Alcohol Septal Ablation for Obstructive Hypertrophic Cardiomyopathy

A Word of Endorsement

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ABSTRACT

Twenty years after the introduction of alcohol septal ablation (ASA) for the treatment of obstructive hypertrophic cardiomyopathy, the arrhythmogenicity of the ablation scar appears to be overemphasized. When systematically reviewing all studies comparing ASA with myectomy with long-term follow-up, (aborted) sudden cardiac death and mortality rates were found to be similarly low. The focus should instead shift toward lowering the rate of reinterventions and pacemaker implantations following ASA because, in this area, ASA still seems inferior to myectomy. Part of the reason for this difference is that ASA is limited by the route of the septal perforators, whereas myectomy is not. Improvement may be achieved by: 1) confining ASA to hypertrophic cardiomyopathy centers of excellence with high operator volumes; 2) improving patient selection using multidisciplinary heart teams; 3) use of (3-dimensional) myocardial contrast echocardiography for selecting the correct septal (sub)branch; and 4) use of appropriate amounts of alcohol for ASA. (J Am Coll Cardiol 2017;70:481–8) © 2017 by the American College of Cardiology Foundation.

Hypertrophic cardiomyopathy (HCM) is the most common inheritable cardiac disease, present in 1 in 500 of the general population (1). Approximately two-thirds of patients with HCM have a significant gradient across the left ventricular outflow tract (LVOT) at rest or during physiological provocation and are classified as having obstructive HCM (2). First-line treatment in patients with significant LVOT obstruction is with negative inotropic drugs (beta-blockers, verapamil, and disopyramide) (3,4). In the 5% to 10% of patients who remain highly symptomatic despite optimal medical therapy, septal reduction therapy is indicated, either by surgical myectomy or alcohol septal ablation (ASA) (3–5).

HISTORY OF SEPtal REDUCTION THERAPY

First performed by Cleland in 1958, surgical myectomy was the first invasive treatment for obstructive HCM (6). Starting from 1960, Morrow used a technique in which a small, rectangular bar of muscle from just below the aortic valve to beyond the site of mitral-septal contact was resected. The results of the first 83 patients treated with this “Morrow procedure” were published in 1975 (7). Since then, numerous different surgical techniques have come and gone. The objective of most of these procedures was enlargement of the LVOT by means of myectomy to eliminate the systolic anterior motion of the anterior mitral valve leaflet and thereby reduce outflow obstruction. Mitral valve plication, extension, and replacement have also been proposed as alternatives to myectomy, and performed in selected patients (8,9).

At the end of the 1980s, an interventional approach to septal reduction began to take shape. Brugada et al. (10) were the first to treat a patient by injecting absolute alcohol into a septal branch of the left anterior descending artery. Their goal was not to treat
LVOT obstruction, however, but chemical ablation of ventricular tachycardia. The idea of reducing LVOT obstruction by a catheter-based method stems from the observation that myocardial function of selected areas of the left ventricle can be suppressed by balloon occlusion of the supplying coronary artery during angioplasty (11). In the years following the chemical ablation procedure reported by Brugada et al. (10), 2 groups of researchers almost simultaneously developed ASA for the treatment of obstructive HCM. Gietzen et al. (12) presented their preliminary findings at the Annual Congress of the German Cardiac Society in April 1994, and Sigwart presented his results at the Royal Brompton Hospital in London in June 1994 and subsequently published the first 3 cases in The Lancet (13).

**NEEDLE VERSUS KNIFE**

Since its introduction, there has been a polarizing debate concerning the role of ASA in the management of obstructive HCM. Publications from the “surgical side” of the discussion are characterized by recycling of selected (early) outcomes of ASA, whereas the “interventional side” frequently disregards the limitations of ASA. Ideally, a randomized controlled trial should be set up to end the discussion about which procedure is best. This would require 1,200 patients eligible and willing to be randomized to a percutaneous or surgical procedure. Because the prevalence of HCM is 1 in 500 and <10% of these patients require septal reduction therapy, such a trial is practically impossible, as Olivetto et al. (14) clearly demonstrated. Hence the only way to compare the 2 techniques at this time is by retrospective analyses.

**STUDIES COMPARING ASA WITH SURGICAL MYECTOMY.**

ASA had to come of age, and the first substantial comparison with surgical myectomy was reported in 2010 by Agarwal et al. (15). In this meta-analysis, 12 studies comparing techniques were included. The most important limitation of this analysis was the short follow-up duration of the included studies (longest median follow-up 2.2 years), thus prohibiting the investigators from making statements on long-term outcomes. The meta-analysis we performed in 2015 therefore only included studies with a follow-up of at least 3 years (16). Remarkably, only 6 studies comparing ASA with myectomy were identified (Table 1) (17–22). In contrast, 44 studies were found describing the outcomes of 1 of the 2 interventions (16), a finding that may also be seen as a sign of the ongoing polarization.

In 2010, ten Cate et al. (17) conducted the first of the 6 studies comparing long-term outcomes of ASA and myectomy head to head. This study (subtitled “A Word of Caution”) is the only study to date that reported a worse outcome following ASA compared with myectomy and is therefore frequently used (>100 citations) by opponents of ASA. Two years later, Sorajja et al. (18), from the Mayo Clinic in Rochester, Minnesota, compared ASA with myectomy by matching patients in a 1:1 fashion. The survival of ASA-treated patients was found to be comparable to the age-and sex-matched general population and to age- and sex-matched myectomy-treated patients. Steggerda et al. (19) compared ASA-treated patients with myectomy-treated patients, focusing on peri-procedural complications and clinical efficacy. The same patients were also included in the largest study of its kind, by Vriesendorp et al. (20), which included 1,047 patients with HCM. During a mean follow-up of 7.6 years, survival after ASA or myectomy was found to be similar and comparable to that of patients with nonobstructive HCM. Finally, Samardhi et al. (21) and Sedehi et al. (22) described outcomes of relatively small groups of patients after ASA and compared these with outcomes following myectomy.

Of the 50 studies found by the systematic review (16), 24 studies were selected for meta-analysis, containing 16 myectomy cohorts (n = 2,791; mean follow-up 7.4 years) and 11 ASA cohorts (n = 2,013; mean follow-up 6.2 years). When we repeated the same search for studies published from 2015 to 2016, we only found 1 additional study, by Yang et al. (23), comparing long-term outcomes following the 2 procedures (Table 1).

**LONG-TERM OUTCOMES.** The initial performance of ASA was shrouded in safety concerns because of the intracoronary injection of cardiotoxic ethanol, creating a potentially arrhythmogenic ablation scar. However, all but 1 of the aforementioned studies showed similar mortality rates after ASA and myectomy despite the more advanced age of most of the ASA cohorts (Table 1) (15,16,18–23). Annual sudden cardiac death rates (including appropriate implantable cardioverter-defibrillator discharge) following ASA were also found to be similar to those in post-myectomy patients, ranging from 0.4% to 1.3%, when including unknown deaths (Table 1) (16,18,20,21).

The primary endpoint of the study by ten Cate et al. (17) was an unusual composite of cardiac death, aborted sudden cardiac death, and appropriate implantable cardioverter-defibrillator discharge, without discriminating between peri-procedural...
Events and late events. Patients undergoing ASA had a 5-fold increase in the estimated annual primary endpoint rate compared with those undergoing myectomy (4.4% vs. 0.9%). When we calculated this composite endpoint for the different ASA cohorts included in the 2015 meta-analysis (16), one-half of them had estimated rates <0.9%/year, and only 3 cohorts were found to have an annual rate >1.5% (Lyné et al. [24], 1.8%; Veselka et al. [25], 1.8%; and Vriesendorp et al. [20], 1.9%).

**Periprocedural Complications and Treatment Effect.** None of the studies discussed in the preceding text found a difference in 30-day mortality rates between the 2 procedures (15,18-21,23), except for the 2015 meta-analysis, which showed a periprocedural mortality rate following myectomy twice as high compared with ASA (16). However, in light of the potentially less-developed periprocedural care in the 20th century, when studies from before 2000 were excluded, the periprocedural mortality rates of both procedures were close to equal.

The only study that found a higher rate of periprocedural ventricular arrhythmias following ASA was by Vriesendorp et al. (20). The 2015 meta-analysis showed a similar incidence of periprocedural ventricular arrhythmias following both procedures (16). However, when studies from before 2000 were again excluded, the periprocedural event rate became 2.2% after ASA compared with 0.6% after myectomy, with borderline significance (p = 0.055). Thus, there are reasons to believe that there is a slightly higher risk of periprocedural ventricular arrhythmias following ASA. This also makes sense from a pathophysiological point of view because of the increased arrhythmogeneity of an acute myocardial infarction. However, as shown before, good periprocedural and post-procedural care prevent increased 30-day mortality rates.

The need for pacemaker implantation following both procedures varies considerably among the studies discussed earlier (0% to 22% following ASA, compared with 0% to 13% following myectomy) (Table 1). In their meta-analysis, Agarwal et al. (15) found an increased risk of permanent pacemaker implantation following ASA, with an odds ratio of 2.6. This finding is identical to the 10% pacemaker implantations following ASA, compared with 4% pacemaker implantations following myectomy, that was found in the 2015 meta-analysis (16).

The meta-analysis by Agarwal already showed a slightly higher LVOT gradient after ASA compared with myectomy (15). However, no significant differences were found in the reintervention rate. It took studies with long-term follow-up to discover a higher need for reinterventions following ASA compared with myectomy (18-21). The observation of a slightly higher LVOT gradient after ASA compared with myectomy was confirmed by the 3 largest

**Table 1**  Outcomes of All Studies Comparing ASA With SM With a Mean Follow-Up Duration of at Least 3 Yrs and Results of Meta-Analyses Comparing ASA With Myectomy

<table>
<thead>
<tr>
<th>First Author, Year (Ref. #)</th>
<th>Country</th>
<th>Period</th>
<th>n</th>
<th>Mean Follow-Up, yrs</th>
<th>Mean Age, yrs</th>
<th>Peri Mortality, %</th>
<th>Peri (A)SCD, %</th>
<th>Pacemaker, %</th>
<th>Mean LVOTG, mm Hg</th>
<th>REDO, %</th>
<th>All-Cause Mortality (Annual), %</th>
<th>(A)SCD (Annual), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal, 2010 (15)</td>
<td>6 countries</td>
<td>1986-2006</td>
<td>380/326</td>
<td>–</td>
<td>55/49*</td>
<td>NS</td>
<td>NS</td>
<td>2.6 (favors SM)</td>
<td>SMD 0.45 (favors SM)</td>
<td>NS</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ten Cate, 2010 (17)</td>
<td>the Netherlands</td>
<td>1999-2007</td>
<td>91/40</td>
<td>5.4/6.6</td>
<td>54/49</td>
<td>2.2/0†</td>
<td>5.5/0†</td>
<td>4/3</td>
<td>8/–</td>
<td>11/5†</td>
<td>1.8/0.8§</td>
<td>–</td>
</tr>
<tr>
<td>Sorajja, 2012 (19)</td>
<td>United States, Rochester</td>
<td>1983-2010</td>
<td>177/177</td>
<td>5.7/5.7</td>
<td>63/62</td>
<td>1.1/0.6</td>
<td>1.7/0.6</td>
<td>22/4</td>
<td>13/–</td>
<td>9/1†</td>
<td>2.5/2.4</td>
<td>1.3/1.1</td>
</tr>
<tr>
<td>Steggerda, 2014 (19)</td>
<td>the Netherlands†</td>
<td>1981-2010</td>
<td>161/102</td>
<td>5.1/9.1</td>
<td>59/56</td>
<td>1.2/2.0</td>
<td>2.5/0</td>
<td>7/9</td>
<td>19/10*</td>
<td>6/1†</td>
<td>1.5/2.2</td>
<td>–</td>
</tr>
<tr>
<td>Vriesendorp, 2014 (20)</td>
<td>Belgium and the Netherlands†</td>
<td>1990-2012</td>
<td>316/250</td>
<td>6.3/7.9</td>
<td>58/52*</td>
<td>1.6/1.2</td>
<td>3.1/0.4*</td>
<td>–</td>
<td>10/9*</td>
<td>10/2*</td>
<td>1.9/2.0</td>
<td>1.0/0.8</td>
</tr>
<tr>
<td>Samardhi, 2014 (21)</td>
<td>Australia</td>
<td>1981-2012</td>
<td>47/23</td>
<td>3.6/3.8</td>
<td>57/47*</td>
<td>0/8.7</td>
<td>4.3/0</td>
<td>15/13</td>
<td>27/13</td>
<td>17/0†</td>
<td>1.2/4.6</td>
<td>0/0</td>
</tr>
<tr>
<td>Sedehi, 2015 (22)</td>
<td>United States, Stanford</td>
<td>1972-2006</td>
<td>52/171</td>
<td>3.2/13.7</td>
<td>57/48*</td>
<td>0/2.9</td>
<td>–</td>
<td>8/6†</td>
<td>36/34‡</td>
<td>–</td>
<td>1.2/1.0</td>
<td>–</td>
</tr>
<tr>
<td>Liebregts, 2015 (23)</td>
<td>China</td>
<td>2001-2014</td>
<td>22/37</td>
<td>3.0/3.0</td>
<td>46/45</td>
<td>0/0</td>
<td>4.5/2.7‡</td>
<td>0/0</td>
<td>–</td>
<td>5/0‡</td>
<td>1.5/0.9</td>
<td>0/0.9§</td>
</tr>
</tbody>
</table>

Values are ASA-treated patients/SM-treated patients. *p < 0.05. †Patients also included in other study. ‡No statistical comparison conducted. §Studies from before the year 2000 were excluded. |Including death from unknown cause. Studies in **bold** are meta-analyses comparing ASA with myectomy. ASA = alcohol septal ablation; (A)SCD = (aborted) sudden cardiac death, including appropriate implantable cardioverter-defibrillator discharge; LVOTG = post-procedural (provocable) left ventricular outflow tract gradient; OR = odds ratio; Peri = periprocedural (~30 days); REDO = reintervention during follow-up (either ASA or SM); SM = surgical myectomy; SMD = standardized mean difference.
PATIENT SELECTION AND SPECIALIZED CARE. The 2011 American College of Cardiology Foundation/American Heart Association guidelines state that surgical myectomy is the gold standard for patients with medical therapy-resistant obstructive HCM, and that ASA should be reserved for older patients or patients with serious comorbidities (3). Despite these recommendations, recent figures show that ~43% of U.S. patients undergo ASA instead of myectomy (26), and these numbers are known to be even higher in Europe (27). This is another reason why we should spend less time discussing which procedure is best and more time discussing how to select the right patient for the right procedure.

Most of the studies discussed previously were conducted in high-volume centers. The corresponding figures are therefore applicable only when patients are referred to such centers. This is in accordance with the guidelines, which state that only experienced operators with cumulative case volumes of at least 20 procedures should perform myectomies (United States) or that a minimal caseload of 10 ASA or myectomies is required (Europe) (3,4). A recent study on hospital volume outcomes after septal reduction therapy in U.S. hospitals showed that 60% of the centers had performed <10 myectomies during the 9-year study period, whereas 4 institutions had performed 36% of all the isolated myectomies during the same time period. This finding is of particular concern because the low-volume centers were found to have 3-fold higher in-hospital mortality rates (15.6%) compared with high-volume centers. The same was found for ASA, with 67% of the centers having performed <10 procedures during the study period. However, undergoing ASA in low-volume centers was not associated with worse outcome (in-hospital mortality 2.3%) when compared with high-volume centers. This finding could be a reflection of a significantly steeper learning curve associated with myectomy and the relative ease with which operators with experience in catheter-based therapy adapt ASA (26). These findings do not mean that ASA can be conducted everywhere, whereas myectomy needs to be confined to a few centers. All care for patients with HCM who require septal reduction therapy should be confined to HCM centers of excellence where both procedures are available and are used in a complementary and not competing manner.

The decision to perform myectomy or ASA is not solely based on the outcomes described previously. Similar to patients undergoing surgical or catheter-based aortic valve replacement (28), all patients undergoing septal reduction therapy should be discussed in a multidisciplinary heart team consisting of

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**FIGURE 1** Decision Tree for Patients With Obstructive HCM and Complicating Patient Factors

- Adult patient with medical therapy resistant obstructive HCM
- **Surgical necessity?**
  - Mitral valve pathology
  - Three-vessel disease
  - Mid-cavity obstruction by papillary muscles

Diagnosis:()

- **YES**
  - MitraClip ± ASA
  - PCI + ASA
  - Conservative treatment

- **NO**

- **Presence of suitable perforator for ASA?**

Diagnosis:()

- **YES**
  - Surgical myectomy
  - ± Valve surgery ± CABG

- **NO**
  - Patient preference
  - Alcohol septal ablation

**Decision tree that can be used by the multidisciplinary heart team for patients with obstructive hypertrophic cardiomyopathy (HCM) and complicating patient factors. ASA = alcohol septal ablation; AVI = aortic valve insufficiency; CABG = coronary artery bypass grafting; CHB = complete heart block; LBBB = left bundle branch block; PCI = percutaneous coronary intervention; RBBB = right bundle branch block.**
an imaging cardiologist, an interventional cardiologist experienced with ASA, and a surgeon experienced with myectomy (3,4). Here, additional patient-related factors can be taken into account. For example, the need for concomitant valve surgery or coronary artery bypass grafting will, in most cases, make myectomy the better choice, as will midcavity obstruction by papillary muscles requiring surgical correction (i.e., hypertrophic papillary muscles, accessory papillary muscles, direct insertion of anterolateral papillary muscle into the anterior mitral leaflet). In contrast, a high operative risk because of advanced age and/or comorbidities will frequently result in the choice for ASA. Sometimes ASA is not possible because of the absence of a suitable septal perforator. Finally, existing conduction disturbances can play a part in making the decision. Because ASA frequently causes a right bundle branch block, a pre-existing left bundle branch block could make myectomy the preferable option. Conversely, because myectomy frequently creates a left bundle branch block, a pre-existing right bundle branch block could
be an argument for ASA. An implanted pacemaker for a pre-existing complete heart block could also play a role in decision making for obvious reasons. **Figure 1** depicts a decision tree that can be used by the multidisciplinary heart team for patients with medical therapy-resistant obstructive HCM and complicating patient-related factors.

When an adult patient has no complicating factors, we can state that, on the basis of the aforementioned results, ASA and myectomy appear to be equally safe. However, patients undergoing ASA have a 1 in 10 chance of permanent pacemaker implantation, whereas that risk is 1 in 25 after myectomy (15,16). Furthermore, there is a 1 in 13 chance that ASA-treated patients will have to undergo reintervention, either by repeat ASA or by myectomy, which is 5 times the risk of a repeat procedure following myectomy. Nonetheless, symptom relief at long-term follow-up is similar after both procedures (Central Illustration) (16).

Through shared decision making, each individual patient can weigh these higher risks following ASA against the somewhat higher burden of rehabilitation after open heart surgery and make a measured decision.

**IMPROVING OUTCOMES OF ASA**

**TECHNICAL ADVANCES.** In the early days of ASA, relatively high volumes of alcohol were used. For example, the first 3 cases described by Sigwart (13) were treated with an average of 4.5 ml. The most frequently heard critique on the study by ten Cate et al. (17) was the use of high volumes of alcohol in its ASA-treated patients (mean 3.5 ml, compared with a median of 2.5 ml in the 2015 meta-analysis). However, in their analysis, no effect of alcohol dosage on their primary endpoint was observed. Over time, clinical experience, combined with better strategies to identify the target septal branches, has led to the use of lower volumes of alcohol during ASA (29,30).

Initially, selection of the appropriate septal perforator was made on the basis of an immediate decrease of the LVOT gradient following balloon occlusion. In 1998, myocardial contrast echocardiography (MCE) was introduced (31,32). With the use of MCE, the perfusion area of a septal branch can be shown on echocardiography after injection of echocardiographic contrast medium. The use of this technique has proved to be a useful influence on interventional strategy in 15% to 20% of cases, by either changing the target vessel or prompting the procedure to be aborted when remote parts of the myocardium light up. In addition, it has improved the success rate of ASA, despite lower infarct sizes (33,34). The latest innovation in ASA is 3-dimensional MCE-guided ASA. With added accuracy and the ability to quantify the expected size of myocardial tissue affected by the ablation, this new technique has the potential to further improve the safety and effectivity of ASA (25).

However, substantial outcome studies on the use of 3-dimensional MCE guided ASA have yet to be conducted.

The introduction of percutaneous mitral valve plication with use of the MitraClip (Abbott Vascular, Santa Clara, California) has brought an interventional alternative to ASA for the treatment of obstructive HCM. To date, only 2 small studies have been conducted, but initial results are promising (36,37). Additional studies with long-term follow-up will be necessary to determine the role of this technique in the treatment of patients with obstructive HCM and increased operative risk. One of the main questions will be whether the technique should be
complementary to ASA or whether the MitraClip can serve as an independent alternative.

**Predictors of Outcome.** Recently, 2 large registries were established to identify predictors of outcome following ASA. The North American Registry included 875 patients who underwent ASA at 9 institutions in the United States and Canada and were followed up during a median of 2.1 years (38). Survival estimates at 1, 5, and 9 years were 97%, 86%, and 74%, respectively. Baseline predictors of mortality were a higher NYHA functional class and a lower ejection fraction. Post-procedural predictors were all concordant in showing that a more effective ablation was associated with a lower likelihood of death (smaller septal thickness 3 months post-ablation, not taking beta-blockers post-ablation, and absence of the need for repeat procedures). Of note is that a relationship between failed myectomy and death has also been reported before (39).

The European ASA (Euro-ASA) registry included 1,275 patients who underwent ASA at 10 tertiary centers from 7 European countries and were followed-up during a median of 5.7 years (40). The 30-day mortality rate was 1%, which is similar to the rates following ASA and myectomy in the 2015 meta-analysis (16). Survival estimates at 1, 5, and 10 years were 98%, 89%, and 77%, respectively. Remarkably, this means that the 10-year survival rates of the largest ASA and largest myectomy cohort to date are identical (Schaff et al. [41] reported a 10-year survival rate of 77% in 749 patients operated on at the Mayo Clinic in Rochester, Minnesota). Baseline predictors of mortality were higher age, NYHA functional class, and septal thickness. The volume of alcohol used for ASA was found to be a predictor of LVOT reduction and was associated with a higher incidence of complete heart block (Figure 2). Reduction of the LVOT gradient was found to be of particular importance because it was an independent predictor of survival and symptom relief at last follow-up. However, a (transient) periprocedural complete heart block resulted in permanent pacemaker implantation in one-third of patients (12% of all patients). On the basis of these findings, ASA alcohol volumes ranging between 1.5 and 2.5 ml were deemed well balanced in terms of efficacy and safety for most patients (Central Illustration).

**Conclusions**

Twenty years after the introduction of ASA for the treatment of obstructive HCM, the arrhythmogenicity of the ablation scar appears to be overemphasized. When systematically reviewing all studies comparing ASA with myectomy with long-term follow-up, (aborted) sudden cardiac death and mortality rates were found to be similarly low. Instead, the focus should be shifted toward how to lower the rate of reinterventions and pacemaker implantations following ASA because ASA still seems to be inferior to myectomy in this regard. Part of the reason for this difference is that ASA is limited by the route of the septal perforators, whereas myectomy is not. Improvement in this area may be achieved, however, by: 1) confining ASA to HCM centers of excellence with high operator volumes; 2) improving patient selection by means of multidisciplinary heart teams; 3) the use of (3-dimensional) MCE for selecting the correct septal (sub)branch; and 4) the use of appropriate amounts of alcohol for ASA.

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