line modality for SRT in the patients with symptomatic drug resistant HOCM based on systematic assessment of the MV and septal anatomy (5). As an alternative modality of SRT, the ability to perform TASA depends on suitable septal arterial anatomy. However, TASA cannot be performed in 5–15% HOCM patients due to restrictions of septal anatomy. So, different alternative methods to damage SAM-septal contact area that does not rely on arterial anatomy should be investigated.

## Methods

#### Search strategy

To identify the relevant literature (case, case report, case series and research articles), we searched MEDLINE and EMBASE from January 1966 to February 2016 using the key words hypertrophic cardiomyopathy or hypertrophic obstructive cardiomyopathy, each together with ablation, reduction, therapy, ra-

diol frequency, cryo, or endocardial. The searches were inclusive of all languages except for Chinese; all studies were written in English (15–22). The search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (26). We omitted conference abstracts. We checked the references of the initially included articles to identify other potentially relevant studies and subjected them to a similar selection process. A total of 8 relevant articles including 59 cases were identified. To prevent the potential duplications, we took into account the results of the last or main research project of one group. The cases or case series which presented by same authors before the publication of main study were excluded from the assessment. Ultimately, we aimed to review potential usage of ESA in the treatment of HOCM.

#### Endocardial septal ablation as an alternative method for septal reduction therapy

As it was shown by our group and the others, radiofrequency catheter ablation has become a principal form of therapy for different cardiac arrhythmias (27–31). Radiofrequency current delivered through a standard 7F 4-mm catheter tip electrode has been highly successful for ablation of arrhythmogenic tissue located within a few millimeters of the ablation electrode. For any given electrode size and tissue contact area, radiofrequency lesion size is a function of radiofrequency power level and exposure time (30, 32). It was shown in animal studies that the radiofrequency ablation procedure by irrigated-tip catheters allows the creation of larger lesions by increasing the power that can be delivered without coagulum formation (33–35). Cardiac magnetic resonance data of our group also showed that endocardial application of radiofrequency energy given by irrigated-tip catheter may cause deep myocardial lesions extending to epicardial site (36). Theoretically, if anterior mitral leaflet-interventricular septum contact point could be damaged by endocardial route, this small amount of scar tissue may interrupt the SAM-septal feedback mechanism and reduce LVOT gradients effectively. But, it should be noted that the location of tissue damage seems to be at least as important as the lesion size.

#### The publications associated with endocardial septal ablation

In 2004, after obtaining ethical approval for a limited series of cases to undergo ESA procedure, Lawrenz et al. (15) performed the first three septal ablation procedures in highly symptomatic HOCM patients. The procedure was unsuccessful in the first two cases. In the first patient, the procedure which was performed via left ventricular approach was unsuccessful due to catheter instability. In the second patient, although LVOT gradient was thoroughly abolished, gradient reduction was attributed the implanted dual chamber pacemaker. First successful case was performed via right ventricular approach (15). Fluoroscopy guidance was used to detect obstructing septal area in this study. Shortly after the publication of this study, Emmel et al. (16)

performed a similar procedure with success in two children via left ventricular approach. The location of the His bundle and left bundle branch was mapped out using Localisa mapping system (Medtronic, Minneapolis, MN, USA). Same group presented to similar results of three children one year later (17). In this three case series, the authors used to irrigated-tip ablation catheter and radiofrequency energy.

Keane et al. (18) firstly presented the results of 3 patients with symptomatic obstructive HCM who underwent percutaneous cryoablation of the interventricular septum. All 3 patients had previously undergone implantation of a dual-chamber pacemaker with ICD capability. They performed the procedure via a transaortic approach in one patient and via a transseptal approach in the other two patients. Acute procedural success, defined as a significant reduction (more than 50%) in LVOT gradient at the end of septal cryoablation, was achieved in 2 of the 3 cases. At 6-month follow up, patient symptoms and echocardiographic parameters were documented. Patient 1 had a mild improvement in dyspnea. Echocardiographic examination showed an interventricular septum diastolic value of 21 mm (no reduction from baseline), and a peak instantaneous LVOT gradient of 44 mm Hg (a reduction of 26 mm Hg). Neither of the other 2 patients reported any symptomatic improvement post-cryoablation.

In 2011, two relatively large studies were published. Lawrenz et al. (19) discussed the results of ESA of 19 adult patients with HOCM. To prevent induction of complete heart block, they navigated the tip of the ablation catheter as far as possible away from the His-bundle region, marked by the electrode catheter or additionally by a "tag" in the CARTO (Biosense Webster) map. The procedure was performed via right ventricular approach in 10 patients and left ventricular approach in 9 patients. As a surprising result, they found no difference between left-sided or right-sided approach for gradient reduction. They showed greater than 2 cm transmural scar in gadolinium-contrast magnetic resonance imaging. After 6 months, NYHA functional class improved from  $3.0 \pm 0.0$  to  $1.6 \pm 0.7$  ( $p < 0.01$ ); the 6-min walking distance improved by 58 m ( $413 \pm 129$  m at baseline;  $458 \pm 108$  m im-

mediately after ESA;  $471 \pm 139$  m after 6 months,  $p < 0.019$ ). During RF ablation, complete heart block occurred in 4 patients with permanent pacemaker dependency. All patients received a dual-chamber pacemaker and were still pacemaker dependent after 6 months. One patient had acute pericardial tamponade during right ventricular ablation caused by perforation of the right ventricle pacing lead, requiring surgical revision.

Sreeram et al. (20) assessed the efficacy of ESA in the treatment of HOCM in children. In this study, 32 children underwent ablation of the hypertrophied septum by using a cool-tip ablation catheter with retrograde aortic approach. An immediate decrease was detected in the catheter pullback gradient and a further reduction in the Doppler echocardiographic gradient was seen at follow-up. As a major complication, one patient died due to a paradoxical increase in left ventricular outflow tract obstruction. One patient underwent implantation of permanent pacemaker due to persistent atrioventricular block. Further procedures consisting of surgery, pacing, or ESA were required in 6 patients during a median follow-up of 48 (3 to 144) months.

Riedlbauchová et al. (21) presented the results of targeted ESA procedure. The target site was identified using intracardiac echocardiography and electroanatomic CARTO mapping. They determined damage of the tissue after RF ablation via intracardiac echocardiography as a change in the tissue opacity.

The last study in this field was published recently by Cooper et al. (22). They used to CARTOSound technology to directly ablate the interventricular septum at the mitral valve SAM -septal contact point using RF energy in 5 patients. Resting LVOT gradient improved from  $64.2 (\pm 50.6)$  to  $12.3 (\pm 2.5)$  mm Hg. Valsalva/exercise-induced gradient reduced from  $93.5 (\pm 30.9)$  to  $23.3 (\pm 8.3)$  mm Hg. Three patients improved NYHA status from III to II, one patient improved from class III to I. The results of all published studies were shown in Table 1.

### The comparison of used procedures

The exact localization of the SAM-interventricular septum contact point is the most important part of ESA procedure. In the relevant literature different techniques (fluoroscopy, trans-

**Table 1. The published articles about potential role of ESA in HOCM**

Study*	Number of patients	Mean age, years	Ablation energy	Approach (LV/RV)	Mapping /Guidance	Mean septal diameter (mm)	Mean pre-ablation Gradient (mm Hg)	Mean post-ablation Gradient (mm Hg)
Keane et al. (9)	3	38.1	Cryo	3/0	Fluoroscopy	20.3	98.6 <sup>†</sup>	66.6 <sup>†</sup>
Lawrenz et al.(10)	19	60.7	RF	9/10	CARTO	22.5	87.4 <sup>†</sup>	34.7 <sup>†</sup>
Sreeram et al. (11)	32	11.1	RF	32/0	Localisa/CARTO	Not indicated	78.5 <sup>†</sup>	36.1 <sup>†</sup>
Riedlbauchová et al. (12)	1	63	RF	1/0	CARTO	22	99 <sup>**</sup>	58 <sup>**</sup>
Cooper et al. (13)	5	59.2	RF	5/0	CARTOSound	19.2	93.5 <sup>**</sup>	23.2 <sup>**</sup>
Present case	1	49	RF	1/0	NavX	32	100 <sup>†</sup>	20 <sup>†</sup>

\*To prevent potential duplications, the case series which are conducted by same groups were not included in the table. <sup>†</sup>Rest gradient <sup>\*\*</sup>Valsalva- or exercise-induced gradient. ESA - endocardial septal radiofrequency ablation; HOCM - hypertrophic obstructive cardiomyopathy; LV - left ventricle; RF - radiofrequency; RV - right ventricle

esophageal echocardiography or intracardiac echocardiography) have used to localize the contact point (15–22). After the possible localization was defined, various electroanatomic mapping systems (CARTO, LocaLisa, Ensite) were used to guide and mark ablation lesions. Although the authors were used usually transesophageal or intracardiac echocardiography to provide high quality images, as it was shown by our presented case study transthoracic echocardiography may provide sufficient quality images for ESA (37). The potential usage of TTE for the detection of the SAM-septal contact area was verified in the patient undergoing TASA procedure (38).

It was shown in the previous literature that failure of TASA may occur when the iatrogenic infarct is exclusively sited in the right ventricular septal myocardium (39, 40); the most common site for undesirable contrast localization has been reported to be the RV septum and moderator band (41). This is the theoretical base of why left sided approach was used for ESA by the majority of investigators (Table 1). Theoretically, left sided approach could allow targeted ablation of contact point of anterior mitral leaflet and interventricular septum. In this way, same ablation target may be achieved by smaller ablative lesions. It was shown by relevant literatures that localized ablation of interventricular septum by using radiofrequency or cryo-energy may cause effective gradient reduction that are similar to those observed during and after the other septal reduction procedures (15–22). However non-randomized nature and small sample size of these studies are the serious obstacle in front of the reliability of their results.

For a long-time, cardiac biomarkers have been used to estimate myocardial lesion size after ablation procedures with different energy sources. It was discussed in our previous study that increase in biomarker levels and the amount of myocardial damage after RF catheter or cryo ablation depend on the number of RF pulses, duration of cryo-application and the site of ablation (42). In our presented case, we detected significant postprocedural increase of cardiac enzymes which may be an evidence of effective endo-myocardial injury induced by radiofrequency energy which results in a similar release of creatine kinase compared with alcohol septal ablation (37).

The results of all published articles suggest that ESA may create a localized myocardial scar on contact point of anterior mitral leaflet and interventricular septum. Although, the mapping of atrioventricular node and bundle branch conduction sites may be an additive effect to avoid inadvertent block complication due to ablation, sample size of the studies are not enough to arrive at this judgement. Furthermore, the septal wall thicknesses were not changed significantly after the procedure. So, severe decrease in the LVOT gradient may be attributed only to a localized reduction of endo-myocardial tissue in contact point. Although, this contact point accepted as the main responsible mechanism for the dynamic obstruction of LVOT, long term results of this procedure may not be speculated from present results.

## Study limitations

This comprehensive review article is aimed to evaluate the potential use of ESA to treat LVOT gradients in HOCM. Although there are some published articles, case numbers of these studies were usually small, and nature of the studies were non randomized and single center. The ability to make secure conclusions about outcome is obviously restricted by the small numbers. The follow-up periods were also short. So, the usage of ESA for a septal reduction strategy should be considered as off label procedure.

## Conclusion

A deeper understanding of the marked heterogeneity of hypertrophy patterns and associated anatomical changes beyond the hypertrophied septum allows targeted therapeutic approaches to relieving LVOT gradient. Surgical myectomy and TASA may have different optimal candidates based on the morphologic variation of both the hypertrophied septum and the mitral valvular apparatus. Although, ESA seems a technically feasible strategy, short and long term results and complications of the procedure were not clearly defined, yet. At this time, ESA should only consider in the patient in whom surgical myectomy is not an option after unsuccessful TASA procedure. Further large scale studies are needed to clarify this issue.

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