Long-term survival after alcohol septal ablation for hypertrophic obstructive cardiomyopathy: a comparison with general population

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Aims
We decided to determine the long-term survival of patients after alcohol septal ablation (ASA) for hypertrophic obstructive cardiomyopathy (HOCM) and compare this with the general population.

Methods and results
A total of 178 highly symptomatic, consecutive patients (58 ± 12 years, 53% women) were treated by ASA between April 1998 and April 2013 and followed-up for 4.8 years (IQR 2.1–7.5). At baseline, 155 patients (87%) suffered from dyspnoea ≥ 3 class of NYHA; at the most recent examination, 87 patients (49%) and 23 patients (13%) reported dyspnoea of NYHA class 1 and ≥ 3, respectively. The left ventricular outflow gradient was significantly reduced (68 ± 42 vs. 20 ± 25 mmHg; P < 0.01). A total of 19 deaths (11%) occurred during 925 patient-years, which means an overall mortality rate of 2.1% per year. Survival free of all-cause mortality at 1, 5, and 10 years was 97% (95% CI, 93–99%), 92% (95% CI, 87–96%), and 82% (95% CI, 70–90%), respectively. This observed mortality was comparable to the expected survival for age- and sex-comparable general population (P = 0.34). According to multivariate analysis, the only independent predictor of all-cause mortality was age at ASA (hazard ratio 1.09, 95% CI 1.04–1.14; P < 0.01).

Conclusions
This study suggests that in patients with HOCM and important symptoms who underwent ASA, long-term survival after the procedure did not differ significantly from that of the general population.

Keywords
Alcohol septal ablation • Prognosis • Hypertrophic cardiomyopathy

Introduction
Hypertrophic cardiomyopathy (HCM) is an inherited myocardial disease characterized by cardiac hypertrophy in the absence of hypertension or heart valve disease. The left ventricular (LV) tract obstruction is present in approximately two-thirds of patients. For highly symptomatic patients with obstruction who are not responsive to medical therapy, a surgical myectomy, alcohol septal ablation (ASA), or double-chamber pacing is recommended.1,2 Although acceptable outcomes of several single-centre studies have led to the increased use of ASA,2–8 there is still debate surrounding the long-term safety of this procedure resulting in myocardial scarring and the potential risk of ventricular arrhythmias.

Recently, it has been demonstrated in the Mayo Clinic series that the long-term survival of carefully selected ASA patients was comparable both to patients after surgical myectomy and the general US population.9 To extend this evidence to European patients, we decided to determine the long-term survival of ASA patients and compare them with the general population.

Methods

Study patients
A total of 178 consecutive patients were treated by ASA between April 1998 and April 2013. Data come from two institutions that closely coordinate their HCM programme. Some of the patients were included in previous reports.

Alcohol septal ablation was offered to highly symptomatic (New York Heart Association or Canadian Cardiovascular Society class II) adult patients, who were diagnosed with HOCM that was refractory to...
medical therapy or were intolerant of medical treatment. A resting LV outflow gradient was > 30 mmHg and/or 50 mmHg with provocative manoeuvres or after extrasystole, ventricular septal thickness had to be ≥ 15 mm and there had to be an absence of significant mitral valve disease or the need for other cardiac operations (Figure 1A). All therapeutic options (myectomy vs. ASA vs. pacing) were discussed with each patient and a decision was made after careful explanation of the risks and potential benefits and also institutional experience and the results of each alternative.

Alcohol septal ablation

All procedures were performed by two experienced interventional cardiologists. Details of the ASA technique were published previously.6,10 Briefly, a temporary pacemaker was placed in the right ventricle in all patients without previous permanent pacemaker implantation. Alcohol ablations were guided by myocardial contrast echocardiography; injection of desiccated alcohol 96% was usually followed by a decrease in pressure gradient (Figure 1B and C). Patients were observed in the coronary care unit for ≥ 2 days; the pacemaker lead was then removed if no episode of high-degree atrioventricular block occurred. Most of the patients remained on continuous cardiac telemetry until discharge. Blood was withdrawn for MB fraction of creatine kinase (CK-MB) at 6 h intervals for 2 days.

Follow-up

All patients were routinely asked to undergo a clinical check-up 3–6 months after ASA and then every year. The follow-up program included clinical examination, evaluation of 12-lead ECG, and echocardiographic examination (Figure 1D). The clinical evaluation was mainly focused on the symptomatic status of patients, risk stratification of sudden death, and haemodynamic changes assessed by Doppler echocardiography. In patients with an implanted pacemaker or defibrillator, the device’s memory and function were assessed; appropriate and inappropriate discharges of defibrillators (ICD) were registered. All clinical adverse events were confirmed by reviewing the medical records and the national database of the departed. For deceased patients who died outside our institution, interviews with next of kin or mail communication with them was performed to find out the cause of death.

Definitions

The primary endpoint was all-cause mortality and the secondary endpoint was all-cause mortality or appropriate ICD discharge; both endpoints were compared with the expected survival of the age- and sex-matched general population. Sudden death was defined as sudden and unexpected death within 1 h after a witnessed collapse in previously stable patients. Death within 30 days after ASA was considered ASA related. Complete heart block was defined as a third-degree AV block.
of at least 10 s in duration. In patients implanted with an ICD, device interventions triggered by ventricular fibrillation or ventricular tachycardia were considered appropriate. Appropriate discharge of ICD for the therapy of malignant arrhythmias was considered in calculations of the secondary endpoint. The occurrence of stroke was defined according to standard criteria.11

Statistical analysis

Normally distributed data are presented as means ± standard deviation (± SD) and non-normally distributed data as medians with IQR. The distribution of data was evaluated by the Kolmogorov–Smirnov test. Student’s t-tests, Wilcoxon’s tests, and Chi-square tests were used when appropriate. The Kaplan–Meier survival analysis was used to estimate survival with 95% confidence intervals. Expected survival was calculated according to age- and gender-specific mortality rates obtained from the Demographic Yearbook of the Czech Republic (http://www.czso.cz/csu/2012ediciplan.nsf/engpubl). Mortality rates were calculated for each individual and combined to form an expected summary curve for the general population. Expected and observed mortality were compared by using the one-sample log-rank test, which provides a standardized mortality ratio and the 95% confidence interval. Cox proportional hazards regression was used to identify predictors of all-cause mortality and all-cause mortality combined with appropriate ICD discharge. The following parameters were evaluated, firstly in a univariate model: age, gender, baseline and residual dyspnoea and synapses, baseline and residual LV pressure gradient, baseline and residual septal thickness, baseline and residual left atrium diameter and post-ASA CK-MB max. Variables with a P-value < 0.15 were then entered into a multivariate analysis, which was performed using a backward stepwise multiple Cox’s regression. A probability less than 0.05 was considered statistically significant. We used the statistical software Stata, release 9.2. (StataCorp LP, College Station, TX, USA).

Results

Patient and procedural characteristics

Among the patients who underwent ASA (178 patients, 58 ± 12 years, 53% women), dyspnoea with NYHA functional class 3 or 4 was present in 165 (87%) patients, 144 patients (81%) suffered from a combination of dyspnoea and angina, and 27 patients (15%) experienced repeated synapses. None of the patients was asymptomatic. Fourteen patients (8%) had an implanted permanent pacemaker before ASA to decrease LV obstruction by pacing.

During the study period, seven patients (54 ± 11 years, four males) were sent primarily to surgery; in one patient, myectomy combined with revascularization was performed, and in another patient myectomy combined with aortic valve replacement was undertaken. Two patients (25%) suffered from postoperative ventricular septal defect requiring urgent reoperation; one of these died early after reoperation. Another patient died of unknown causes 2 years after surgery; five other patients are alive. Six patients (59 ± 12 years, four males) underwent primarily dual-chamber pacing, three (50%) of whom subsequently died of sudden death, respiratory failure, and heart failure.

Alcohol septal ablation was combined with percutaneous coronary intervention in five patients (2.8%) and with patent foramen ovale occlusion in one case (0.6%). Alcohol injection volumes were 1.7 ± 0.8 mL (range 0.6–4 mL) with a subsequent CK-MB peak of 2.6 ± 1.6 μkat/L (ULN for CK-MB was 0.42 μkat/L).

Early adverse events

One patient (0.6%) died of pulmonary embolism early after ASA and another patient (0.6%) died of sudden death outside hospital 1 month after ASA (in-hospital mortality was 0.6%; ASA-related mortality was 1.1%). Sustained ventricular arrhythmias occurred during the hospital stay in six patients (3%) and all of these cases required immediate electrical cardioversion. A total of 25 patients (14%) developed periprocedural complete heart block; the new permanent pacemakers for CHB were implanted in 14 patients (8% from all patients; 56% from all patients with complete heart block). None of the patients required urgent surgical operation.

Cardioverter-defibrillator implantation

A total of nine patients (5%) underwent ICD implantation. Four patients (44%, 2.2% from all patients) and two patients (22%, 1.1% from all patients) experienced appropriate and inappropriate discharges after ASA, respectively. Four patients had an ICD implanted to prevent sudden cardiac death before ASA; two of these patients experienced repeated appropriate discharges after implantation, while two other patients experienced repeatedly inappropriate discharges for supraventricular arrhythmias. Two patients experienced periprocedural malignant arrhythmias and subsequently underwent ICD implantations. Both these patients remained without discharges. Two patients underwent an ICD implantation for synapses longer time after ASA (range 6 months–2 years); one of them experienced appropriate ICD discharges. One patient was resuscitated 6 years after ASA and underwent ICD implantation with subsequent appropriate discharges.

Long-term outcomes

The median follow-up duration was 4.8 years (IQR 2.1–7.5; mean 5.2 ± 3.7; maximum 15.1 years) and none of the patients was lost to follow-up. Clinical and echocardiographic outcomes are summarized in Table 1. At baseline, 155 patients (87%) suffered from dyspnoea ≥3 class of NYHA; at the most recent examination, 87 patients (49%) and 23 patients (13%) reported dyspnoea of NYHA class 1 and ≥3, respectively. A reduction of dyspnoea ≥1 class of NYHA occurred in 89% of patients. Six patients (3%) did not

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical and echocardiographic characteristics at baseline and follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>Age, years</td>
<td>58 ± 12</td>
</tr>
<tr>
<td>Dyspnoea, NYHA class</td>
<td>2.9 ± 0.5</td>
</tr>
<tr>
<td>Angina, CCS class</td>
<td>1.9 ± 1</td>
</tr>
<tr>
<td>Episodes of syncope, %</td>
<td>15</td>
</tr>
<tr>
<td>Left ventricular outflow gradient, mmHg</td>
<td>68 ± 42</td>
</tr>
<tr>
<td>Left ventricular diameter, mm</td>
<td>43 ± 5</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>77 ± 9</td>
</tr>
<tr>
<td>Basal septum thickness, mm</td>
<td>21 ± 4</td>
</tr>
</tbody>
</table>
Long-term survival after ASA for HOCM

Mortality events at least partially attributable to HCM (post-ASA pulmonary embolism, sudden death, infective endocarditis, stroke, heart failure) occurred in 15 patients (8.4%; 1.6%/year).

Survival free of all-cause mortality at 1, 5, and 10 years was 97% (95% CI, 93–99%), 92% (95% CI, 87–96%), and 82% (95% CI, 70–90%), respectively. This observed mortality was comparable with the expected survival for age- and sex-comparable members of the general population ($P = 0.34$) (Figure 2). According to multivariate analysis, the only independent predictor of all-cause mortality was age at ASA (hazard ratio 1.09, 95% CI 1.04–1.14; $P < 0.01$).

Survival free of all-cause mortality combined with the first appropriate ICD discharge at 1, 5, and 10 years was 96% (95% CI, 92–98%), 90% (95% CI, 84–94%), and 78% (95% CI, 65–86%), respectively. This observed mortality was comparable with the expected survival for the age- and sex-comparable general population ($P = 0.08$) (Figure 3).

### Survival

A total of 19 deaths (11%) occurred during 925 patient-years, which means an overall mortality rate of 2.1% per year. Causes of deaths are summarized in Table 2. In these patients, ASA was performed at an average age of 66 ± 11 years and the mean survival was 4.5 ± 3.9 years. The main causes of death were stroke (42%), sudden death (21%), and cancer (21%). Patients who died of stroke ($n = 8.69 ± 11$ years at death) had a left atrial diameter at last examination of 49.4 ± 6.7 mm, which was a numerically, but not statistically, larger diameter than that seen in the rest of patients (48 ± 6.2 mm; $P = 0.55$). Only one patient had atrial fibrillation at the last check-up and was anti-coagulated.

The annual mortality of sudden death beyond 30 days after ASA and the annual mortality beyond 30 days after ASA, including the first appropriate ICD discharge, were 0.3 and 0.9%, respectively.

### Table 2 Causes of death during follow-up

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at ASA, years</th>
<th>Length of follow-up, years</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>0.01</td>
<td>Post-procedural pulmonary embolism</td>
</tr>
<tr>
<td>2</td>
<td>49</td>
<td>0.1</td>
<td>Sudden cardiac death</td>
</tr>
<tr>
<td>3</td>
<td>76</td>
<td>0.8</td>
<td>Sudden death</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>1.0</td>
<td>Stroke</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>1.0</td>
<td>Cancer</td>
</tr>
<tr>
<td>6</td>
<td>75</td>
<td>1.0</td>
<td>Infective endocarditis</td>
</tr>
<tr>
<td>7</td>
<td>63</td>
<td>1.4</td>
<td>Stroke</td>
</tr>
<tr>
<td>8</td>
<td>84</td>
<td>1.5</td>
<td>Stroke</td>
</tr>
<tr>
<td>9</td>
<td>78</td>
<td>2.2</td>
<td>Stroke</td>
</tr>
<tr>
<td>10</td>
<td>48</td>
<td>3.0</td>
<td>Stroke</td>
</tr>
<tr>
<td>11</td>
<td>73</td>
<td>4.6</td>
<td>Bowel obstruction (cancer)</td>
</tr>
<tr>
<td>12</td>
<td>74</td>
<td>5.0</td>
<td>Sudden death</td>
</tr>
<tr>
<td>13</td>
<td>62</td>
<td>7.3</td>
<td>Sudden death</td>
</tr>
<tr>
<td>14</td>
<td>62</td>
<td>7.5</td>
<td>Stroke</td>
</tr>
<tr>
<td>15</td>
<td>56</td>
<td>8.3</td>
<td>Stroke</td>
</tr>
<tr>
<td>16</td>
<td>55</td>
<td>8.9</td>
<td>Stroke</td>
</tr>
<tr>
<td>17</td>
<td>70</td>
<td>9.3</td>
<td>Cancer</td>
</tr>
<tr>
<td>18</td>
<td>76</td>
<td>10.2</td>
<td>Cancer</td>
</tr>
<tr>
<td>19</td>
<td>68</td>
<td>12.5</td>
<td>Heart failure</td>
</tr>
</tbody>
</table>

### Figure 2

Kaplan–Meier survival curves describing all-cause mortality including 95% confidence interval compared with that expected in the general population after adjustment for sex and age.

### Figure 3

Kaplan–Meier survival curves describing all-cause mortality and the first appropriate ICD discharge including 95% confidence interval compared with that expected in the general population after adjustment for sex and age.
Multivariate analysis was performed to identify the predictors of all-cause mortality combined with appropriate ICD discharge. In this model, higher age at ASA (hazard ratio 1.08, 95% CI 1.04–1.13; \( P < 0.01 \)) and pre-ASA septum thickness (hazard ratio 1.20, 95% CI 1.06–1.36; \( P < 0.01 \)) were identified as independent predictors of this endpoint.

**Discussion**

A major concern associated with ASA is the potentially increased risk of ventricular arrhythmias and sudden cardiac death in long-term follow-up. The present study demonstrates that ASA results in long-term survival similar to the expected survival of the age- and sex-matched general population. Moreover, causes of deaths were determined in all expired patients with a predominance of non-cardiac death (stroke 42% and cancer 21%). These results are largely incremental to the recently published Mayo Clinic data, demonstrating similar survival in post-ASA patients and the matched general population. Additionally, the current observation presents the follow-up of ASA patients up to 15 years, which is one of the longest reported follow-ups to date.

It seems clear that highly symptomatic patients with HOCM can benefit symptomatically from procedures to reduce LV obstruction. However, it is still not proven that LV obstruction relief in these patients’ results in an improvement of prognosis. As was demonstrated in the past, highly symptomatic HOCM patients have a better prognosis after myectomy than without any operation. Therefore, it was speculated that myectomy might improve prognosis in this group of patients. Moreover, this assumption was supported by the fact that the LV obstruction was identified as an independent risk factor for heart failure and cardiac death in HOCM patients. Similar evidence for the potentially positive effect of ASA has been lacking until last year, when Sorajja et al. demonstrated in the past, highly symptomatic HOCM patients have a better prognosis after myectomy than without any operation. Therefore, it was speculated that myectomy might improve prognosis in this group of patients. Moreover, this assumption was supported by the fact that the LV obstruction was identified as an independent risk factor for heart failure and cardiac death in HOCM patients. Similar evidence for the potentially positive effect of ASA has been lacking until last year, when Sorajja et al. demonstrated in the past, highly symptomatic HOCM patients have a better prognosis after myectomy than without any operation. Therefore, it was speculated that myectomy might improve prognosis in this group of patients. Moreover, this assumption was supported by the fact that the LV obstruction was identified as an independent risk factor for heart failure and cardiac death in HOCM patients.

Causes of death demonstrated in this study suggest that discussion about the long-term risks of post-ASA ventricular arrhythmias and the general risk of sudden death in HCM patients may overshadow the importance of other therapeutic aspects of HCM management. In this study, the leading cause of death was stroke (42%). Interestingly, also Maron et al. demonstrated recently that the most common cause of HCM-related death in patients >60 years of age was embolic stroke. Therefore, the focus during follow-up of HCM patients should be drawn to detection and treatment of atrial fibrillation in order to reduce the high number of strokes.

Additionally, there appear to be further implications of these findings for cardiologists: (i) In tertiary referral centres dealing with HCM patients, early ASA-related mortality is \( \approx 1\% \), which was also demonstrated in the past. However, ASA-related morbidity is much higher and the incidence of ASA-related complications is approximately 20%. Therefore, in discussion about optimal therapy of LV obstruction, we have to bear in mind that extremely redundant mitral leaflets or anomalous papillary muscles may play a key role in the development of obstruction and patients with these anomalies should be sent to surgery. (ii) Age at ASA and pre-ASA septal thickness was the only independent predictors of post-ASA survival and the incidence of sudden death was low; this suggests that survival in patients after ASA is not determined by ASA, but HCM per se. (iii) Among the six patients with early post-procedural ventricular arrhythmias, there were no further adverse clinical events. Therefore, one may speculate that most early post-ASA ventricular arrhythmias are related to the procedure and have no further clinical consequences. (iv) At long-term follow-up, 89% of patients showed improved dyspnoea by NYHA functional class \( \geq 1 \) and only 5% of patients underwent repeated procedures leading to LV obstruction relief. Thus, symptomatic improvement after ASA seems to be remarkable and durable. (v) Several reports in the past demonstrated different survival of patients after ASA or myectomy. However, we have to bear in mind that mid- or long-term survival is predominantly influenced by baseline patient characteristics including age and the clinical status of patients at the time of procedure. Therefore, it is important to compare survival with age- and sex-matched control groups, which might improve the evaluation of post-procedural outcomes. On the other hand, retrospective studies are limited by selection bias, which was suggested in a recent study demonstrating an even numerically lower annual mortality rate in post-ASA patients than in the general age- and sex-matched population \( (P = 0.06) \). It was hypothesized that post-ASA myocardial damage might lead to undesirable LV remodelling in the longer term after procedures. The present study demonstrates, in one of the longest follow-up periods reported to date, that this hypothesis has not been justified. Moreover, only one patient \( (80 \text{ years of age}) \) died of heart failure during the study period.

In the arena of HCM prognostication, a knowledge gap still exists with regard to post-ASA annual mortality. In this study, the overall annual mortality rate was 2.1% compared with 3.2% in Bielefeld’s study \( (n = 644, \text{mean age at ASA 58 years, mean follow-up 1.4 years}), 14 \% \text{ in a Scandinavian study} (n = 279, \text{mean age at ASA 59 years, median of follow-up 3.7 years}), 15 \% \text{ in the Mayo Clinic study} (n = 177, \text{mean age at ASA 63 years, median of follow-up 5.7 years}), 9 \% \text{ and 1.2% in a dual-centre study performed in Bad Oeynhausen and Copenhagen (n = 470, mean age at ASA 56 years, mean follow-up 8.4 years}). 20 \text{ This comparison showed that studies with longer follow-up periods (Mayo Clinic study, Danish-Germany study or the present study) had slightly lower annual mortality rates, which might have been partly caused by the fact that ASA-related deaths (≈1% of cases) were divided by more years of follow-up. However, the most important factor influencing post-ASA long-term mortality is believed to be pre-procedural patient’s selection with regard to age, which can pose a greater threat to survival than long-standing HCM treated by ASA. 20,29 Recently, it has been reported by Maron et al. that the prognosis of HCM patients \( \geq 60 \text{ years of age is based largely on comorbidities and HCM can have only potentially deleterious interactions with other diseases in this age group (atrial fibrillation or stroke)}. 30 \text{ Similarly, patients in this study died mainly of stroke or cancer and the annual mortality rate of sudden death or appropriate ICD discharge was <1%. Thus, although we do not have a direct comparison between}}
the prognosis of HCM patients treated or untreated by ASA, we can hypothesize that the long-term prognosis of ASA patients is similar not only to the general population, but also to other HCM patients. Additionally, we have to bear in mind that the prognosis of younger HCM patients is strongly dependent on the presence of risk factors for sudden cardiac death, as was repeatedly reported.1,30,31

**Study limitations**

This study has several limitations. First, several inherent limitations of this sort of retrospective and non-randomized study performed in a tertiary referral centre exist, including selection bias. Therefore, we cannot be certain that these data are entirely representative and generalizable for non-tertiary referral centres with less experience in the management of HCM and ASA. Second, although this study suggested that patients after ASA have similar survival to the general population, we are still aware that HCM is an extremely heterogeneous disease with a different number of risk factors for sudden death in each HCM patient. Moreover, nine patients underwent an ICD implantation, which is not comparable with the general population. Third, since these patients were referred for ASA, it is not possible to compare outcomes to published reports of surgical myectomy due to likely differences in baseline characteristics. Fourth, survival analysis used in this study can be sensitive to decisions made in statistical analysis.12 Since some appropriate ICD discharges in clinical practice are likely to occur for non-fatal arrhythmias, we selected the all-cause mortality as the primary endpoint and the all-cause mortality combined with appropriate ICD discharge as a secondary endpoint. Fifth, although it is one of the largest studies dealing with the long-term post-ASA survival, we have to bear in mind relatively small number of included patients. Moreover, ultimate clarifying whether ASA increases sudden death risk will require studies with even longer follow-up.

**Conclusions**

This study suggests that in patients with HOCM and important symptoms who underwent ASA, long-term survival after the procedure did not differ significantly from that of the general population.

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**References**


