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THE SAHLGRENSKA ACADEMY

# Degree Project

# The effects of treatment with alcohol septal ablation in patients with Hypertrophic obstructive cardiomyopathy

**Ane Bakken Wold**

**Department of Cardiology, Sahlgrenska University Hospital**

**Gothenburg, Sweden**

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| Supervisor: | Entela Bollano, Associate Professor, Dept. of Cardiology, Sahlgrenska University Hospital |

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## List of abbreviation

**HCM** - Hypertrophic cardiomyopathy
**HOCM** - Hypertrophic obstructive cardiomyopathy
**LVOT** - Left ventricle outflow tract
**SCD** - Sudden cardiac death
**LVOTO** - Left ventricle outflow tract obstruction
**SAM** - Systolic anterior motion
**NYHA** - New York Heart Association
**ESC** - European Society of Cardiology
**CMRI** - Cardiac magnetic resonance imaging
**ICD** - Implantable cardioverter-defibrillator
**ASA** - Alcohol septal ablation
**MCE** - Myocardial contrast echocardiography
**AVB-III** - Third degree atrioventricular block
**RBBB** - Right bundle branch block
**LBBB** - Left bundle branch block

## Abstract

# The effects of treatment with alcohol septal ablation in patients with Hypertrophic obstructive cardiomyopathy


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**Background**: Hypertrophic Cardiomyopathy is the most common of the inherited cardiomyopathies. When the hypertrophic myocardium affects the interventricular septum, it can cause left ventricular outflow tract obstruction (LVOTO), resulting in Hypertrophic obstructive cardiomyopathy (HOCM).
Patients are treated with negative ionotropic drugs in order to relieve symptoms. Patients who still have symptoms while on appropriate medical therapy are candidates for septal reduction therapy. Septal reduction therapy includes myectomy and the newer and less invasive alternative of alcohol septal ablation (ASA).

**Aim**: To describe the group of patients who have been treated with ASA at Sahlgrenska University Hospital and assess the effectiveness of treatment.

**Methods**: In this study, we used an observational cohort design. The cohort included 68 patients with HOCM who received treatment with ASA. Data was collected from preexisting medical records.

**Results**: There was a reduction in New York Heart Association (NYHA) functional class from a mean of 2.8 at baseline to 2.1 at the time of follow-up ($p<0.001$). A decrease in LVOTO from a median of 81 mmHg to 20 mmHg was documented after treatment with ASA ($p<0.001$). The dosing of beta-blockers was reduced from a median of 175 mg/day at baseline to 150 mg/day at the time of follow-up examination ($p=0.016$). At baseline, 22.4% of patients had the anti-arrhythmic drug Disopyramide. This number was reduced to 11.5% at the time of follow-up ($p=0.021$). Time to follow-up after intervention had a mean of 6.3 months.

**Conclusion:** ASA is an effective form of septal reduction therapy for selected patients with HOCM. Reduction of LVOTO led to symptomatic improvement for most of the patients. In addition, the observed reduction in use and dose of beta-blockade and Disopyramide after treatment with ASA further supports the effectiveness of treatment.

# 1. Background

## 1.1. Cardiomyopathy

Cardiomyopathies are diseases that affect the heart, and they may be divided into primary or secondary types (1, 2). Primary cardiomyopathies are when the disease is only confined to the heart. Secondary cardiomyopathies are when the disease of the heart is caused by another underlying systemic disease, such as Amyloidosis or Glycogen storage disease (3). The primary cardiomyopathies are divided into types based on morphology. The different phenotypes of primary cardiomyopathies were classically divided into Hypertrophic cardiomyopathy (HCM), Dilated cardiomyopathy, and Restrictive cardiomyopathy (4). Later on, due to developments in diagnostics methods, Arrhythmogenic right chamber cardiomyopathy/dysplasia and Left ventricle non-compaction cardiomyopathy was added to the updated classification of primary cardiomyopathies (5). The acquired forms of primary cardiomyopathies are Takotsubo, which is a type of stress-induced cardiomyopathy, Tachycardia induced cardiomyopathy, Peripartum cardiomyopathy, and Inflammatory cardiomyopathy (2).

Maron *et al*.(2) describes the different primary cardiomyopathies and the morphological patterns the classification schema is based upon. They also discuss the potential difficulties when the diagnosis of diseases is based upon morphological findings. The authors highlight that many of the different groups of primary cardiomyopathies have potential overlap in morphology, and that in some cases the natural progression of the disease is such that it may evolve from one category into another. One example of such an evolution is the natural progression of HCM, which in the beginning of the disease is characterized by a non-dilated hypertrophic left ventricle, often with normal or increased ejection fraction. However, in the so-called “burnt-out”, final stage, HCM may convert to a dilated form of cardiomyopathy that is marked by systolic dysfunction and which may have a decreased ejection fraction (6).

## 1.2. Hypertrophic cardiomyopathy

HCM is defined morphologically by a hypertrophic and non-dilated left ventricle. Since HCM is a primary cardiomyopathy, the hypertrophy of the left ventricle cannot be explained by other underlying conditions, such as hypertension or aortic valve stenosis (7). Symptoms and degree of hypertrophy are highly variable, and many patients remain undiagnosed due to a low degree of symptoms and associated adverse events. However, other patients with HCM

are highly symptomatic, and if the disease is left untreated, may lead to morbidity and HCM related mortality (6).

HCM is divided into two subcategories; Hypertrophic obstructive cardiomyopathy (HOCM) and Hypertrophic cardiomyopathy (HCM) without outflow obstruction (3). The obstructive feature of HOCM aims at the left ventricular outflow tract obstruction (LVOTO), which happens during systole and causes an increased peak velocity of blood flow from the left ventricle into the ascending aorta (8). Maron *et al*. (9) examined the effect of obstruction on the clinical outcome in two groups of patients, one group with HOCM and one with non-obstructive HCM. They observed that patients with HOCM have a higher risk of developing symptoms of heart failure and death than patients with non-obstructive HCM.

### 1.3. Epidemiology and inheritance

HCM is the most common of the inheritable primary cardiomyopathies and it is estimated by epidemiological studies that there is a prevalence of 1:500 in the general population (3). The prevalence is assessed to be the same in American, European, Asian, and African populations indicating that prevalence has no connection to ethnicity (7, 10).

In approximately 60% of patients, the mutation that is found is on genes encoding for cardiac sarcomere proteins (1). Sarcomeric gene mutations are inherited in an autosomal dominant fashion, which implies a 50% risk of transmission to the next generation (11). Genetic counseling and testing are indicated in patients newly diagnosed with HCM. This is to enable identification of the causative mutation and to further support decision-making when it comes to genetic screening of first-degree relatives (11, 12). The type of mutation does not determine disease severity. Family members with the same mutation often have different ages of presentation and develop different extent of symptoms during the progression of the disease (1). However, some studies have shown that patients with sarcomeric mutation have a higher risk of heart failure and other cardiac events, including sudden cardiac death (SCD) (13-15).

The disease has an age-dependent penetrance, and the majority of patients do not develop hypertrophy and associated symptoms until they have reached adulthood (16, 17). Some individuals are diagnosed, usually in association with a family genetic screen, with non-hypertrophic HCM. These patients have not developed hypertrophy, and are so-called

genotype-positive phenotype-negative individuals (18). Genotype-positive individuals carry the mutation, and there is still a 50% risk of transmission to the next generation (7).

### 1.4. Pathophysiology

The diagnostic criteria for HCM in adults are a thickness of any cardiac segment ≥ 15 mm or ≥ 13 mm in patients with a family history of HCM (19, 20). Many different patterns of hypertrophy may be seen in patients with HCM and HOCM. The most common pattern of hypertrophy seen is asymmetrical hypertrophy of the interventricular septum (21). The hypertrophic part of the septum extends into the left ventricle cavity, reducing its size and causing obstruction of blood flow through the left ventricular outflow tract (LVOT). Basal septal hypertrophy (also termed a sigmoid septum) refers to when the hypertrophic area of the septum is located just below the aortic valve (22). A pattern of basal septal hypertrophy can be observed in patients with HOCM, but basal septal hypertrophy can also be seen in patients where hypertrophy is caused by long-standing hypertension (23). A pattern of midventricular septal hypertrophy can be seen in patients with HOCM, and it is often combined with hypertrophy of the papillary muscles. Patients with a mid-ventricular pattern of hypertrophy and with abnormally thick papillary muscles are usually very symptomatic. This is due to large papillary muscles also being a physical obstacle for blood flow during systole and by causing additional mitral valve dysfunction (10, 11). A concentric pattern of hypertrophy can also be seen in HOCM patients and is when the hypertrophy affects a large area of the left ventricle wall, this may also be termed symmetrical hypertrophy (24).
An example of a pattern of hypertrophy seen in non-obstructive HCM is apical hypertrophy, which is when the hypertrophy is confined to the apical portion of the left ventricle (25). Another example of a pattern in non-obstructive HCM is when the hypertrophy only affects the posterior wall of the left ventricle (22). It has been estimated that of all symptomatic HCM patients, only 10% are non-obstructive HCM, and 90% are HOCM (7).

The LVOTO is dynamic in character, which is why patients experience a certain variability in symptoms (7, 10). A dynamic obstruction implies that the velocity of blood flow over the LVOT changes depending on different loading conditions (26). In situations when preload and afterload are reduced, the LVOTO increases. Examples of conditions that reduce preload are the Valsalva maneuver and hypovolemia. Situations that reduce afterload is systemic vasodilation and mitral regurgitation. The LVOTO causes an increase in left ventricular

systolic pressure, which in turn leads to increased left ventricle wall stress (27). Long-standing heightened left ventricle wall stress leads to further development of hypertrophy and contractile dysfunction (26).

Abnormal motion of the mitral valve is identified as a contributing factor to the LVOTO in addition to the physical obstacle of the hypertrophic interventricular septum. Systolic anterior motion (SAM) of the mitral valve happens during systole when forces form blood flow through the LVOT drags the anterior leaflet of the mitral valve towards the interventricular septum. Figure 1 illustrates the mechanism of SAM. SAM contributes to the LVOTO and may also lead to secondary mitral regurgitation due to insufficient closure of mitral valve leaflets during systole (8, 10, 28).

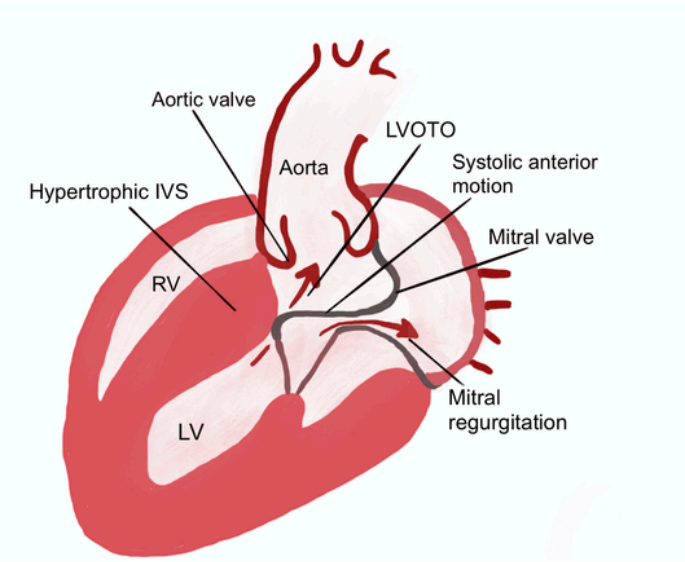


**Figure 1:** Illustration of systolic anterior motion (SAM) of the mitral valve.
RV = Right ventricle, LV = Left ventricle, IVS = Interventricular septum,
LVOTO = Left Ventricle Outflow Tract Obstruction
Figure adapted from Charles *et al.* (29)

It is common for patients with HOCM to have SAM, but it is not a defining feature of the disease. Maron *et al.* (30) conducted a study including over 700 patients. These patients had a number of different cardiac diseases, and as it turned out, 97% of them also had SAM of the mitral valve.

The mitral apparatus in patients with HOCM may have different abnormalities, which contribute to the LVOTO. Examples of such abnormalities are long mitral valve leaflets that have noticeable SAM or abnormal positioning of the papillary muscles in the left ventricle

wall. These forms of abnormalities to the mitral valve apparatus can exaggerate the LVOTO (31, 32).

In terms of microscopic findings, HCM is characterized by fibrosis in the myocardium (10). A biopsy of hypertrophic heart tissue classically shows cardiomyocytes that are organized in a disordered pattern and with the presence of fibrosis in the myocardium (33). One theory of why fibrosis develops in HCM is attributed to the development of hypertrophy of the medial layer in the vascular wall of intermural small vessels. Hypertrophy of the wall in these small vessels leads to a progressive reduction in the size of the lumen, which in turn gradually decreases blood supply to areas of the myocardium. Decreased in blood supply may result in myocardial ischemia, and myocardial ischemia eventually develops into areas of fibrosis (34).

### 1.5. Symptoms

Many patients with HOCM remains asymptomatic for their whole life. Some may experience minor symptoms, while others may develop severe symptoms demanding medical treatment and eventually requiring septal reduction therapy (35). The LVOTO has a prominent place in the development of symptoms in patients with HOCM (22). The most common presenting symptoms are increased fatigue and exercise intolerance (7). The mechanism behind exercise intolerance is the LVOTO, which makes it difficult to increase cardiac output in times of heightened requirement, such as exercise (36). Exertional dyspnea is also commonly experienced by patients. The mechanism behind dyspnea during exercise is the high left ventricle filling pressure and the diastolic dysfunction caused by hypertrophy and fibrosis (37). Furthermore, the addition of mitral regurgitation secondary to LVOTO and SAM phenomenon also contributes to the exertional dyspnea (38).

It has been reported that atrial fibrillation is the most common arrhythmia seen in patients with HOCM (39). The addition of atrial fibrillation contributes to the worsening of symptoms by increasing the LVOTO due to the decreased preload caused by disorganized atrial contraction. Atrial fibrillation may develop due to the presence of long-standing mitral regurgitation, which causes enlargement of the left atrium (22).

It has been estimated that between 25-50% of symptomatic HOCM patients experience periods of chest pain (34, 40). The driving pathophysiological mechanism behind anginal pain is the microvascular dysfunction of small vessels in the myocardium, causing myocardial ischemia and subsequent fibrosis (34). However, in cases of classical anginal pain, patients

should be examined with coronary angiography to exclude the protentional development of additional coronary artery disease (37). Presyncope and syncope in patients with HCM may be due to sustained ventricular tachycardia, heart block, or by the LVOTO causing decreased cardiac output (28). A history of cardiac syncope is important to detect in the anamnesis due to cardiac syncope being an established risk factor SCD (10, 11).

New York Heart Association (NYHA) functional class is a classification schema used in clinical practice and in connection to research in order to classify the severity of heart failure symptoms. The classification is based on the subjective evaluation of the patient's physical ability. Table 1 summarizes the NYHA classification. Patients with HCM can be assigned to one of the classes based on whether symptoms are limiting their physical abilities. The NYHA classification is also used to evaluate the effects of medical therapy, and it is recommended by the European Society of Cardiology (ESC) to be used as criteria for when to perform surgical or non-surgical interventions to alleviate the LVOTO (11).

**Table 1:** NYHA classification

| Class | Patient Symptoms |
|---|---|
| I | No limitation of physical activity. |
| II | Limitation in physical activity. Patient is comfortable at rest. Average physical activity result in symptoms, such as fatigue, palpitation, or dyspnea. |
| III | Marked limitation of physical activity. Patient is comfortable at rest. Less than average activity results in symptoms, such as fatigue, palpitation, or dyspnea. |
| IV | Unable to do any physical activity. Symptoms are present during resting conditions. |

Adapted from (41)

Symptoms of congestive heart failure, such as orthopnea, paroxysmal nocturnal dyspnea, and edema, are uncommon in the early stages of HCM but may occur in later stages of the disease (38). The so-called late "burnt out" phase of HCM may be associated with systolic dysfunction, and a decreased ejection fraction may result in congestive heart failure symptoms (11).

### 1.6. Diagnosis

The method of diagnosing HCM is by cardiac imaging, where left ventricular hypertrophy is detected. Transthoracic echocardiography is used to diagnose and to evaluate disease progression. In addition to echocardiography, cardiac magnetic resonance imaging (CMRI) is

used to get a comprehensive look at the cardiac anatomy, and the presence of myocardial fibrosis may be detected with late gadolinium enhancement during a CMRI (18).

Echocardiography with Doppler is the best modality to evaluate cardiac hemodynamic, especially when examining the degree of LVOTO, the presence of SAM phenomenon, and mitral valve regurgitation (8). Standard two-dimensional echocardiography is used when measuring the thickness of the left ventricle wall, including the interventricular septum. It is also used to measure the area and volume of heart cavities. Color-flow Doppler is used to show the site of obstruction and to detect valve insufficiencies. Continuous-wave Doppler is used when measuring the obstructive gradient across the LVOT (42).

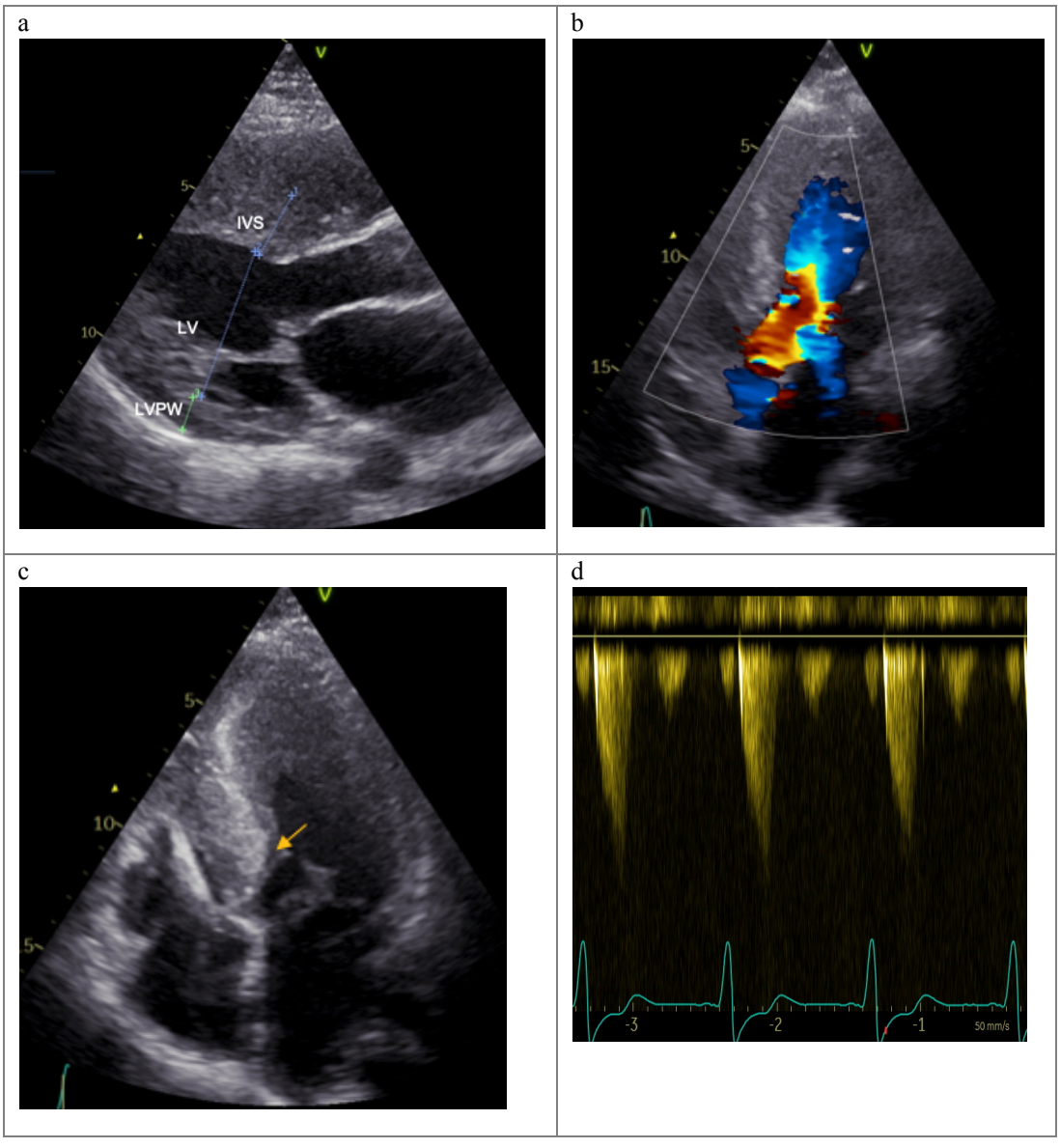

**Figure 2**: Echocardiogram pictures from a patient with HOCM
a) Parasternal long-axis view show hyperthophy of the interventricular septum (IVS). The left ventricle (LV) cavity is of normal dimension. The left ventricle posterior wall (LVPW) is slightly thicker than normal. b) Color-flow Doppler showing turbulent flow across the left ventricular outflow tract (LVOT) indicating the site of obstruction. c) Four chamber view show asymetrical hyperthophy of the interventricular septum (arrow). d) Continous wave doppler echocardiogram meassuring the velocty of blood flow over the LVOT during resting condition.

As previously described, the LVOTO is dynamic, and when examining a patient with echocardiography, a gradient across the LVOT may not be present at rest, a so-called latent obstruction. It is recommended to provoke the gradient in patients with latent obstruction during echocardiography examination (11). During a regular bedside transthoracic echocardiography, provocation of the gradient may be achieved by having the patient perform the Valsalva maneuver, both in sitting and standing positions. If a gradient of $\geq$ 50 mmHg is not found during the Valsalva maneuver; it is recommended to proceed with exercise stress echocardiography in order to sufficiently provoke the gradient (43). An LVOTO is defined as gradient $\geq$ 30 mmHg at rest, or $\geq$ 50 mmHg during provocation (11)

### 1.7. Medical treatment and risk assessment for sudden cardiac death

Medical management of patients with HOCM focuses on decreasing symptoms. Negative ionotropic drugs, such as beta-blockers, are first-line agents. Beta-blockers reduce cardiac contractility, which is efficient in reducing the LVOTO. HOCM is, as previously described, characterized by a high left ventricle wall stress. When stress on the left ventricle wall becomes high, the force of contraction also increases due to the law of Frank-Starling. Thus, a hypertrophic heart is in a state of permanent heightened inotropy, and negative inotropic drugs result in elongation of systole and a decrease in the force of contraction, leading to a decreased gradient across the LVOT (37). A slow heart rate or other side effects may be reasons why patients do not tolerate treatment with beta-blockers.

A calcium channel antagonist should be tried for patients who have contraindications or do not tolerate beta-blockers. Agents such as Verapamil, which have little effect on vasodilation, can be considered in patients with HOCM. However, calcium channel antagonist with vasodilatory properties are contraindicated in patients with HOCM due to the risk of decrease in afterload, which may worsen the LVOTO (11).

Disopyramide is a class 1A anti-arrhythmic agent with negative inotropy. Disopyramide should be used in combination with beta-blockers and is added when beta-blockers do not sufficiently reduce the LVOTO. The anti-arrhythmic mechanism of Disopyramide can also help with keeping patients in sinus rhythm if they have comorbid atrial fibrillation (22). A side effect of Disopyramide is the risk of developing a long QT interval which can result in ventricular tachycardia. Disopyramide may have anticholinergic side effects, which can be limiting for patients using the drug (37).

HCM has been recognized as one of the most common causes of cardiac death in young patients (44). The risk of SCD in patients with HCM has been estimated to be ≈ 0.5% - 1% per year (20, 45). Therefore, assessing the risk for SCD is important in the management of patients with HCM. The ESC has developed a risk model (HCM Risk-ICD) to estimate the 5-year risk of SCD, and this model should only be used in patients ≥ 16 years of age. This risk model places patients in either a low (< 4%), moderate (4-6%), or a high (≥ 6%) risk group for SCD (46). The HCM Risk-ICD model considers several risk factors when calculating the 5-year risk for SCD, and these are summarized in table 2.

**Table 2:** Risk factors for SCD used in the risk model HCM Risk-ICD and how to evaluate them

| **Risk factor** | **Mode of evaluation** |
|---|---|
| Left ventricle maximal wall thickness | Echocardiogram or CMRI |
| Family history of SCD | History |
| Unexplained syncope | History |
| Maximal LVOT gradient | Echocardiogram |
| Left atrial diameter | Echocardiogram or CMRI |
| Non-sustained ventricular tachycardia | 48-hour ambulatory electrocardiogram monitoring |
| Age | Younger patients have a higher risk of SCD than older |

HCM = hypertrophic cardiomyopathy, ICD = implantable cardioverter-defibrillator,
CMRI = cardiac magnetic resonance imaging, SCD = sudden cardiac death
(11, 46)

For patients with a high risk of SCD, an implantable cardioverter-defibrillator (ICD) is recommended. For patients with moderate risk, an ICD can be considered after individual evaluation. For patients with a low risk, an ICD is not recommended (11).

For patients that have previously survived a prior resuscitated cardiac arrest, ventricular fibrillation, or sustained ventricular tachycardia, an ICD is strongly recommended and should be implanted as secondary prevention of SCD (11).

### 1.8. Septal reduction therapy

Patients with HOCM that experience symptoms despite optimal medical treatment are candidates for septal reduction therapy. It has been estimated that less than 10% of patients with HOCM require septal reduction therapy in order to reduce symptoms (47). Surgical myectomy and alcohol septal ablation (ASA) are the two established modes of septal reduction therapy. Septal reduction therapy is only advantageous in patients where the outflow obstruction is responsible for symptoms. The American Heart Association guidelines recommend an NYHA class of III and a resting or provoked LVOT gradient of ≥ 50 mmHg to be criteria for treatment with septal reduction therapy (12). It is recommended by the ESC with a septal thickness of ≥ 15 mm for patients undergoing septal reduction therapy. This requirement of ≥15 mm reduces the risk of potentially creating ventricular septal defects as a complication after septal reduction therapy (11). It is highlighted by both American and European guidelines that septal reduction therapy should be centralized to specialized hospitals and performed by experienced operators in order to reduce complication rates and mortality (11, 12).

#### 1.8.1. Surgical myectomy

Surgical myectomy has long been considered the gold standard when it comes to septal reduction therapy (22). The technique was first developed by Morrow and has been performed since the 1960s (47). Surgical myectomy is done by a transaortic approach and involves dissection of the part of the interventricular septum that causes the outflow obstruction (1). Several studies show good results in reducing symptoms, decrease in outflow obstruction and long-term survival after surgical myectomy (48, 49).

Surgical myectomy is a highly invasive procedure with a subsequent long recovery time and period of rehabilitation. Therefore, it is recommended by the ESC guidelines that patients with a high surgical risk, determined by age and comorbidities, should undergo septal reduction therapy with ASA rather than surgery (11, 50).

The American Heart Association guidelines state that surgery is recommended in patients with additional cardiac disease requiring surgical treatment. Examples of such conditions are mitral valve abnormalities or three vessel coronary artery disease requiring a coronary artery bypass graft (12, 51). A septum measuring ≥ 30 mm has been termed extreme hypertrophy. ESC guidelines recommend that patients with extreme hypertrophy undergo surgical myectomy as a mode of septal reduction therapy. This is due to few studies being conducted on patients with extreme hypertrophy treated with ASA, and thus there is a lack of evidence when it comes to results after treatment with ASA in this small subgroup of patients (11).

### 1.8.2. Alcohol septal ablation

The first patients with HOCM were treated with ASA in 1995 by Sigwart (52). Since then, the method has been advanced, and several studies published have shown good results when it comes to the improvement of symptoms, decrease in LVOTO, good short- and long-term survival (26, 53-57). The basic principle behind the procedure is to induce a myocardial infarction at the site of obstruction. This is done by injecting a small amount of concentrated ethanol into a septal perforating artery. This, in turn, will lead to eventual thinning of the interventricular septum due to the fibrotic process following the myocardial infarct (58).
The operator uses guiding catheters, a guidewire, and balloon catheters during the procedure. The guidewire is threaded through the aorta and into the left main coronary artery and successively into the left anterior descending coronary artery. From the left anterior descending coronary artery, several septal perforating arteries branch of and supply the interventricular septum. The small balloon catheter is placed and inflated in the septal perforating artery that supplies the part of the hypertrophic septum responsible for the outflow tract obstruction. The inflation of a balloon catheter is to prevent the possibility of spillback of ethanol into the left anterior descending coronary artery (59).

Myocardial contrast echocardiography (MCE) is used during the procedure to select the most appropriate septal perforating artery. The use of MCE also ensures that the septal perforator in question does not supply other important structures, such as left ventricular papillary muscles. The guiding with MCE has been shown to reduce the rate of procedural complications (60). Faber *et al*. (61) reported that the rate of permanent pacemaker implantation due to third-degree atrioventricular block (AVB-III) being 7% with the guiding of MCE. This was then compared to 17% occurrence of AVB-III and pacemaker implantation without the use of

MCE. MCE has also been shown to precisely predict the size and localization of the myocardial infarction that follows the injection of ethanol (62).

Patients are awake during the procedure but are pre-medicated with sedative agents. Patients may complain of pain and chest pressure during the slow injection of ethanol and may require additional sedative and pain-relieving agents. The amount of ethanol injected is usually between 0.5 ml and 3 ml, and the amount of injected alcohol is dependent on how thick the interventricular septum is and by the size of the septal perforating artery (59).

Before the procedure, all patients receive a temporary pacemaker. This is to protect against possible disturbances on the electrical conduction system of the heart during the procedure. Conduction system disturbances are the main complication associated with ASA. The development of AVB-III requires the insertion of a permanent pacemaker and has been cited as the most frequent major complication after treatment with ASA (58). Right bundle branch block (RBBB) has also been documented as a common minor complication after treatment with ASA (63). Fitzgerald *et al*.(64) reported a rate of 37-70% occurrence of RBBB after treatment with ASA. An isolated RBBB does not require the insertion of a pacemaker. However, in patients with a pre-excising left bundle branch block (LBBB), there is a possible risk for creating a total heart block if treatment with ASA is complicated by an RBBB (59). In contrast, there is a higher risk of creating an LBBB after surgical myectomy. This is shown in the meta-analysis conducted by Quin *et al*. (65), who reported a rate of 93% occurrence of LBBB after myectomy. Fifer *et al*.(38) suggest that the presence of either a pre-excising LBBB or RBBB should be taken into consideration when selecting patients for treatment with either ASA or myectomy.

The result of ASA is not seen immediately after the procedure. The morphologic evolution of a myocardial infarction takes up to two months to complete, and the last step is a fibrotic scar due to remodeling and collagen deposits (66). The fibrotic area is thinner than healthy myocardium. This thinning of the myocardium is the goal of ASA, and thus the full result is seen only months after the actual procedure has been performed. Yoerger *et al*. (67) describe the decrease in LVOT gradient after treatment with ASA as consisting of three phases. There is first seen an immediate decrease in LVOT gradient. This first decrease is attributed to the immediate stunning of the myocardiocytes, which leads to the septum becoming hypokinetic. After three days, some of the myocardiocytes recover from the initial stunning, and there is

again seen a rise in LVOT gradient. Only after three months, when the remodeling and the fibrotic process is complete, can the result and measurement of LVOT gradient be properly examined.

### 1.8.3. Alcohol septal ablation vs. Myectomy

There have been several retrospective studies and meta-analyses comparing the two methods of septal reduction therapy (26, 38, 50, 68). The general consensus is that the choice between ASA or surgical myectomy should be individualized to the patient and that several factors should be taken into consideration when choosing between methods. Some of these factors are summarized in table 3. In addition, patient preference should also be taken into consideration when choosing between methods (22). Liebregts *et al.* (47) highlight the importance of HOCM patients being discussed in specialized cardiac teams to determine which septal reduction therapy is most appropriate for the individual patient.

**Table 3:** Factors to consider when choosing which septal reduction therapy is most appropriate for the individual patient.

| **Supports decision for Myectomy** | **Supports decision for ASA** |
|---|---|
| Patients with low surgical risk | Patients with high surgical risk |
| Younger patients | Older patients |
| Other cardiac diseases requiring cardiac surgery | ASA is more accessible than surgery |
| Extreme hypertrophy of the interventricular septum (> 30 mm) | Less invasive procedure and a shorter recovery time |
| Pre-existing LBBB. There is risk for RBBB with ASA creating total heart block | Pre-existing RBBB. There is risk for LBBB with myectomy creating total heart block |

ASA = Alcohol septal ablation, LBBB = left bundle branch block, RBBB = Right bundle branch block (26, 38, 47, 53)

Studies that have compared ASA and myectomy have all been retrospective studies, and there have been no randomized clinical trial comparing ASA and myectomy (26, 69). This is because of the number of HOCM patients requiring septal reduction therapy is relatively low, and thus a randomized clinical trial comparing the two methods would be difficult to conduct (69).

The systematic literature review from 2020 conducted by Bytyçi *et al*. (50) compared treatment with ASA and myectomy. They concluded that ASA and myectomy having similar procedural risk and mortality, but the need for reintervention to achieve sufficient treatment

result were more common after treatment with ASA than with myectomy. The rate of periprocedural complications was higher associated with myectomy. They propose that myectomy should be continued to be considered the gold standard when it comes to septal reduction therapy for young patients with low surgical risk, but that ASA should be the choice of method in elderly patients with other comorbidities and a higher surgical risk.

## 2. Aim and specific objectives

Treatment with ASA has been available at Sahlgrenska University Hospital since 2016, and patients with HOCM from a large part of Sweden are being treated. This project aimed to describe the group of patients who had been treated with ASA and then further assess the effects of treatment with ASA.

Research questions:
1. Does ASA lead to improvement of symptoms and NYHA functional class?
2. Does ASA lead to objective findings measured with echocardiography?

## 3. Material and methods

An observational cohort design was used in this study. The cohort consisted of patients with HOCM that underwent treatment with ASA at Sahlgrenska University Hospital in the time period between January 2017 to December 2020. Data were collected from preexisting echocardiogram examinations and from medical records written by physicians, physiotherapists, or nurses.

Variables were collected for each patient at two points in time; at baseline and at follow-up examination. Baseline and follow-up examination were defined as the medical examination with an associated echocardiogram performed. The baseline examination was defined as the one examination performed closest in time before intervention with ASA. Time to follow-up examination was required to be a minimum of three months after ASA had been performed. In the end, a total of 68 patients were included in the study. Six patients were excluded due to the time to follow-up examination being less than three months. Figure 3 explains the process of exclusion.

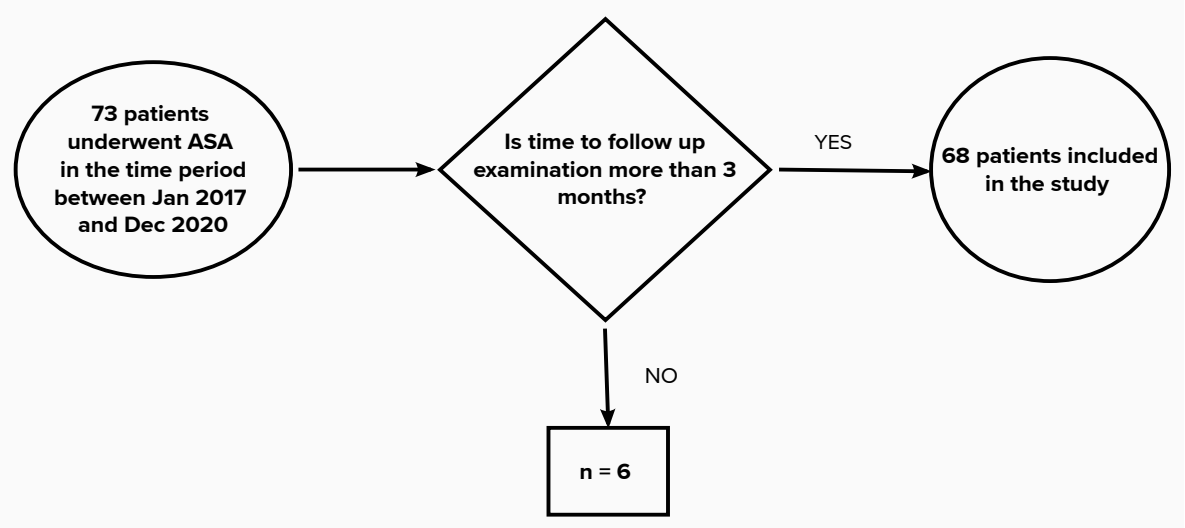


**Figure 3:** Process of exclusion

## 4. Data collection procedure

Variables such as gender, age at diagnosis, age at intervention, and how long the patient stayed at the hospital in association with the procedure were recorded from medical notes in order to describe the cohort. When documenting the length of hospitalization in association with the procedure, there were some cases where the patient had been transferred to his/her local hospital for specialized care after the procedure. Period of hospitalization at the local hospital was then added to the day(s) the patient spent at Sahlgrenska University Hospital in association with the procedure.

### 4.1. Echocardiography

As previously described in the background, the LVOTO is dynamic in character. Patients may have a latent obstruction, meaning that they have no obstruction during resting conditions; however, they may have a clinically significant obstruction when provoked. When comparing the baseline and follow-up LVOTO, care was taken to ensure that both measurements were matched in the same patient. However, it was not possible to ensure that all patients included in the study had both resting and provoked LVOT gradient. If a patient already has a clinically significant gradient during resting conditions, it is not recommended to proceed with exercise cardiac echocardiography (11). Thus, the LVOT gradient is intra-personally matched when it comes to the measurement being resting or provoked, but it is not inter-personally matched.

Obstruction over the LVOT is most commonly reported as a gradient expressed in mmHg. However, in some instances, the obstruction was instead reported as maximum blood velocity expressed in m/s. To convert blood velocity to pressure gradient, the modified Bernoulli equation, $\Delta P = 4v_2^2$, was used (70).

When performing an echocardiogram examination, the echocardiographer reports a number of variables that are recorded in the medical records. When conducting echocardiogram examination on patients with HOCM, the echocardiographer often focuses on the LVOT gradient and septum thickness and may sometimes not comment on other measurements. In cases of missing variables in the echocardiogram, additional measurements were conducted on preexisting echocardiogram pictures.

### 4.2. Symptoms

NYHA functional class was recorded at baseline and follow-up. In most cases, there was a note in the medical records stating which NYHA class the patient was occupying. In other cases, there was no such note but rather a description of patient symptoms. In such cases, the most appropriate NYHA class that corresponded to the description of symptoms was recorded. In some cases, there was no description of symptoms or exercise tolerance in the medical records. When there was no information about symptoms or exercise tolerance, the NYHA variable was recorded as missing.

### 4.3. Medical treatment

Medical treatment with both beta-blockers and Disopyramide were recorded at baseline and at follow-up. Most patients were treated with the beta-blocker Metoprolol, but some patients (n = 17) was treated with other types of beta-blockers. These were then converted to the corresponding dosing of Metoprolol so as to be able to compare the dosing of beta-blockers. See table 4 for the basis behind converting beta-blocker doses.

**Table 4**: Conversion of beta-blocker doses

| | | |
|---|---|---|
| Bisoprolol 5 mg | = | Metoprolol 50 mg |
| Atenolol 50 mg | = | Metoprolol 50 mg |
| Propranolol 40 mg | = | Metoprolol 50 mg |

Adapted from (71)

### 4.4. Statistical methods

For continuous variables with extreme outliers in the data set, median and interquartile range was used to describe the central tendency and the variability. For continuous variables where no extreme outliers were present, mean and standard deviation were used to describe the data. In order to describe the categorical variables, amount and percentage was used.

When comparing inter-individual variables *Paired sample t-test* was used when the data was normally distributed. When the data did not meet the assumption of normal distribution *Wilcoxon signed-rank test* was employed as a non-parametric alternative. Binary paired data were analyzed using the *McNemar test.*

A p-value of $< 0.05$ was considered statistically significant.
Microsoft Excel was used during the data collection procedure and when creating Figures 4 and 5. Statistical analysis was done using the statistical program SPSS, version 28.

## 5. Students contribution

During the course of the study project, the student collected all the data used in this study from preexisting medical notes. In cases where the written report associated with the echocardiogram pictures did not report the needed variables, additional measurements were undertaken on the preexisting echocardiogram picture. This was done after a period of training and with the help from an experienced clinician at Sahlgrenska University Hospital. When all the data had been collected, the statistical analysis and interpretation of results were done by the student with guidance by the supervising doctor on this project.

## 6. Ethical considerations

In order to ensure the anonymity of patients, all data was encrypted, and the code used to connect patient's personal identification number to the recorded data was stored at a different locked location. All the work done in respect to medical notes was done on password-protected computers at Sahlgrenska University Hospital.

All data used in this study project was from clinical examinations that had already been conducted. No additional examinations were conducted, and thus, no additional risk or inconvenience was posed upon the patients included in this study. The study has received approval from the ethical review board (Dnr: 935-17, 2018).

# 7. Results

## 7.1. Description of the cohort

The total amount of patients included in the study was 68. 36 (52.9%) of the included patients were female, and 32 (47.1%) were male. The median age of when the patients received their diagnosis of HCM was 58 (± 19) years, and the median age of the patients when intervention with ASA was performed was 61 (±18) years. The oldest patient in the cohort that received intervention with ASA was 85 years, and the youngest was 31 years of age. After being treated with ASA, the patients stayed at the hospital for a median of 5 (± 2) days before they were discharged. Time to follow up examination after intervention with ASA had a mean of 6.3 (± 3.8) months. No patient had a time to follow-up shorter than three months. The longest time to follow-up examination was 16 months. All of the descriptive variables recorded are presented further down in table 5.

In order to sufficiently describe the cohort, a series of comorbid diseases was documented at the time of baseline examination. The most frequent comorbid disease recorded was hypertension, which 35 (51.2%) patients had. A previous history of coronary artery disease was also relatively common and recorded in 19 (27.9%) of the patients. Atrial fibrillation was recorded in 10 (14.7%) patients, chronic kidney disease in eight (11.7%) patients, diabetes mellitus in seven (10.3%) patients, and chronic obstructive pulmonary disease was recorded in six (8.8%) patients. The frequency of comorbid diseases can be seen listed in table 5.

**Table 5:** Description of the cohort

| | |
|---|---|
| Total number of patients included | 68 |
| Female<br>n (%) | 36 (52.9) |
| Age at diagnosis (years)<br>Median (IQR) | 58 (19) |
| Age at intervention (years)<br>Median (IQR), [min - max] | 61 (18), [31 - 85] |
| Stay at hospital (days)<br>Median (IQR) | 5.0 (2) |
| Time to follow-up examination after intervention with ASA (months)<br>Mean (SD), [min - max] | 6.3 (3.8), [3 - 16] |
| **Comorbidity:** | |
| Systemic hypertension<br>n (%) | 35 (51.5) |
| Diabetes mellitus<br>n (%) | 7 (10.3) |
| History of coronary artery disease<br>n (%) | 19 (27.9) |
| Atrial fibrillation<br>n (%) | 10 (14.7) |
| Chronic kidney disease<br>n (%) | 8 (11.7) |
| COPD<br>n (%) | 6 (8.8) |

IQR = interquartile range, SD = standard deviation, n = number,
COPD = Chronic obstructive pulmonary disease

### 7.2. Medical therapy and cardiac devices

The frequency of patients using beta-blockers did not change substantially after intervention with ASA. At baseline, 55 patients had beta-blockade, and at the time of follow-up examination, 57 patients had beta-blockade medication ($p>0.999$). However, the dosing of beta-blockers did change, from a median value of 175 (±200) mg/day to 150 (± 100) mg/day at the time of follow-up examination ($p=0.016$) (Table 6).

Patients having an ICD at baseline was seven (10.8%), which increased to nine (13.8%) at the time of follow-up examination ($p=0.500$). At baseline 13 (20.0%) patients had a pacemaker and this amount increased to 25 (38.5%) patients at the time of follow-up examination ($p<0.001$) (Table 6).

**Table 6:** Symptoms, medical treatment and the presence of pacemaker and/or ICD

| Variable | Baseline | Follow-up | p-value |
|---|---|---|---|
| Beta-blocker therapy<br>n (%) | 55 (98.2) | 57 (98.3) | >0.999 |
| Beta-blocker therapy (mg/day)<br>Median (IQR) | 175 (200) | 150 (100) | **0.016** |
| Disopyramide<br>n (%) | 15 (22.4) | 7 (11.5) | **0.021** |
| ICD<br>n (%) | 7 (10.8) | 9 (13.8) | 0.500 |
| Pacemaker<br>n (%) | 13 (20.0) | 25 (38.5) | **<0.001** |
| NYHA functional class<br>Mean (SD) | 2.8 (0.53) | 2.1 (0.77) | **<0.001** |

NYHA = New York Heart Association, ICD = Implantable cardioverter-defibrillator,
IQR = interquartile range, SD = standard deviation, n = number

### 7.3. NYHA functional class

It was documented a statistically significant improvement in NYHA functional class after treatment with ASA. NYHA functional class decreased from a mean of 2.8 (± 0.53) at baseline to a mean of 2.1 (± 0.77) at the time of follow-up examination ($p<0.001$) (Table 6).

Figure 4 and figure 5 give a more detailed picture of the changes seen in NYHA functional class after intervention with ASA. Figure 4 illustrates how, before intervention with ASA, 2% of patients were in NYHA class I, 11% were in NYHA class II, 81% were in NYHA class III, and 6% were in NYHA class IV. After the intervention with ASA, 23% was in NYHA class I, 40% was in NYHA class II, and 37% was in NYHA class III.

Figure 5 demonstrates the overall tendency of change seen in NYHA functional class after intervention with ASA. 56.2% of patients improved in their NYHA functional class. These patients either improvement one or more NYHA functional classes after treatment with ASA. 43.8% had no change in their NYHA class after intervention with ASA. There was no patient that worsened in their NYHA class after intervention with ASA.

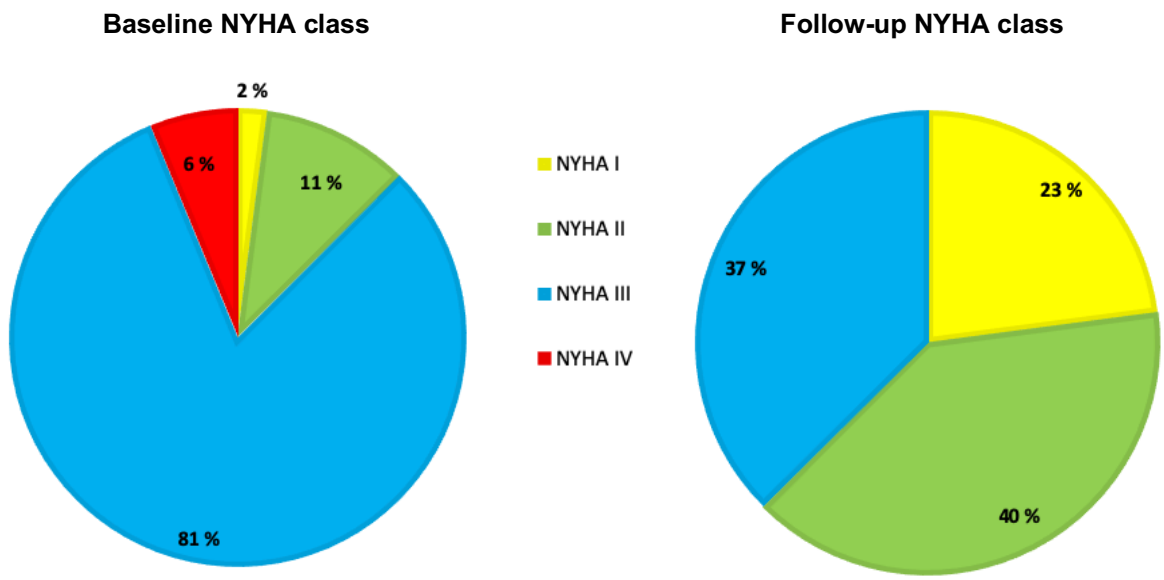


**Figure 4:** Frequency of patients in each NYHA class at the time of baseline and at follow-up examination, (n= 48)
NYHA = New York Heart Association, n = number

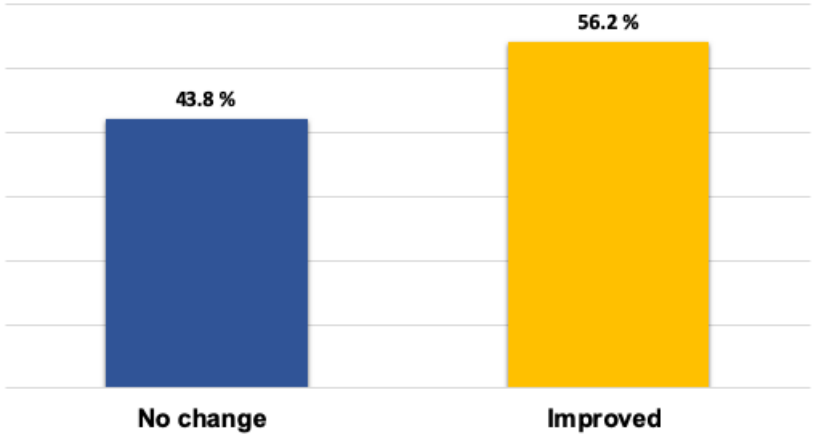


**Figure 5:** Change in NYHA class after treatment with ASA, (n= 48)
56.2% of patients improved in symptoms and reduced their NYHA class by one or more classes after treatment with ASA. In 43.8% of patients there was no change in NYHA class between baseline and follow-up examination. No patient worsened in their NYHA class after treatment with ASA.
NYHA = New York Heart Association, ASA = Alcohol septal ablation, n = number

### 7.4. Echocardiogram measurements

It was documented an improvement in the LVOT gradient after intervention with ASA. At baseline examination, there was recorded an LVOT gradient with a median of 81.0 (± 33.0) mmHg, and at the time of follow-up examination, the LVOT gradient had decreased to a median of 20.0 (± 51.1) mmHg ($p<0.001$). The number of patients having a gradient more or equal to 50 mmHg changed from 64 (95.5%) patients at baseline examination to 19 (29.2%) patients at the time of follow-up ($p<0.001$) (Table 7).

At the time of baseline examination, the measurement of the interventricular septum had a mean of 17.7 (± 4.2) mm. The measurement of the interventricular septum decreased to a mean of 15.4 (± 3.7) mm at the time of follow-up examination ($p<0.001$) (Table 7). When examining the measurements of the posterior left ventricle wall, left ventricle end-diastolic diameter (LVEDD), left atrial area (LAA), and ejection fraction (EF), no significant changes between baseline and follow-up examination was recorded. The results concerning echocardiogram measurements are presented in more detail in table 7.

**Table 7**: Echocardiography measurements

| Variable | Baseline | Follow-up | p-value | Reference values * |
|---|---|---|---|---|
| LVOT gradient (mmHg)<br>Median (IQR) | 81.0 (33.0) | 20.0 (51.1) | **<0.001** | |
| LVOT gradient ≥50 mmHg<br>n (%) | 64 (95.5) | 19 (29.2) | **<0.001** | |
| Septum (mm)<br>Mean (SD) | 17.7 (4.2) | 15.4 (3.7) | **<0.001** | 6 - 10 |
| Posterior LV wall (mm)<br>Mean (SD) | 11.1 (2.4) | 10.8 (2.2) | 0.411 | 6 - 10 |
| LVEDD (mm)<br>Mean (SD) | 47.0 (6.3) | 46.7 (5.7) | 0.878 | 42.0 - 58.4 |
| LAA ($cm^2$)<br>Median (IQR) | 24.3 (9.1) | 22.0 (7.6) | 0.228 | 11 - 23 |
| EF (%)<br>Mean (SD) | 63.8 (5.4) | 62.8 (4.9) | 0.182 | 54 - 72 |

*Reference values are adapted from the article by Lang *et al*. (72)
SD = Standard deviation, IQR = interquartile range, LVOTO = left ventricle outflow tract obstruction, LVEDD = Left ventricle end-diastolic diameter, LAA = Left atrium area, EF = Ejection fraction, IQR = interquartile range, SD = standard deviation

### 7.5. Procedural complications and rate of reinterventions

The most common procedural complication recorded was the occurrence of a total atrioventricular block (AVB-III), which occurred in 11 (14.8%) patients after intervention with ASA. All of these 11 patients had a permanent pacemaker implanted after the procedure due to the AVB-III. A permanent left bundle branch block (LBBB) occurred in one patient (1.5%), and a permanent right bundle branch block (RBBB) occurred in four (5.9%) of the patients after intervention with ASA. One patient had a myocardial infarction in association to the procedure with ASA. One patient developed a major injection site complication from the insertion of the catheter in the femoral artery at the beginning of the procedure. One patient had the severe complication of cardiogenic chock in association with the procedure, which later developed to cardiopulmonary failure and was subsequently treated at the intensive care unit for a longer period of time (Table 8). There was recorded no mortality in association with the procedure.

In table 8, the number of patients requiring a reintervention with ASA is also presented. Nine (13.2%) of patients were judged to have benefits of a second intervention with ASA after the results from the first intervention were examined. The decision to do a reintervention with ASA is based on inadequate symptom relief after the first intervention.

**Table 8:** Procedural complications and number of patients requiring reintervention

| Complication | Amount (n) | Percent (%) |
|---|---|---|
| AVB-III and subsequent implantation of a PPM | 11 | 14.8 |
| Permanent LBBB | 1 | 1.5 |
| Permanent RBBB | 4 | 5.9 |
| Myocardial infarction | 1 | 1.5 |
| Major injection site complications | 1 | 1.5 |
| Cardiogenic shock | 1 | 1.5 |
| Reintervention | 9 | 13.2 |

AVB-III = Third degree atrioventricular block, PPM = permanent pacemaker, LBBB = left bundle branch block, RBBB = right bundle branch block, n = number

# 8. Discussion

## 8.1. NYHA functional class and medical therapy

We found that treatment with ASA led to a significant improvement of symptoms, and over 50% of patients did improve their NYHA class. This improvement in NYHA class was statistically significant, with a mean of 2.8 at baseline reduced to 2.1 at the time of follow-up examination. The improvement in NYHA functional class implies that treatment with ASA reduces symptoms and increases patients´ physical ability. Several other studies (68, 73, 74) have shown a similar result when it comes to a significant reduction in NYHA functional class after treatment with ASA. Veselka *et al*.(73) conducted a large multicenter European study including 1275 HOCM patients treated with ASA. They reported a reduction in NYHA functional class from 2.9 at baseline to 1.6 at follow-up. In a study from 2007, which included 312 patients treated with ASA, Faber *et al*.(74) found a reduction in NYHA functional class from 2.9 at baseline to 1.5 one year after intervention with ASA. In addition to NYHA functional class, which is subjectively reported by patients, Faber *et al*. (74) also documented exercise capacity during exercise stress testing, and they reported an increase both in exercise capacity and peak oxygen consumption after patients had been treated with ASA.

In our study, it was shown that the doses of beta-blockers were reduced after treatment with ASA. Beta-blocker doses were reduced from a median of 175 mg/day at baseline to a median of 150 mg/day at follow-up. Beta-blockers alleviate symptoms caused by the LVOTO (37). The reduction seen in beta-blocker doses may further indicate the effectiveness of treatment with ASA, seen in the fact that a smaller dose of negative ionotropic drugs reduces symptoms of LVOTO after the treatment with ASA. However, the frequency of patients treated with beta-blocker was approximately the same before and after intervention with ASA. One reason that the rate of beta-blocker use was not reduced could be due to the short follow-up time. Beta-blockers are slowly titrated out of the medical regiment, and the time between intervention and follow-up medical examinations was relatively short (mean of 6.3 months). If the follow-up time had been longer, a more substantial reduction in the dose of beta-blockers might have been seen.

There was seen a statistically significant reduction in the use of Disopyramide after treatment with ASA. The rate of patients having Disopyramide at baseline was reduced from 22.4% to 11.5% at the time of follow-up examination. As previously described in the background,

Disopyramide is added when beta-blockers do not sufficiently reduce the LVOTO. The reduction in the rate of patients using Disopyramide can also be seen as an indication of effectiveness of treatment due to symptoms caused by the LVOTO being elevated by the treatment with ASA.

### 8.2. Echocardiogram findings

In this study, it was found a statistically significant reduction in LVOT gradient after treatment with ASA. The LVOT gradient was reduced from a baseline of 81.0 mmHg to 20.0 mmHg at the time of follow-up examination. There was also seen a significant reduction in the frequency of patients having an LVOT gradient ≥50 mmHg after treatment with ASA. Before treatment with ASA, 64 patients had an LVOT gradient ≥50 mmHg. After treatment with ASA, 19 patients had a gradient ≥50 mmHg. The result seen in our study is thus added to the list of other studies that have shown ASAs effectiveness in reducing the LVOT gradient (21, 75-77). A reduction of LVOT gradient may have implications on long-term clinical outcomes. As seen in the study by Maron *et al*. (9) an LVOTO during resting conditions was a strong predictor of whether patients develop severe heart failure symptoms later on.

We documented a significant reduction in interventricular septum thickness from a mean of 17.7 mm at baseline to 15.4 mm at follow-up. The thickness and anatomical shape of the interventricular septum have an integral connection to the LVOTO, both by causing physical obstruction of blood flow and by contributing to SAM phenomenon.
Similar result regarding the thinning of the interventricular septum after treatment with ASA was shown in the study by Dąbrowski *et al*.(21). They showed a reduction in the interventricular septum, measured with echocardiography, from 23.6 mm at baseline to 19.3 mm at follow-up examinations.

### 8.3. Stay at hospital, procedural complications and rate of reinterventions

Length of hospitalization was documented to be an average of 5 days following treatment with ASA. Patients who undergo intervention with ASA stay at the hospital after the procedure in order to be monitored. This is to make sure that the possible occurrence of an atrioventricular block is detected. The temporary pacemaker that was implanted before the procedure is left for at least 72 hours while the patient is monitored at the cardiac intensive care unit. Our results are similar to other studies that have recorded length of hospitalization

associated with ASA. For example, Steggerda *et al.* (56) measured the length of hospitalization in patients treated with ASA and with myectomy. They also reported a median of 5 days hospitalization after treatment with ASA and 9 days hospitalization for patients treated with myectomy.

In our study, the most common complication recorded in association with ASA was the development of AVB-III and subsequent implantation of a permanent pacemaker (14.8%). This rate is similar to other studies that have reported complications associated with ASA. The large European multi-center study conducted by Veselka *et al.* (73) reported a rate of permanent pacemaker implantation due to AVB-III to be a total of 12% after treatment with ASA.

Recorded in this study project, nine patients (13.2%) underwent reintervention due to the lack of improvement in symptoms after the first intervention. The rate of reinterventions has been seen to be more frequent after ASA compared to after treatment with myectomy. This was shown in the meta-analysis from 2015 by Liebregts *et al*. (78), who reported that the rate of reintervention after treatment with ASA was 7.7%. The authors then compared this to the rate of reinterventions seen after myectomy, which was only 1.6%.

### 8.4. Modifications to the study and future possibilities

In terms of modification, it might have been beneficial to add some measurements to the echocardiogram variables. The presence of mitral regurgitation and SAM phenomenon would be interesting to document. As previously described in the background, these two variables are often a function of the LVOTO. If these two variables had been added, the study could examine if these become improved after the reduction of LVOTO and septum thickness.

This study examines short-term results after treatment with ASA. The median time to follow-up examinations was 6.3 months, and thus, long-term results after treatment with ASA are not evaluated in this study. Additional studies might be done by building upon the data available from this study and further examine the long-term treatment result.

At Sahlgrenska University Hospital, surgical myectomy is also performed as a mode of septal reduction therapy for patients with HOCM. A study that compares ASA and myectomy would be one idea for future studies that can build upon the data collected in this study.

Javidogonbadi *et al.* (79) described a cohort of patients with HOCM that have been treated with the implantation of a pacemaker programmed with dual-chamber pacing. Treatment with dual-chamber pacing was shown in this study to reduce outflow tract obstruction and to improve patients' symptoms. A comparison between these two treatment methods, ASA and pacing, might also be a possibility for future studies.

### 8.5. Methodological considerations

The small cohort size can be seen as a weakness of this study due to the amount of missing data in some variables. See the appendix for a list of the total missing data points in each paired variable. Missing variables do not have implications on the statistical methods that were employed in this study due to no imputation techniques being used. However, the size of the study sample is reduced when missing variables are present. This is notable when discussing the reduction in NYHA functional class. Due to NYHA functional class not being an obligatory, nor a very common, clinical measurement for physicians to document, the NYHA functional class ended up being the one study variable with the highest amount of missing data. The result was that only 48 patients had documented NYHA functional class at both baseline and follow-up examination. In future projects, it might be wise to design the study so as to ensure that the NYHA functional class, or other surrogate variables for evaluating patient symptoms, is recorded in a greater number. Ways to ensure this might be, for example, by conducting interviews with patients or by perhaps sending out questionnaires.

The study aimed to describe the group of patients who underwent treatment with ASA. This is sufficiently done by the descriptive values documented, such as gender and age, and by recording comorbidities. The main objectives were answered by evaluating the change in NYHA functional class and by recording changes in echocardiogram variables after treatment with ASA. The efficiency of treatment was also further evaluated by recording changes in medical therapy and by recording the rate of reinterventions.

## 9. Conclusion

ASA is an effective form of septal reduction therapy for patients with symptomatic HOCM refractory to medical treatment. Reduction in symptoms was shown by the significant reduction in NYHA functional class. The improvement of symptoms was further demonstrated by the decrease in dosing of beta-blockers and by the reduction in the frequency of patients using Disopyramide. Effectiveness of treatment has also been shown by the significant decrease in LVOT gradient documented after treatment with ASA.
ASA is a safe form of septal reduction therapy. There was reported no mortality associated with the procedure. The most common major complication seen was AVB-III with subsequent pacemaker implantation. Only short-term results were documented in this study, and future studies might build upon the data collected in this study to evaluate the long-term follow-up results after treatment with ASA.

## 10. Acknowledgments

I would like to thank Angela Poller at the department of molecular and clinical medicine at Sahlgrenska University Hospital for assisting with the additional measurements on preexisting echocardiogram pictures. I would also like to thank Dan Ioanes, senior consultant cardiologist at Sahlgrenska University Hospital, for answering questions regarding the procedural aspects of ASA. Finally, I would like to thank Entela Bollano, associate professor and senior consultant cardiologist, Department of Cardiology at Sahlgrenska University Hospital, who was the supervising doctor on this project. Thank you for answering all my questions and for the guidance during the course of this study project.

## Populärvetenskaplig sammanfattning

## Behandling av förtjockad hjärtevägg med alkoholablation


| | |
|---|---|
| Författare: | Ane Bakken Wold |
| Examensarbete: | 30 hp |
| Program: | Läkarprogrammet |
| År: | 2022 |
| Handledare: | Entela Bollano, Docent vid Sahlgrenska Universitetssjukhus, Kardiologisk avdelning |
| Nyckelord: | Hypertrofisk obstruktiv kardiomyopati, alkoholablation, behandlingsresultat. |


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Hypertrofisk kardiomyopati är en vanlig genetisk sjukdom som gör att hjärtmuskelväggen blir förtjockad. Symptombilden kan variera stort, en del har nästan inga symptom, medan andra har större besvär med betydande funktionsnedsättning.

Hjärtat består av två förmak och två kammare. Hos patienter med hypertrofisk kardiomyopati är det oftast den väggen som separerar de två kamrarna som blivit förtjockad. Denna vägg kallas för septum. När septum blir tjockare än vanligt resulterar detta i ett ökat motstånd i utflödesdelen från hjärtats vänstra kammare ut i kroppens huvudpulsåder, detta kallas för Hypertrofisk obstruktiv kardiomyopati. Symtomens allvarlighetsgrad är relaterad till motstånden kamrarna måste överkomma för att pumpa ut blodet ur hjärtat. De vanligaste symptomen patienter upplever är andfåddhet vid träning, generell trötthet, bröstsmärta, yrsel och svimning.

Behandlingen av hypertrofisk obstruktiv kardiomyopati består först av att minska symptomen med hjälp av läkemedel. Patienter som fortfarande har symptom trots läkemedelsbehandling kan bli aktuella för invasiv behandling. Det finns två invasiva behandlingsmetoder. Den första och äldsta metoden är kirurgi. Den nyare och mindre invasiva metoden är alkoholablation (ASA). Vid ASA börjar man proceduren på samma sätt som vid en ballongsprängning, dvs man för in en slang i ett stort kärl i handleden eller ljumsken som leder till hjärtat. Väl framme med slangen i hjärtat tillförs alkohol i det kärlet som ger blod till den förtjockade delen av hjärteväggen. Injektionen av alkohol gör att det orsakas en liten infrakt i hjärtmuskeln. I vanliga fall tänker man att en hjärtinfarkt är något farligt och något man vill undvika, men i detta sammanhangen är hjärtinfarkten faktiskt själva behandlingen. Efter det framkallade infrakten sker en naturlig omorganisering av hjärtmuskelcellerna, där vanliga hjärtmuskelceller blir till fibrotiska fibrer, likt som i ett ärr. Omorganiseringen resulterar i en tunnare hjärtmuskelvägg, vilket gör att blodet kan flöda lättare från hjärtat och ut i kroppen.

Syftet med studien var att utvärdera behandlingsresultatet hos patienter som behandlats med ASA. Studien inkluderade 68 patienter.
Patientens fysiska förmåga i vardagen kan mätas med den så kallade New York Heart Association (NYHA) funktionella klassificeringen. I NYHA klassificeringen betyder nivå 1 inga hinder i vardagen och nivå 4 betyder att patienten har markanta hinder i sin vardag. I denna studien såg man en förbättring av fysisk förmåga, och man såg en förbättring från en genomsnittlig NYHA nivå på 2,8 innan behandling till nivå 2,1 efter behandling med ASA. Blodets förhöjda motstånd ut ur hjärtat blev också förbättrat. Innan behandlingen med ASA hade patienterna en median på motståndet ut ur hjärtat på 81 mmHg. Detta motstånd blev reducerat till 20 mmHg efter behandlingen med ASA.
Konklusionen som kan dras utifrån resultaten i denna studie är att ASA är en effektiv form för behandling av utvalda patienter med Hypertrofisk obstruktiv kardiomyopati.

# Appendix

**Paired variables with missing data points:**

| Variable | Number of missing paired data | Percentage of total |
|---|---|---|
| NYHA class | 20 | 13.6% |
| Beta-blocker therapy | 10 | 6.8% |
| Disopyramide therapy | 8 | 5.4% |
| ICD and Pacemaker | 3 | 2% |
| LVOT gradient | 3 | 2% |
| Septum | 11 | 7.5% |
| Posterior LV wall | 15 | 10.2% |
| LVEDD | 15 | 10.2% |
| LAA | 14 | 9.5% |
| EF | 16 | 10.9% |

NYHA = New York Heart Association, ICD = Implantable cardioverter-defibrillator,
LVOT = Left ventricular outflow tract, LV = left ventricle, LVEDD = left ventricle end-diastolic diameter,
LAA = left atrium area, EF = ejection fraction

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