

James Madison University

**JMU Scholarly Commons**

---

Physician Assistant Capstones

The Graduate School

---

Summer 5-5-2016

## Improving Clinical Outcome in Patients with Hypertrophic Obstructive Cardiomyopathy

Elizabeth P. Thompson  
*James Madison University*

Elise Shellenberger  
*James Madison University*

Follow this and additional works at: <https://commons.lib.jmu.edu/pacapstones>



Part of the [Medicine and Health Sciences Commons](#)

---

### Recommended Citation

Shellenberger E, Thompson E. Improving clinical outcome in patients with hypertrophic obstructive cardiomyopathy. JMU Scholarly Commons Physician Assistant Capstones. <http://commons.lib.jmu.edu/pacapstones/3/> Published August 1, 2016.

This Article is brought to you for free and open access by the The Graduate School at JMU Scholarly Commons. It has been accepted for inclusion in Physician Assistant Capstones by an authorized administrator of JMU Scholarly Commons. For more information, please contact [dc\\_admin@jmu.edu](mailto:dc_admin@jmu.edu).

# OUT WITH THE OLD, IN WITH THE NEW? Improving Clinical Outcome in Patients with Hypertrophic Obstructive Cardiomyopathy

*Elise Shellenberger & Elizabeth Thompson*

## Abstract

**Objective:** Review two studies that assess alcohol septal ablation (ASA) and surgical myectomy as treatment options for patients with drug refractory hypertrophic obstructive cardiomyopathy (HOCM). **Background:** Controversy exists regarding these two forms of treatment for HCOM. **Design:** Two observational cohort studies. **Methods:** A search was done on PubMed, utilizing the terms “hypertrophic cardiomyopathy,” “alcohol septal ablation,” and “myectomy.” The following limits were used: published in the last 15 years, humans, English, and comparative studies. **Results:** Study One<sup>4</sup> showed that the patients undergoing ASA had a lower periprocedural complication frequency compared to those undergoing myectomy (14% [22 of 161] versus 28% [29 of 102], p-value 0.004). Patients undergoing ASA also had a significantly shorter follow-up stay than those undergoing myectomy (5 days versus 9 days, p-value <0.001). Multivariate analysis showed that age was the only independent predictor of long-term mortality (hazard ratio 1.34, 95% CI 1.08-1.65, p-value 0.007). Study Two<sup>5</sup> showed that the resting pressure gradient (PG) was significantly decreased following both procedures (64 ± 39 mmHg to 24 ± 19 mmHg for ASA, and 62 ± 43 mmHg to 11 ± 6 mmHg for myectomy, both p < 0.0001) at 3-month follow up. The NYHA functional class was also significantly improved in both groups; ASA patients from 3.5 ± 0.5 to 1.9 ± 0.7, and myectomy patients from 3.3 ± 0.5 to 1.5 ± 0.7, both p-values < 0.0001). **Conclusion:** Both ASA and surgical myectomy provide comparable clinical outcomes in patients. ASA is associated with decreased hospital stay and less periprocedural complications. Surgical myectomy provides more complete reduction in pressure gradient, but is a more invasive procedure. ASA is a relatively new procedure therefore further studies will be helpful to validate its efficacy in comparison to myectomy.

## Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited myocardial disorder and the most common cause of sudden death in young athletes. HCM affects 1 out of every 500 people and is more common in men than women.<sup>1</sup> The genetic mutations are passed in an autosomal dominant fashion and include defects in the cardiac sarcomere proteins. These defects cause enlarged heart muscle cells and thick ventricular walls resulting in abnormal diastolic function with impaired ventricular filling. The characteristic left ventricular hypertrophy (LVH) results in a resting or exercise provoked left ventricular outflow tract (LVOT) obstruction in 70% of patients. If the LVOT is obstructed, the condition is characterized as hypertrophic obstructive cardiomyopathy

(HOCM)<sup>2</sup>. Any exercise that is strenuous enough to increase afterload will worsen the hypertrophy and therefore worsen the obstruction and symptoms.

Dyspnea is the presenting symptom in 90% of HOCM patients. Other symptoms include chest pain, palpitations, dizziness, syncope, and sudden death. Additionally, patients can experience high blood pressure or arrhythmias due to disruption of the heart's electrical signals. For patients who are still symptomatic despite the use of first line pharmacologic treatments such as beta blockers; surgical myectomy and alcohol septal ablation (ASA) are two procedures that can reduce the LVOT obstruction and improve New York Heart Association (NYHA) functional class.

Surgical myectomy has been performed for decades and involves direct removal of the septal muscle. The removal of the hypertrophied muscle relieves the obstruction and increases the amount of blood able to leave the left ventricle thereby improving systolic function of the heart. Complications of the procedure include a ventricular septal defect, a left bundle branch block, or complete heart block necessitating a permanent pacemaker. Because myectomy requires a thoracotomy, patients often desire a less invasive procedure. Alcohol septal ablation (ASA) is performed percutaneously as part of a cardiac catheterization. During the procedure, ethanol is injected into a branch of a septal perforator coronary artery to create a localized infarction and subsequent septal remodeling over time, which results in a reduction in myocardial mass and therefore, improved systolic function<sup>3</sup>. Complications of ASA include coronary artery dissection, large myocardial infarction, complete heart block, and ventricular tachyarrhythmias. ASA has also been associated with an increased risk of residual LVOT gradient due to non-complete ablation, therefore requiring a repeat septal reduction procedure.

### **Clinical Question & Scenario**

**P. In patients with symptomatic hypertrophic obstructive cardiomyopathy**

**I. Does alcohol septal ablation**

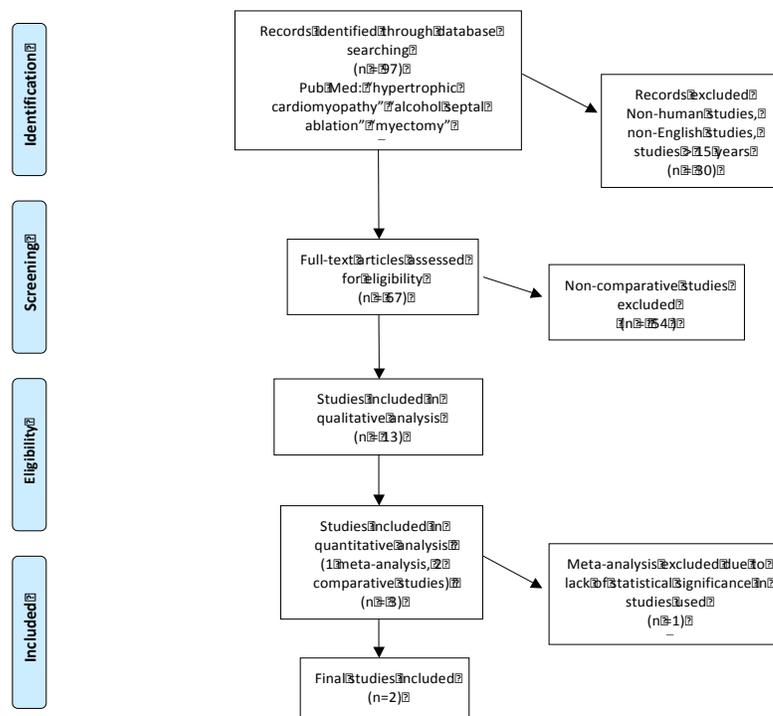
**C. Compared to surgical myectomy**

**O. Decrease symptoms and improve long term outcome**

**A 55 year old male with diagnosed HOCM is severely symptomatic despite pharmacologic treatments. Is septal myectomy or alcohol ablation the best procedure for this patient?**

## Methods

An initial search of PubMed was performed in September 2015 using the terms hypertrophic cardiomyopathy, alcohol septal ablation, and myectomy. Limits included “published in the last 15 years,” “humans,” “comparative studies,” and “English”. This yielded 13 articles. Ultimately, two promising studies were identified. Both studies were single center non-randomized observational studies. Study 1 evaluated the peri-procedural complications and long-term outcomes after ASA and myectomy, and study 2 evaluated three month follow up after both procedures.



## Results

### Study # 1:

*Periprocedural Complications and Long-Term Outcome After Alcohol Septal Ablation Versus Surgical Myectomy in Hypertrophic Obstructive Cardiomyopathy.* Steggerda et al.<sup>4</sup>

#### Objective:

To compare surgical myectomy and alcohol septal ablation (ASA) for periprocedural complications and long-term clinical outcome in patients with symptomatic hypertrophic obstructive cardiomyopathy

#### Study design:

This was a nonrandomized, observational study of myectomy and ASA procedures performed in a Netherlands hospital between 1981 and 2010. Surgical myectomy was carried out beginning in 1981 and ASA was carried out beginning in 2000. A retrospective analysis of baseline characteristics for patients who underwent treatment is seen below in Table 1.

Patients who underwent myectomy were more likely to have angina and coronary artery disease, while those who underwent ASA had increased septal and posterior wall thickness.

Table 1: Baseline Patient Characteristics

	Myectomy (n=102)	ASA (n= 161)	P value
Angina	2.3 ± 0.6	2.0 ± 0.5	0.002
Coronary a. disease	17%	5%	0.004
Septal thickness, mm	20(17-24)	21(19-24)	0.003
Posterior wall thickness, mm	14 ± 3	15 ± 4	0.01
Gradient baseline, mmHg	50 (25-75)	32 (18-75)	0.088

To be eligible for either procedure, all patients were required to be severely symptomatic despite medical therapy and all had a resting gradient of 30 mmHg or a provocative gradient of at least 50 mmHg. Provocation testing using a Valsalva maneuver, venodilators, or exercise stress testing is often required to induce the left ventricular outflow tract obstruction associated with HOCM.

Myectomy was the required procedure for patients with hypertrophic cardiomyopathy in addition to subvalvular disease or coronary artery disease. Patients who were eligible for myectomy or ASA were explained the risks and benefits and were able to choose between the two procedures. 161 patients underwent ASA and 102 patients required myectomy.

A transthoracic echocardiogram was performed in all patients before intervention to measure the degree of left ventricular outflow tract (LVOT) obstruction. In patients undergoing surgical myectomy, a transesophageal echocardiogram was used intraoperatively to measure the post-surgical LVOT gradient. In patients undergoing ASA, the LVOT was measured invasively following the ablation procedure. Records were obtained from all patients who had a follow up echocardiogram to determine the last known ejection fraction and LVOT gradients after the procedures.

Periprocedural (30-day) complications were obtained through a retrospective analysis of hospital records. Clinical outcome and long-term survival were investigated in 2010 using hospital records in addition to a mailed questionnaire with follow up telephone inquiry when necessary. Questions focused on post procedural symptoms such as chest pain and syncope, as well as the patients' New York Heart Association functional class status (1 to 4). Hospital records were obtained for clinical events that required a re-admittance for heart failure or repeat cardiac intervention. For patients who were not alive at the time of follow up, a cause of death was obtained from records.

All-cause mortality of both ASA and myectomy during a maximal follow-up period of 11 years was the primary endpoint of the study. Annual cardiac death rates, cerebral vascular accidents, myocardial infarctions, NYHA functional class, and heart failure requiring re-hospitalization were all included as secondary endpoints.

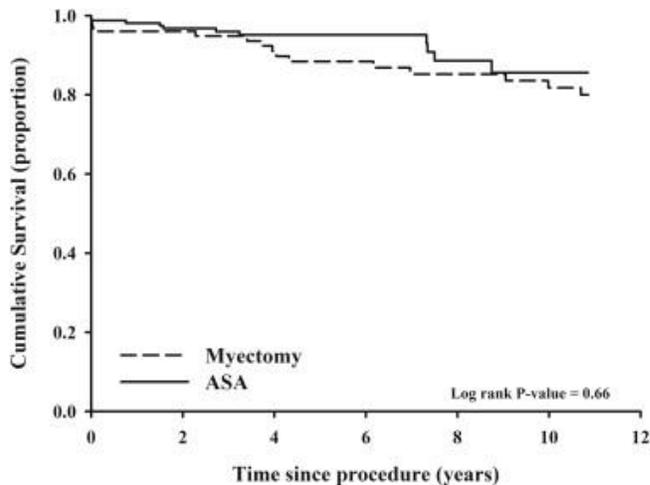
Statistical analysis was performed using the Mann-Whitney U test and Student t test to compare variables between the ASA and myectomy group. The Mann-Whitney test was used to compare the two treatments and for analyzing the difference between the medians of the data sets. The Student t test was then used to determine if the two sets of data were significantly different. Because the sample groups in this study were independent, this was an appropriate statistical analysis to use.

All cause mortality was determined using the Cox proportional hazard analysis. This analysis is commonly used to estimate the risk of death for an individual after taking into account different variables. In this particular study the baseline variables included age, sex, NYHA functional class, medical history and echocardiogram findings. A p-value of less than 0.05 was considered to be statistically significant.

#### Study results:

Periprocedural complications (30 days) were measured and included death, CVA, ventricular tachycardia/fibrillation, tamponade, pacemaker implantation, and urgent repeat thoracotomy. The ASA group had a lower periprocedural complication frequency compared to the myectomy group (14% [22 of 161] versus 28% [29 of 102], p-value = 0.004). ASA group also had a significantly shorter follow-up stay than the myectomy group (5 days versus 9 days, p-value = <0.001)

Maximal follow-up duration of 11 years showed that all-cause mortality was comparable between ASA and myectomy groups (Figure 1). Univariate analysis was used to deal with only one variable at a time without taking other variables into consideration. In this study it demonstrated that age (per 5 years) and coronary artery disease were the only statistically significant predictors of all-cause mortality. Age had a hazard ratio of 1.42 (95% CI 1.18-1.71, p-value <0.001) and coronary artery disease had a hazard ratio of 2.96 (95% CI 1.11-7.90, p-value 0.030). These hazard ratios were used to measure how often death occurred in one group compared to how often it occurred in another group. Multivariate analysis incorporated multiple prediction variables and it showed that age was the only independent predictor of long-term mortality (hazard ratio 1.34, 95% CI 1.08-1.65, p-value 0.007)



(figure 1: Survival after ASA vs Myectomy)

96% of patients were still alive at follow-up and questionnaires regarding their symptomatic status were administered. There were no differences in CVA, MI, re-hospitalization for heart failure, or overall symptomatic status between the ASA and myectomy groups. 92% of patients underwent a repeat echocardiogram during the late follow-up period ( $3.9 \pm 4.7$  years) to measure the LVOT gradient. Patients who received ASA had a higher gradient at late follow-up than the myectomy patients. This is contrasted to the decreased gradient post procedure in the ASA group compared to the myectomy group. There were a total of 10 reinterventions performed after ASA due to a significant residual gradient following the procedure but only 1 intervention was necessary in the surgical myectomy group. Table 2 summarizes significant periprocedural complications and clinical outcomes between the two procedure groups.

Table 2: Complications & Outcomes

	<b>Myectomy (n=102)</b>	<b>ASA (n=161)</b>	<b>P value</b>
<b>Periprocedural complications</b>	<b>28%</b>	<b>14%</b>	<b>0.004</b>
<b>Length of hospital stay, days</b>	<b>9 (6-12)</b>	<b>5 (4-6)</b>	<b>&lt;0.001</b>
<b>Post-procedural gradient, mmHg</b>	<b>12( 8-20)</b>	<b>10 (0-20)</b>	<b>&lt;0.001</b>
<b>Late follow up gradient, mmHg</b>	<b>9 (4-10)</b>	<b>10 (7-19)</b>	<b>0.003</b>
<b>Reintervention within long term follow up</b>	<b>1% (1)</b>	<b>6.3% (10)</b>	<b>0.055</b>

Study #2:

*Outcome of Patients with Hypertrophic Obstructive Cardiomyopathy After Percutaneous Transluminal Septal Myocardial Ablation and Septal Myectomy Surgery.* Qin et al.<sup>5</sup>

Objective:

To evaluate the subjective and objective follow-up results in patients undergoing alcohol septal ablation and surgical myectomy for treatment of drug refractory hypertrophic obstructive cardiomyopathy (HCOM).

Study design

This was a non-randomized cohort study of 51 symptomatic patients with hypertrophic obstructive cardiomyopathy. The diagnosis of HOCM was based on the presence of a hypertrophied, non-dilated left ventricle. All patients were symptomatic and presented with angina (42%), dyspnea (78%), or syncope (24%), and a New York Heart Association (NYHA) Functional class of at least III. Additionally, patients were refractory to drug treatment and had a left ventricular outflow tract (LVOT) gradient  $\geq 50$  mmHg.

All 51 patients were informed of the two treatment methods, and gave informed consent prior to the procedures. Twenty-six of the 51 patients underwent surgical myectomy, and twenty-five underwent alcohol septal ablation. All patients had a conventional two-dimensional ECHO and a doppler ECHO performed before the procedure, immediately after the procedure, and at 3 month follow up. A transesophageal echocardiogram TEE was only performed if suitable images could not be obtained prior to the procedure. The interventricular septum thickness, the posterior wall thickness, and the LV left ventricular ejection fraction were all assessed prior to undergoing a procedure. Additionally, the peak pressure gradient through the LVOT was estimated using the Bernoulli equation. This equation estimates the speed of a liquid based on the inverse relationship between velocity and pressure as it moves from point A to point B.

Both procedures were deemed successful when the resting pressure gradient (PG) was less than 16 mm Hg, or the percentage of pressure gradient reduction was more than 50%. The reduction was calculated using:

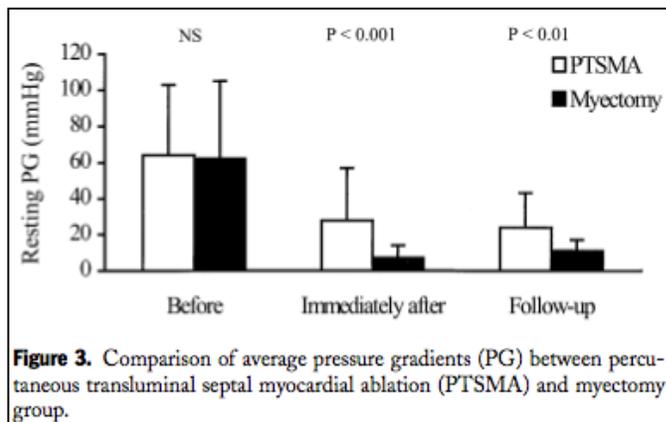
$$\frac{(\text{PG before procedure} - \text{PG after procedure})}{(\text{PG before procedure})} \times 100\%$$

After discharge following these procedures, all 51 patients underwent a clinical evaluation by a cardiologist, which included assessment of NYHA functional class. Follow up for myectomy was  $128 \pm 84$  days, and follow up for ASA was  $117 \pm 36$  days.

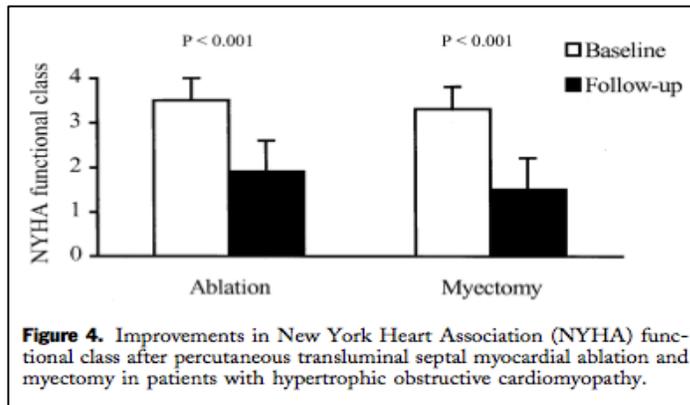
## Study 2 Results

Patients who underwent alcohol septal ablation were significantly older (mean age  $63 \pm 14$  years) and tended to have more comorbid conditions that could increase the risk of surgery compared to those who underwent surgical myectomy (mean age  $48 \pm 13$  years). Additionally, 58% of patients undergoing both procedures were on beta-blockers, 30% on calcium channel blockers, and 12% on both at the time of the procedure. There was no difference in the intraventricular septal thickness between the two groups before the procedures, but the interventricular septum (IVS) thickness was significantly reduced at follow up ( $2.3 \pm 0.4$  cm vs.  $1.9 \pm 0.4$  for ASA compared to  $2.4 \pm 0.6$  cm vs.  $1.7 \pm 0.2$  cm for myectomy).

In those patients undergoing ASA which was referred to as percutaneous transluminal septal myocardial ablation (PTSMA) in this study, the resting pressure gradient decreased from  $64 \pm 39$  mmHg to  $28 \pm 29$  mmHg after the procedure, and to  $24 \pm 19$  mmHg at 3 month follow up. Twenty-two of the 25 patients had a post procedure PG of  $<16$ mmHg or a  $>50\%$  reduction in PG at follow up, deeming the procedure successful. In those undergoing myectomy, the resting pressure gradient decreased from  $62 \pm 43$  mmHg to  $7 \pm 7$  mmHg after the procedure, and to  $11 \pm 6$  mmHg at 3 month follow up. One hundred percent of the ASA patients had post procedure PG of  $<16$ mmHg or a  $>50\%$  reduction in PG at follow up, deeming the procedure successful. Between the post procedure and the follow up period, four patients had resting PG increase slightly, but it was still much lower than the PG before the procedure. At the 3-month follow-up the PG was completely eliminated in 81% of patients receiving myectomy, while only 52% of of ASA patients showed a PG  $<16$ mmHg. These results are seen in Figure 3.



New York Functional Class was assessed both before and after treatment. This is a standard classification used to assess the degree of heart failure. Class one patients have cardiac disease but no symptoms, class two patients have mild symptoms, class three patients have marked limitation in activity due to symptoms, and class four patients have severe limitations.<sup>6</sup> All 51 patients in this study had a NYHA functional class of  $\geq 3$ . ASA patients had an average class of  $3.5 \pm 0.5$  that was decreased to  $1.9 \pm 0.7$  after the procedure. Myectomy patients had an average class of  $3.3 \pm 0.5$  that was decreased to  $1.5 \pm 0.7$  after the procedure. Both of these values had a p value of  $< 0.001$ . These results are seen in Figure 4.



There were no deaths reported within the 3 months following both treatments. After undergoing ASA, 9 patients had complete right bundle branch block, and two patients had complete left bundle branch block. Sixteen patients had left bundle branch block after undergoing myectomy. The mean hospital stay for ASA patients was  $5.6 \pm 2.3$  days compared to  $8.1 \pm 3.5$  days for the myectomy patients. Pacemakers were required in six patients who underwent ASA and in 2 patients who underwent myectomy. These results are seen in Table 3.

Table 3: Complications & Outcomes

	Myectomy (n=26)	ASA (n=25)	P value
Resting pressure gradient, mmHg	<u>Before procedure</u> $62 \pm 43$	<u>Before procedure</u> $64 \pm 39$	< 0.0001
	<u>3 month follow-up</u> $11 \pm 6$	<u>3 month follow-up</u> $24 \pm 19$	
NYHA Functional Class (1-4)	<u>Before procedure</u> $3.3 \pm 0.5$	<u>Before procedure</u> $3.5 \pm 0.5$	< .001
	<u>3 month follow up</u> $1.5 \pm 0.7$	<u>3 month follow up</u> $1.9 \pm 0.7$	
Length of hospital stay, days	$8.1 \pm 3.5$	$5.6 \pm 2.3$	0.01
Post procedural complications	<ul style="list-style-type: none"> <li>• No deaths</li> <li>• 16 pts with LBBB</li> </ul>	<ul style="list-style-type: none"> <li>• No deaths</li> <li>• 2 pts with LBBB</li> <li>• 9 pts with RBBB</li> </ul>	> 0.05
Permanent pacemaker required after procedure	7.7%	24%	> 0.05

In general, both alcohol septal ablation and surgical myectomy were found to improve NYHA functional class, reduce the hypertrophied interventricular septum, and decrease LVOT obstruction. Patients undergoing myectomy had a greater reduction in LVOT PG, and those undergoing alcohol septal ablation had a shorter hospital stay.

### **Discussion**

According to the two studies reviewed, clinical outcomes for HOCM patients are comparable following both ASA and myectomy. Because ASA is a fairly new procedure compared to myectomy, additional studies need to be done to arrive at a more definitive conclusion.

Study 1 is the first to analyze both periprocedural (30 day) complications as well as long-term (11 years) outcomes of the two treatments for HOCM. Previous studies (such as Study 2, Qin et al.) did not address long-term results. Strengths of Study 1 included comparable clinical baseline characteristics in the ASA and myectomy groups except for concomitant coronary artery disease and a slight difference in the degree of left ventricular hypertrophy. Average age was also similar in both groups. Follow-up was another strength of this study, as questionnaires were administered to 96% of the patients. Telephone follow up was used to ensure accurate information when needed.

The fact that this was a non-randomized, observational study was a limitation however a randomized control trial would be nearly impossible to conduct with HOCM patients. The choice between an ablation and a myectomy is a personal one and patients should have the right to choose the procedure that they feel is best for them and is most appropriate procedure based on their individual condition. This study was conducted in the Netherlands therefore may not be representative of the general HOCM population. A potential source of bias was the fact that ASA procedures involved in this study began in 2000, whereas the myectomy procedures dated as far back as 1981. Additionally, bias may have resulted because certain baseline characteristics were specific to each treatment. Those with angina and coronary artery disease were more likely to undergo myectomy while patients with posterior wall thickness were slightly increased in those who underwent ASA. Furthermore, certain patients were required to have myectomy while other patients were given the choice between the two procedures.

Study 1 concluded that long term symptomatic improvement and long-term survival were comparable between the ASA and myectomy groups. ASA was shown to be associated with less periprocedural complications than surgical myectomy, which had not been reported in previous studies. The complications with myectomy, however, were attributed to the more invasive nature of the procedure, and were not associated with a worse long-term outcome. The surgical myectomy procedure also resulted in an increased hospital stay compared to the less invasive alcohol septal ablation.

Strengths of Study 2 include systematic screening and follow up on all patients with ECHO right after the procedure and at 3-month follow-up. The same parameters were measured before and after the procedures were completed.

The two groups were dissimilar in many aspects. Older patients with significant comorbid conditions underwent alcohol septal ablation, while younger patients had myectomy. Follow-up was fairly short, and long-term results are unknown at this point. Additionally, there was no criterion for dividing the patients into the two procedures, treatment was chosen based on patient and physician preference. The sample size was small therefore a student t test was used which compared the average of the study groups to find significant differences.<sup>7</sup> A p value of  $< 0.01$  was considered statistically significant, and a Chi squared test was used to compare success rates and complications between the two study groups. All parameters measured in this study were statistically significant (p value  $< 0.01$ ) with the exception of the larger end diastolic diameter of the LV in ASA group before the procedure (p= 0.03), and the end diastolic diameter of the LV increasing after ASA (p= 0.01) and after myectomy (p= 0.06). Additionally, the presence of bundle branch blocks after procedure (p $> 0.05$ ), and permanent pacemakers required (p $>0.05$ ) were not statistically significant.

Study 2 concluded that both ASA and surgical myectomy reduce the hypertrophied interventricular septum, decrease pressure gradient across the left ventricle and improve NYHA functional class, thereby reducing symptoms. Those who underwent ASA had a shorter hospital stay compared to those who underwent myectomy, but patients who underwent myectomy had a greater reduction in PG,

## Conclusion

In summary, long term survival and symptomatic improvement after both ASA and myectomy is comparable. ASA is associated with decreased length of hospital stay following the procedure as well as a decreased rate of periprocedural complications. Because ASA is a less invasive procedure than surgical myectomy, it should be considered when deciding on HOCM surgical treatment. As convenient and less invasive as it is, it's important to note that ASA will not be replacing surgical myectomy in the treatment of symptomatic HOCM patients. Surgical myectomy may be the necessary method if the patient has multivessel coronary artery disease or septal anatomy that is unsuitable for alcohol ablation. For our clinical scenario, the 55-year-old patient should meet with his cardiologist and surgeon to ensure that his personal preference is taken into consideration in addition to his individual cardiovascular history.

## Works Cited

1. Hypertrophic Cardiomyopathy. (n.d.). Retrieved November 1, 2015, from [http://www.heart.org/HEARTORG/Conditions/More/Cardiomyopathy/Hypertrophic-Cardiomyopathy\\_UCM\\_444317\\_Article.jsp#](http://www.heart.org/HEARTORG/Conditions/More/Cardiomyopathy/Hypertrophic-Cardiomyopathy_UCM_444317_Article.jsp#)
2. Patel, P. (2004, April 1). Hypertrophic Cardiomyopathy. Retrieved December 1, 2015, from <http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/cardiology/hypertrophic-cardiomyopathy/>
3. Fifer, M. (2007). Most Fully Informed Patients Choose Septal Ablation over Septal Myectomy. Retrieved November 15, 2015, from <http://circ.ahajournals.org/content/116/2/207.full>
4. Steggerda RC et. al. Periprocedural complications and Long-Term Outcome After Alcohol Septal Ablation Versus Surgical Myectomy in Hypertrophic Pbsructive Cardiomyopathy. J Am Coll of Cardiol 2014; Vol 7, No.11: 1981-2010.
5. Qin JX et. al. Outcome of patients with hypertrophic obstructive cardiomyopathy after percutaneous transluminal septal myocardial ablation and septal myectomy surgery. J Am Coll of Cardiol 2001;38: 1994-2000.
6. Classes of Heart Failure. (n.d.) Retrieved November 4, 2015, from [http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure\\_UCM\\_306328\\_Article.jsp#.VmTkResik1g](http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp#.VmTkResik1g)

7. Dependent T test for Paired Samples. (2013) Retrieved November 4, 2015 from <https://statistics.laerd.com/statistical-guides/dependent-t-test-statistical-guide.php>