Influence of Septal Thickness on the Clinical Outcome After Alcohol Septal Ablation in Hypertrophic Cardiomyopathy

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Background—We assessed the influence of interventricular septal thickness (IVSd) on the clinical outcome and survival after alcohol septal ablation (ASA) in patient with hypertrophic cardiomyopathy.

Methods and Results—We analyzed 531 patients with hypertrophic cardiomyopathy (age: 56±14 years, men 55%) treated with ASA. Survival status was obtained 7.9±4.0 years after ASA. Baseline IVSd was inversely associated with survival (hazard ratio [HR] for 1 mm increment, 1.13; confidence interval, 1.05–1.21; P<0.001) after adjustment for age, sex, body mass index, and ASA-performing center. Compared with patients with baseline IVSd <20 mm, patients with baseline IVSd ≥25 mm had reduced survival (HR, 5.0; CI, 2.1–12), whereas patients with baseline IVSd 20 to 24 mm had similar survival (HR, 1.4; CI, 0.7–2.8). Baseline IVSd was not correlated with New York Heart Association class, Canadian Cardiology Society class, or syncope. Clinical outcome was assessed 0.6±0.6 years after ASA. IVSd was not related to left ventricular outflow tract gradient reduction at rest (P=0.883) or during Valsalva maneuver (P=0.885). The proportion of patients in New York Heart Association class 3 to 4 was reduced from 86% to 10%; in Canadian Cardiology Society class 3 to 4 from 26% to 2%; and with syncope from 25% to 2%. There were no correlations between baseline IVSd and New York Heart Association class (P=0.067), Canadian Cardiology Society class (P=0.106), or syncope (P=0.426) after ASA.

Conclusions—ASA had equal effects on left ventricular outflow tract gradients and symptoms throughout the spectrum of septal hypertrophy. Severe septal hypertrophy before ASA remained a marker of reduced survival after ASA with a 5-fold increased risk of all-cause mortality in patients with baseline IVSd ≥25 mm compared with patients with baseline IVSd <20 mm. (Circ Cardiovasc Interv. 2016;9:e003214. DOI: 10.1161/CIRCINTERVENTIONS.115.003214.)

Key Words: cardiomyopathy ■ chest pain ■ dyspnea ■ hypertrophy ■ syncope

Massive myocardial hypertrophy in hypertrophic cardiomyopathy (HCM) has traditionally been considered a risk factor for sudden cardiac death.1,2 Hypertrophy of the interventricular septum predisposes to left ventricular outflow tract (LVOT) obstruction.3 Because of the complex hemodynamics of the LVOT, the obstruction may extend to midventricular obstruction and cause systolic obliteration of the ventricular cavity.4 Thus, myectomy has been suggested as the treatment of choice in patients with pronounced septal hypertrophy, severe symptoms, and high LVOT gradients.1,5,6 The association between massive hypertrophy (wall thickness ≥30 mm) and mortality has not been reported consistently in previous reports of general HCM populations.2,7-9 Also, Desai et al.6 found no association between hypertrophy and survival in a cohort of myectomy-treated patients (n=699).

During the past 2 decades, alcohol septal ablation (ASA) has developed into an effective and safe procedure, with reports of favorable long-term outcomes from several centers.10-14 However, the influence of the degree of septal hypertrophy on the outcome after ASA in patients with HCM has been described only briefly.11 In this multicenter registry study, we evaluated the influence of the degree of septal hypertrophy at baseline on the clinical outcome and survival after ASA treatment.

Methods

Study Population

This study population represents a merged cohort of patients participating in 2 previously reported studies.12,14 We included HCM patients treated with ASA between January 1996 until March 2010 from 5 Northern European centers including (1) Heart and Diabetes Center Nordrhein-Westfalen, Bad Oeynhausen, Germany, 2010 from 5 Northern European centers including (1) Heart and Diabetes Center Nordrhein-Westfalen, Bad Oeynhausen, Germany, (2) Heart and Diabetes Center Nordrhein-Westfalen, Bad Oeynhausen, Germany, (3) Heart and Diabetes Center Nordrhein-Westfalen, Bad Oeynhausen, Germany, (4) Heart and Diabetes Center Nordrhein-Westfalen, Bad Oeynhausen, Germany, (5) Heart and Diabetes Center Nordrhein-Westfalen, Bad Oeynhausen, Germany.
WHAT IS KNOWN

- Severe hypertrophy is associated with reduced survival and sudden cardiac death in patients with HCM.
- ASA is a safe and effective treatment of LVOT obstruction in patients with hypertrophic obstructive cardiomyopathy.
- Survival after ASA is comparable to survival in the background population.

WHAT THE STUDY ADDS

- ASA is an effective treatment of LVOT obstruction and associated symptoms in patients with severe septal hypertrophy.
- Severe septal hypertrophy is associated with reduced survival also after ASA.

Alcohol Septal Ablation

ASA was performed according to a previously reported protocol.\(^1\)\(^2\) In brief, a septal perforating artery supplying the obstructing part of the septum was identified on the coronary angiogram and chosen as target vessel. After occlusion of the septal target branch by a percutaneous coronary intervention balloon, the area of perfusion was visualized by echocardiography after injection of 1 to 2 mL of echocardiography contrast medium.\(^1\)\(^9\) The risk of backflow into the left anterior descending artery was tested for by injection of radiographic contrast into the target vessel during fluoroscopy. Under analgesic medication, a volume of \(\approx 0.1\) mL \(96\%\) alcohol per mm septum was slowly injected into the target vessel through the balloon catheter. The alcohol volume was adjusted in each case based on anatomy and septal thickness according to previous reports.\(^1\)\(^2\)\(^3\)\(^10\)\(^11\)\(^12\) The balloon was deflated and removed after 10 minutes. The occlusion of the target vessel was verified angiographically at the end of the procedure.

ASA Indication and Study Outcomes

The indication for ASA was: (1) presence of severe drug refractory symptoms (New York Heart Association [NYHA] class 3–4 symptoms, in combination with (2) LVOT gradients \(\geq 50\) mm Hg at rest or \(\geq 100\) mm Hg during provocation by a Valsalva maneuver, or, alternatively, by dynamic exercise testing. Canadian Cardiology Society (CCS) class 3 to 4 angina or repeated syncope was considered alternative symptomatic indications.

The effect of ASA on these parameters has previously been reported.\(^1\)\(^2\)\(^3\)\(^4\)\(^11\)\(^12\)\(^14\) In this study, we analyzed the influence of baseline septal hypertrophy on ASA efficacy in terms of clinical end points and long-term survival after ASA.

Statistics

Baseline data, follow-up data, and survival status were analyzed using SAS statistical software package version 9.3. Data are presented as mean±SD when normally distributed and median (quartiles) when non-normally distributed. Proportions are presented as percentages (%). A paired Student \(t\) test was used for paired comparisons of continuous variables. Unpaired Student \(t\) test was used for comparison of continuous variables between 2 groups and ANOVA was used for testing of continuous variables between multiple groups. Proportions were compared with \( \chi^2 \) test or Fishers exact test. All comparisons of categorical outcomes were unpaired. For presentation of data, patients were stratified into mild (IVSd <20 mm), moderate (IVSd 20–24 mm), and severe (IVSd \(\geq 25\) mm) hypertrophy. The term massive hypertrophy was used for IVSd \(\geq 30\) mm.\(^1\)\(^2\) Summary data are presented according to this stratification. Regression analysis of continuous variables was performed by linear regression with IVSd treated as a continuous variable. Regression analyses of categorical variables were performed by logistic regression with IVSd treated as a continuous variable. The effect of IVSd, as continuous variable, on survival was analyzed in: (1) a univariate Cox regression model and (2) a Cox proportional hazards model adjusted for the possible effects of predefined confounders (age, sex, body mass index [BMI], and ASA-performing center). Other baseline and procedural variables were tested in a stepwise forward regression analysis and kept in the model if significance (\(P < 0.05\)) was reached. No postprocedural variables were allowed in the model. The model was controlled for interactions between variables. Hazard ratios (HRs) were calculated for each of the moderate and severe hypertrophy group versus the mild hypertrophy group. HRs were also calculated treating LVOT as continuous variable and represent the HR for 1 mm increment of IVSd.

Results

Baseline Characteristics

Data on 531 patients (age: 56±14 years; males 55%; follow-up: 7.9±4.0 years) was analyzed. Forty-eight patients died during 4189 patient-years (mortality rate: 1.1% per year). Cardiovascular death was confirmed in 18 patients (38%), and 16 of these deaths were categorized as sudden cardiac death. Ten patients (21%) died of cancer diseases and 5 (10%) from neurological diseases. The remaining 6 patients died of other noncardiovascular diseases. The cause of death remained uncertain in 9 patients. An implantable cardioverter defibrillator was implanted in 11 patients (3 for secondary prevention) before and in 34 patients (7 for secondary prevention) after ASA. Baseline characteristics stratified by intervals of IVSd are shown in Table 1. IVSd was correlated with left ventricular posterior wall dimension (\( \beta = 0.58\); \(P < 0.001\); \(r^2 = 0.15\)), increased left atrial diameter (LAd) (\( \beta = 0.13\); \(P < 0.001\); \(r^2 = 0.05\)) and LVOT gradients at rest (\( \beta = 0.01\); \(P = 0.030\); \(r^2 = 0.009\)). There were no correlations between symptoms and LVOT gradient during Valsalva maneuver (Table 1).

Cardiac Remodeling After ASA

Left atrial dimension decreased from 48±7 to 46±7 mm (\(P < 0.001\)) with no association between baseline IVSd and the reduction of left atrial dimension (\(P = 0.934\)). Left ventricular end-diastolic dimension increased from 45±6 mm to 46±6 mm (\(P = 0.003\)), and baseline IVSd was correlated with...
Jensen et al  Septal Thickness and Alcohol Septal Ablation

the increase in left ventricular end-diastolic dimension (0.2 mm left ventricular end-diastolic dimension increase per mm IVSd; \(P=0.007; r^2=0.018\)). Left ventricular posterior wall dimension was reduced from 13±3 to 12±2 mm (\(P<0.001\)) with a weak association between left ventricular posterior wall dimension reduction and baseline IVSd (\(P=0.063\)). Left ventricular ejection fraction was reduced from 67±12% to 66±11% (\(P=0.010\)), and the reduction was not associated with baseline IVSd.

### Effect of IVSd on Clinical Outcome After ASA

The symptomatic and echocardiographic effects of ASA were assessed 0.6±0.6 years after the ASA. The LVOT gradient was reduced from 60 (35–80) to 7 (1–20) mm Hg (\(P<0.001\)) at rest and from 110 (90–140) to 30 (1–60) mm Hg (\(P<0.001\)) during Valsalva maneuver. There was no correlation between baseline IVSd and the absolute reduction in LVOT gradient at rest (\(P=0.883\)) or during Valsalva maneuver (\(P=0.885\)) (Figure 1). The proportion of patients in NYHA class 3 to 4 was reduced from 86% to 14% (\(P=0.060\)); there was no association between baseline IVSd and NYHA class before (\(P=0.820\)) or after (\(P=0.426\)) ASA (Table 2). The proportion of patients with syncope decreased from 25% to 2% after ASA with no association between baseline IVSd and the proportion of patients with syncope before (\(P=0.820\)) or after (\(P=0.426\)) ASA.

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of Patients Treated With Alcohol Septal Ablation Stratified According to IVSd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrophy (n)</td>
</tr>
<tr>
<td>IVSd, mm</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td>Echocardiography</td>
</tr>
<tr>
<td>IVSd, mm</td>
</tr>
<tr>
<td>LVEDd, mm</td>
</tr>
<tr>
<td>LVWPd, mm</td>
</tr>
<tr>
<td>EF, %</td>
</tr>
<tr>
<td>LAd, mm</td>
</tr>
<tr>
<td>LVOT gradient</td>
</tr>
<tr>
<td>Rest, mm Hg</td>
</tr>
<tr>
<td>Valsalva, mm Hg</td>
</tr>
<tr>
<td>Symptoms</td>
</tr>
<tr>
<td>Syncope, %</td>
</tr>
<tr>
<td>NYHA 3–4, %</td>
</tr>
<tr>
<td>CCS 3–4, %</td>
</tr>
<tr>
<td>AF, %</td>
</tr>
<tr>
<td>Hypertension, %</td>
</tr>
</tbody>
</table>

Results are presented as mean±SD, median (quartiles), or as percentage. AF indicates atrial fibrillation; BMI, body mass index; CCS, Canadian Cardiology Society; EF, ejection fraction; IVSd, interventricular septum dimension; LAd, left atrial diameter; LVEDd, left ventricular end-diastolic dimension; LVOT, left ventricle outflow tract; LVWPd, left ventricular posterior wall dimension; and NYHA, New York Heart Association.

![Figure 1. Reduction of the left ventricular outflow tract (LVOT) gradients at rest and during Valsalva maneuver after alcohol septal ablation (ASA) stratified according to baseline interventricular septum dimension (IVSd). There were no significant differences between the responses to ASA in different IVSd categories.](http://circinterventions.ahajournals.org/)

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The 10-year survival after ASA was 83%. IVSd, handled as a continuous variable, was not significantly associated with survival in a unadjusted univariate regression analysis ($P=0.051$).

In a multivariable proportional hazard model adjusted for the possible confounding effects of age ($P<0.001$), sex ($P=0.220$), BMI ($P=0.020$), and ASA-performing center ($P=0.039$), there was an inverse association between baseline IVSd and survival (HR for 1 mm increment, 1.13; CI, 1.05–1.21; $P<0.001$). The multivariate model satisfied the proportional hazards assumption for IVSd as a continuous variable. There were no interactions between IVSd and age ($P=0.480$), BMI ($P=0.337$), sex ($P=0.116$), or ASA-performing center ($P=0.086$), respectively (Table II in the Data Supplement).

Other possible predictors of all-cause mortality were tested in a stepwise forward regression analysis without reaching significance (Table 3). When analyzing IVSd as a categorical variable in a multivariate model that satisfy the proportional hazards assumption, the IVSd $\geq 25$ mm was associated with a 5-fold risk of all-cause mortality (HR, 5.0; CI, 2.1–12; $P<0.001$), and IVSd 20 to 24 mm was not associated with reduced all-cause mortality ($P=0.323$) compared with patients with IVSd $<20$ mm (Table 2). Baseline IVSd was inversely correlated with age ($\beta=-0.03$; $P<0.001$; $r^2=0.03$). There was no association between IVSd and BMI ($P=0.851$).

IVSd in males was 20.1±3.9 mm and 19.5±4.1 mm in females ($P=0.134$). Mean IVSd ranges from 17.1±3.9 mm to 20.3±3.8 mm.

### Figure 2.
New York Heart Association (NYHA) functional class before and after alcohol septal ablation (ASA) stratified according to baseline interventricular septum dimension (IVSd). There were no significant differences between the responses to ASA in different IVSd categories.

### Table 2. Clinical Outcome in Patients Treated With ASA Stratified According to IVSd

<table>
<thead>
<tr>
<th>Hypertrophy, n</th>
<th>Total (n=531)</th>
<th>Mild (n=278)</th>
<th>Moderate (n=190)</th>
<th>Severe (n=63)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVSd, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up, y</td>
<td>7.8±4</td>
<td>7.5±4</td>
<td>8.5±4</td>
<td>7.5±4</td>
<td>0.029</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVSd, mm</td>
<td>16±4</td>
<td>15±3</td>
<td>17±4</td>
<td>20±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDd, mm</td>
<td>46±6</td>
<td>44±7</td>
<td>46±5</td>
<td>47±7</td>
<td>0.513</td>
</tr>
<tr>
<td>LVPWd, mm</td>
<td>12±2</td>
<td>12±2</td>
<td>13±2</td>
<td>14±3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EF, %</td>
<td>66±11</td>
<td>65±11</td>
<td>67±11</td>
<td>66±11</td>
<td>0.124</td>
</tr>
<tr>
<td>LAa, mm</td>
<td>46±7</td>
<td>45±6</td>
<td>47±7</td>
<td>47±7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVOT gradient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest, mm Hg</td>
<td>7 (1–20)</td>
<td>1 (1–16)</td>
<td>8 (1–25)</td>
<td>19 (3–33)</td>
<td>0.001</td>
</tr>
<tr>
<td>Valsalva, mm Hg</td>
<td>30 (1–60)</td>
<td>27 (1–59)</td>
<td>35 (1–60)</td>
<td>46 (20–77)</td>
<td>0.001</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope, %</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0.426</td>
</tr>
<tr>
<td>NYHA 3–4, %</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>13</td>
<td>0.067</td>
</tr>
<tr>
<td>CCS 3–4, %</td>
<td>2</td>
<td>3</td>
<td>0.6</td>
<td>0</td>
<td>0.106</td>
</tr>
<tr>
<td>Survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, CI</td>
<td>N/A</td>
<td>1</td>
<td>1.4 (0.7–2.8)</td>
<td>5.0 (2.1–12)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>48</td>
<td>19</td>
<td>18</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Annual mortality rate (% per year)†</td>
<td>1.1</td>
<td>0.9</td>
<td>1.1</td>
<td>2.3</td>
<td>0.0284</td>
</tr>
</tbody>
</table>

Results are presented as mean±SD, median (quartiles), or as percentage. ASA indicates alcohol septal ablation; BMI, body mass index; CCS, Canadian Cardiology Society; CI, 95% confidence interval; EF, ejection fraction; HR, hazard ratio; IVSd, interventricular septum dimension; LAa, left atrial diameter; LVEDd, left ventricle end-diastolic dimension; LVOT, left ventricle outflow tract; LVPWd, left ventricular posterior wall dimension; and NYHA, New York Heart Association.

*P value represents significance level of a multivariate Cox regression model adjusted for the confounding effects of age, sex, BMI, and ASA-performing center with IVSd handled as continuous variable (HR for 1 mm, 1.13; CI, 1.05–1.21).

†Unadjusted observed mortality rate.
between ASA-performing centers \((P<0.001)\). Unadjusted survival curves are presented in Figure 3. There was an association of borderline significance between alcohol volume and reduced survival \((HR, 1.17; CI, 0.99–1.4; P=0.071)\) in a univariate model. In the multivariate model, however, alcohol volume \((P=0.155)\) was clearly not associated with reduced survival after including IVSd and adjusting for prespecified confounders (Table 3).

### Massive Hypertrophy

Ten patients (age: 50±14 years) had IVSd \(\geq 30\) mm at baseline. LVOT gradients were reduced from 85 (65–93) mm Hg to 19 (1–29) mm Hg at rest \((P<0.001)\) and from 113 (93–168) mm Hg to 50 (11–65) mm Hg \((P<0.001)\) during Valsalva maneuver. Syncope was reduced from 10% to 0%; NYHA class 3 to 4 from 80% to 30%, and CCS class 3 to 4 from 20% to 0%. The subgroup of patients with IVSd \(\geq 30\) mm had increased all-cause mortality compared with patients with IVSd<20 mm \((HR, 6.6; CI, 1.5–30)\) after adjustment for age, sex, BMI, and ASA-performing center.

### Discussion

The major novel findings in this study of outcomes after ASA were that the success rate of ASA was independent of septal thickness and that survival after ASA was inversely related to septal thickness. Compared with patients with mild hypertrophy, we found a 5-fold risk of all-cause mortality in patients with IVSd\(\geq 25\) mm \((63/531\) patients) after adjustments for confounding effects of age, sex, BMI, and ASA-treating center. The degree of hypertrophy has been shown to correlate with the severity of diastolic dysfunction and intramyocardial fibrosis, confirming that IVSd is a readily available important structural marker of prognosis and disease severity in patients with HCM with or without ASA. The degree of hypertrophy in patients with HCM has previously been negatively associated with survival in studies by Spirito et al\(^2\) \((n=480)\) and Elliott et al\(^7\) \((n=630)\), whereas a smaller study by Olivotto et al\(^23\) \((n=237)\) failed to confirm this relationship. Likewise, Desai et al\(^6\) failed to confirm the association using univariate analysis in a large myectomy cohort \((n=699)\).

In this study, we demonstrated that the univariate analysis of the association between IVSd and survival did not reach significance. Importantly, we adjusted the model with predefined possible confounders and found that age was negatively correlated with IVSd. Thus, the expected relatively good survival in the youngest patients may be counterbalanced by reduced survival in cases with more pronounced hypertrophy. It is not surprising that this relationship is missed in a univariate analysis. By adjusting for confounders, we demonstrated a clinically important 5-fold risk of death in subjects with IVSd\(\geq 25\) mm compared with patients with IVSd<20 mm. In this manner, we confirmed the inverse relationship between hypertrophy and survival in our ASA-treated HCM cohort, but in absence of procedure-related association with survival, our findings support the long-term safety of the ASA procedure. These results and the reduced survival compared with the background population reported

### Table 3. Baseline Predictors of Survival in Patients Treated With ASA

<table>
<thead>
<tr>
<th>Variable of Interest</th>
<th>(P) Value</th>
<th>HR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVSd, mm</td>
<td>&lt;0.001</td>
<td>1.13 (1.05–1.21)</td>
</tr>
<tr>
<td>Predefined adjustments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>&lt;0.001</td>
<td>1.07 (1.04–1.11)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>0.220</td>
<td>…</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>0.020</td>
<td>0.91 (0.83–0.98)</td>
</tr>
<tr>
<td>ASA-performing center</td>
<td>0.039*</td>
<td>…</td>
</tr>
</tbody>
</table>

**Stepwise forward regression analysis**

\(ASA\) date† | 0.294 |
| Alcohol volume, ml | 0.155 |

**LVOT \(^{\dagger}\) gradients**

<table>
<thead>
<tr>
<th>LVOT gradient</th>
<th>(P) Value</th>
<th>HR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest, mm Hg</td>
<td>0.491</td>
<td>…</td>
</tr>
<tr>
<td>Valsalva, mm Hg</td>
<td>0.948</td>
<td>…</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.264</td>
<td>…</td>
</tr>
<tr>
<td>LVEDd, mm</td>
<td>0.478</td>
<td>…</td>
</tr>
<tr>
<td>LVPWd, mm</td>
<td>0.148</td>
<td>…</td>
</tr>
<tr>
<td>LAd, mm</td>
<td>0.113</td>
<td>…</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.238</td>
<td>…</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.145</td>
<td>…</td>
</tr>
<tr>
<td>NYHA</td>
<td>0.300</td>
<td>…</td>
</tr>
<tr>
<td>CCS</td>
<td>0.892</td>
<td>…</td>
</tr>
<tr>
<td>Syncope</td>
<td>0.99</td>
<td>…</td>
</tr>
</tbody>
</table>

ASA indicates alcohol septal ablation; BMI, body mass index; CCS, Canadian Cardiology Society; CI, 95% confidence interval; HR, hazard ratio; IVSd, interventricular septum diastolic dimension; LAd, left atrial diameter; LVEDd, left ventricular end-diastolic dimension; LVOT, left ventricular outflow tract; LVPWd, left ventricular posterior wall dimension; and NYHA, New York Heart Association.

*No HR given in respect participating centers.
†Date of ASA: analyzed for possible effect of learning curves or treatment development.
by Sorajja et al\textsuperscript{9} in a general HCM cohort with massive hypertrophy (≥30 mm) illustrate that although HCM is a benign condition in the majority of patients, small subsets of patients are at increased risk, and patients with pronounced hypertrophy represent such a subset.

In this multicenter approach, we accumulated a ASA-treated HCM cohort sufficiently large to separately analyze clinical outcomes of ASA in the subgroup of patients with severe hypertrophy (IVSd≥25 mm). We found a homogenous effect of ASA on LVOT gradients and symptoms in patients with all degrees of hypertrophy. The LVOT gradients at rest and during Valsalva maneuver were higher in patients with more pronounced hypertrophy at baseline, and this relation was preserved after ASA, leaving mostly insignificant residual gradients in patients with the highest IVSd at baseline. In potential agreement with our findings, Sorajja et al\textsuperscript{13} (n=177) found that residual LVOT gradients after ASA were associated with reduced survival, but effects of baseline hypertrophy on survival was not assessed in that study. In this study, we analyzed the clinical outcome 0.6±0.6 years after ASA. A previous study from the Scandinavian HOCM (hypertrophic obstructive cardiomyopathy) database have shown that most reinterventions (myectomy or re-ASA) were performed between 12 and 24 months after the first ASA procedure, and LVOT gradients after 24 months were stable with low reinterventions rates.\textsuperscript{14} Thus, the final long-term residual LVOT gradients in this cohort may be lower than that reported in this study.

Limitations
In this multicenter cohort, the number of procedure-related data are limited, and the number of treated septal branches is not available. It is important to notice that this cohort represents a cohort of patients with HCM selected for suitability of performing ASA. Hemodynamic and anatomic features have been thoroughly evaluated, comorbidities have been assessed, and treatment options have been discussed in each case before deciding on treatment strategy. In this process, many patients have been selected for other treatment options such as medical or surgical therapy and implantable cardioverter defibrillator implantation for primary sudden cardiac death prevention. Such patient selection represents an inherent limitation to studies of this kind. Thus, this cohort has been subject to profound selection, and similar results can only be expected in patients selected likewise.

Conclusions
ASA had equal effects on LVOT gradients and symptoms regardless of the degree of septal hypertrophy. Severe septal hypertrophy before ASA remained a marker of reduced survival after ASA with a 5-fold increased risk of all-cause mortality in patients with IVSd >25 mm compared with patients with IVSd <20 mm.

ASA can be successfully used in treatment of LVOT obstruction caused by any degree of septal hypertrophy in patients with HCM. The excess mortality in patients with severe septal hypertrophy before ASA illuminates an unresolved issue in treatment of HCM patients in general and patients treated with ASA in particular. Severe hypertrophy is considered to be a risk factor for sudden cardiac death, and much effort has been invested in analyzing the risk of sudden cardiac death in HCM. With contemporary HCM treatment, the risk of sudden cardiac death is probably <1% per year, which implies certain limitation to the effort of developing improved risk stratification algorithms. This study returns the attention to reduction of all-cause mortality as the most important clinical goal and end point in future studies. The survival rates in contemporary HCM cohorts have been reported to be close to those of the background population, but these data may conceal poor outcomes of patients with severe hypertrophy. Attention should be raised on the subgroup of patients with severe hypertrophy (≥225 mm) that in this study exhibited a 5-fold increased risk of death compared with other patients with HCM treated with ASA.

Disclosures
Dr Bundgaard receives lecture fees from AstraZeneca, Shire, Sanofi-Avenis, and MSD. The other authors report no conflicts.

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Influence of Septal Thickness on the Clinical Outcome After Alcohol Septal Alation in Hypertrophic Cardiomyopathy

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The influence of septal thickness on the clinical outcome after alcohol septal ablation in hypertrophic cardiomyopathy

Morten K. Jensen¹, Linda Jacobsson², Vibeke Almaas³, Frank van Buuren⁵, Peter R. Hansen⁴, Thomas F. Hansen⁴, Svend Aakhus³, Maria J. Eriksson², Henning Bundgaard¹, Lothar Faber⁵

Supplemental Table 1 Baseline characteristics of included and excluded patients

<table>
<thead>
<tr>
<th></th>
<th>Included</th>
<th>Excluded</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>531</td>
<td>121</td>
<td></td>
</tr>
<tr>
<td>Follow up</td>
<td>7.9(4.0)</td>
<td>3.5(2.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>56.1(14.1)</td>
<td>57.4(14.9)</td>
<td>0.360</td>
</tr>
<tr>
<td>BMI</td>
<td>27.1(4.0)</td>
<td>28.6(5.1)</td>
<td>0.007</td>
</tr>
<tr>
<td>LVOT gradient (rest)</td>
<td>60(35-80)</td>
<td>62(48-87)</td>
<td>0.207</td>
</tr>
<tr>
<td>LVOT gradient (Valsalva)</td>
<td>111(90-140)</td>
<td>86(64-118)</td>
<td>0.080</td>
</tr>
<tr>
<td>Syncope (%)</td>
<td>25</td>
<td>18</td>
<td>0.114</td>
</tr>
<tr>
<td>NYHA 3-4 (%)</td>
<td>86</td>
<td>95</td>
<td>0.009</td>
</tr>
<tr>
<td>CCS 3-4 (%)</td>
<td>26</td>
<td>19</td>
<td>0.115</td>
</tr>
<tr>
<td>AF (%)</td>
<td>16</td>
<td>0</td>
<td>0.229</td>
</tr>
</tbody>
</table>

BMI body mass index. LVOT left ventricle outflow tract. NYHA New York Heart Association classification. CCS Canadian Cardiology Society classification. AF Atrial fibrillation. Results are presented as mean +/- SD, median (quartiles) or as percentage.
Supplemental Table 2 Analysis of interactions with the effect of IVSd on survival in a multivariate Cox regression model adjusted for age, sex, BMI and ASA performing center.

<table>
<thead>
<tr>
<th></th>
<th>HR(CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (p=0.480)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (p=0.116)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.18(1.08-1.29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>1.05(0.93-1.18)</td>
<td>0.457</td>
</tr>
<tr>
<td>BMI (p=0.337)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA performing center (p=0.086)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.17(1.09-1.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>1.05(0.89-1.24)</td>
<td>0.587</td>
</tr>
<tr>
<td>3</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

IVSd Interventricular septum dimension. BMI Body mass index. ASA Alcohol septal ablation. HR Hazard ratio for the effect of IVSd on survival. CI Confidence interval.
*For three centers HR’s cannot be calculated due to low number of patients (<25) and events (<5)