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Long-term clinical outcome after alcohol septal ablation for obstructive hypertrophic cardiomyopathy: results from the Euro-ASA registry

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Aims The first cases of alcohol septal ablation (ASA) for obstructive hypertrophic cardiomyopathy (HCM) were published two decades ago. Although the outcomes of single-centre and national ASA registries have been published, the long-term survival and clinical outcome of the procedure are still debated.

Methods and results We report long-term outcomes from the as yet largest multinational ASA registry (the Euro-ASA registry). A total of 1275 (58 ± 14 years, median follow-up 5.7 years) highly symptomatic patients treated with ASA were included. The 30-day post-ASA mortality was 1%. Overall, 171 (13%) patients died during follow-up, corresponding to a post-ASA all-cause mortality rate of 2.42 deaths per 100 patient-years. Survival rates at 1, 5, and 10 years after ASA were 98% (95% CI 96–98%), 89% (95% CI 87–91%), and 77% (95% CI 73–80%), respectively. In multivariable analysis, independent predictors of all-cause mortality were age at ASA ($P < 0.01$), septum thickness before ASA ($P < 0.01$), NYHA class before ASA ($P = 0.047$), and the left ventricular (LV) outflow tract gradient at the last clinical check-up ($P = 0.048$). Alcohol septal ablation reduced the LV outflow tract gradient from 67 ± 36 to 16 ± 21 mmHg ($P < 0.01$) and NYHA class from 2.9 ± 0.5 to 1.6 ± 0.7 ($P < 0.01$). At the last check-up, 89% of patients reported dyspnoea of NYHA class ≤2, which was independently associated with LV outflow tract gradient ($P < 0.01$).

Conclusions The Euro-ASA registry demonstrated low peri-procedural and long-term mortality after ASA. This intervention provided durable relief of symptoms and a reduction of LV outflow tract obstruction in selected and highly symptomatic patients with obstructive HCM. As the post-procedural obstruction seems to be associated with both worse functional status and prognosis, optimal therapy should be focused on the elimination of LV outflow tract gradient.

Keywords Alcohol septal ablation • Prognosis • Survival

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Introduction

Hypertrophic cardiomyopathy (HCM) is characterized by the presence of an increased thickness of the left ventricular (LV) wall that is not solely explained by abnormal loading conditions, including hypertension and/or valvular diseases.[1,2] Two-thirds of patients with HCM have evidence of LV outflow tract obstruction, which is usually based on basal septal hypertrophy in combination with elongated mitral leaflet(s), causing systolic anterior motion of the mitral valve.[1–3] In patients who remain highly symptomatic despite optimal medical therapy, surgical myectomy has traditionally been performed to relieve obstruction and its associated symptoms.[1,2] Alcohol septal ablation (ASA) was introduced two decades ago by Ulrich Sigwart as an alternative percutaneous technique.[4] He demonstrated that the injection of a small amount of desiccated alcohol into an appropriate septal branch of the left anterior descending artery is followed by basal septal necrosis and subsequent shrinkage, resulting in a decrease in LV obstruction. Although encouraging results of single-centre or national ASA registries have been published,[5–14] the long-term safety and efficacy of the procedure have been debated over the following decades.[1,15,16] Twenty years after the introduction of ASA, we therefore report long-term outcomes from the largest multinational ASA registry (the Euro-ASA registry) to date.

Methods

Patients

A total of 1275 (58 ± 14 years, 49% females), highly symptomatic, consecutive patients treated with ASA were included. Procedures were performed in 10 tertiary invasive centres from seven European countries (Germany—Bad Oyenhausen; Czech Republic—Prague, Trinec, Brno; Denmark—Copenhagen, Gentofte; the Netherlands—Nieuwegein; Austria—Innsbruck; Poland— Warsaw; Norway—Oslo) between January 1996 and February 2015. All patients had been prospectively included in institutional registries and subsequently also in the Euro-ASA registry. Individual centres began with the ASA programme in the years 1996–2005.

The diagnosis of obstructive HCM was made by cardiologists experienced in managing patients with this disease, based on typical clinical, electrocardiographic, echocardiographic, and/or cardiac magnetic resonance imaging features, with LV hypertrophy (wall thickness ≥15 mm) occurring in the absence of any other cardiac or systemic disease that could have been responsible for the hypertrophy. Alcohol septal ablation was offered to highly symptomatic adult patients in functional (NYHA) class III/IV, who were refractory or intolerant to medical therapy. In exceptional cases, patients with severe angina pectoris or documented exertional syncope were also included. The maximal (provocable) LV outflow tract gradient had to be ≥50 mmHg in the absence of severe mitral valve disease or other indication for cardiac surgery. Decisions regarding the choice of ASA or surgical myectomy were made after a detailed multidisciplinary evaluation and a consensus among experts in the management of HCM, based on clinical experience at the individual sites.

Alcohol septal ablation technique

All interventions were performed by experienced interventional cardiologists. Details of the ASA technique have been published in the past.[4,17,18] Although there were some small differences in ASA technique among sites, all procedures were guided by myocardial contrast echocardiography and the volume of injected alcohol was gradually decreased over the study period.[19,20] Blood was drawn for determination of the MB fraction of creatine kinase (CK-MB) in the first 2 days post-ASA.

Follow-up

There were differences in post-ASA follow-up between centres participating in the registry. Generally, all patients had a routine clinical check-up 3–6 months after ASA and then every year. In patients with an implanted pacemaker or cardioverter-defibrillator (ICD), devices were evaluated for both implant function and memory, including registration of discharges. The survival of patients treated in the Czech Republic and Denmark were continuously checked in the National Database of Deaths. The survival of patients treated in other countries was updated in 2014–2015, by clinical visit, telephone call, or mail communication. For deceased patients who died outside hospitals, interviews or mail communication with the general practitioner or next of kin was performed to ascertain the cause of death.

Endpoints and definitions

In this study, we aimed to determine: (i) survival and clinical outcome in patients treated with ASA, (ii) predictors of mortality events and clinical outcome, (iii) relationships between alcohol dose injected during ASA, improvement of LV outflow tract pressure gradient, and the occurrence of complete heart block.

All-cause mortality was defined as death due to any cause. Sudden mortality events included sudden deaths, appropriate ICD discharges, and successful resuscitations. Sudden death was defined as sudden and unexpected death within 1 h after a witnessed collapse in a previously stable patient or death that occurred during sleep. In patients with an implanted ICD, device interventions triggered by ventricular fibrillation (VF) or ventricular tachycardia (VT) were considered as appropriate discharges. Cardiovascular death was defined as death related to any cardiovascular disease, including stroke.

The relative delta pressure gradient was used to express the percentage reduction of LV outflow gradient and was defined as follows: (pressure gradient at baseline − pressure gradient at last clinical check-up)/pressure gradient at baseline.

Statistical analysis

All data were evaluated by two independent statisticians. Data were presented as means ± standard deviations (± SD) for continuous variables and proportions for categorical variable; where continuous variables had skewed distributions (Kolmogorov–Smirnov test), data were expressed as median (25th, 75th percentiles—IQRs). Student's *t*-tests and Wilcoxon signed-rank tests assessed the statistical significance of continuous variables, and χ^2 test analysed categorical variables.

Cox proportional hazard regression was used to identify predictors of mortality. The following clinical and echocardiographic variables with a potential impact on patient outcome were evaluated, first in a univariate model: age, gender, baseline, and residual NYHA class, baseline and residual left ventricular pressure gradient, baseline and residual septal thickness, and amount of alcohol injected during ASA. Variables with a *P*-value of <0.15 were then entered into a multivariable analysis, which was performed using a backward stepwise multiple Cox's regression or logistic regression. Estimates for long-term survival were made by the Kaplan–Meier method and differences in survival were assessed by the log-rank test.

Median regression was used to describe the relationship between the delta pressure gradient and potential predictors. Simple logistic

regression was used to describe the relationship between alcohol dose and the occurrence of peri-procedural complete heart block. Locally weighted scatterplot smoothing curve was used to display the relationship between alcohol dose and the occurrence of peri-procedural complete heart block (*Figure 2*). A value of $P < 0.05$ was considered statistically significant. All reported *P*-values were two-sided. The statistical software GraphPad, release 6.05 (GraphPad Software, La Jolla, CA, USA), was used.

Results

Baseline and alcohol septal ablation procedure characteristics

A total of 1275 consecutive patients underwent ASA (49% women, 3.7% with implanted pacemaker, and 4.1% with implanted ICD). Baseline clinical and echocardiographic characteristics of the patient cohort are summarized in *Table 1*. During the study period, 250 patients were sent primarily to surgical myectomy and <5% of ASA procedures have been aborted for the lack of an appropriate septal branch.

The volumes of injected alcohol during ASA were 2.2 ± 0.9 mL, with a subsequent CK-MB peak of 2.9 ± 2.2 μkat/L (Czech centres, upper limit of normal 0.42 μkat/l) or 141 ± 211 IU/L (remaining centres, upper limit of normal 80 IU/L). Although the alcohol dose used during ASA procedure ranged from 0.4 to 11 mL, the median was 2.0 and 90% of patients were treated with an alcohol dose of 1–3 mL.

A total of 13 (1%) patients died within 1 month of ASA: four died of heart failure, three of pulmonary embolism, two of cardiac tamponade, one of sepsis, one of stroke, one of carcinoma, and one of sudden cardiac death (VF). Intraprocedural or early post-procedural (48 h) sustained VT/VF requiring electrical cardioversion occurred in 16 patients (1.3%) and a further 4 (0.3%) patients required electrical cardioversion between 2 and 30 days after ASA. The most frequent complication was a transient peri-procedural complete heart block. This occurred in 468 (37%) patients until 30 days after ASA, with 151 (12% of all patients) patients subsequently requiring permanent pacemaker implantation.

Clinical outcome

At the latest clinical check-up (median 3.9 [IQR 1.4–7.4] years), ASA had reduced LV outflow tract gradient from 67 ± 36 to 16 ± 21 mmHg ($P < 0.001$) and NYHA class from 2.9 ± 0.5 to 1.6 ± 0.7 ($P < 0.001$; *Table 1*); 89% of patients reported dyspnoea of NYHA class ≤2, and 86% of patients experienced improvement of ≥1 NYHA class. According to multivariable analysis, NYHA class ≤2 at the last clinical check-up with the absence of myectomy or mortality event(s) during follow-up was independently associated with LV outflow tract gradient at the same check-up (OR 0.98, 95% CI 0.97–0.99; $P < 0.001$).

The relationship between alcohol dose and relative delta pressure gradient is expressed in *Figure 1*. According to multivariable analysis, independent predictors of the delta pressure gradient were the volume of injected alcohol (regression coefficient 1.77, 95% CI 1.07–2.47; $P < 0.001$), septum thickness at the last clinical check-up (regression coefficient −0.21, −0.37 to −0.05; $P < 0.001$), and also with NYHA class at the last check-up (regression coefficient −1.43, 95% CI −2.44 to −0.43; $P = 0.005$). Although a larger volume of alcohol was more effective in decreasing LV outflow tract gradient, it was also associated with a higher occurrence of the complete heart block (OR 1.19, 95% CI 1.05–1.35; $P = 0.006$; *Figures 1* and *2*). A total of 105 (8%) patients were excluded from this analysis because of missing data.

Up to the last clinical check-up, 87 (7%) patients underwent a re-ASA procedure and 42 (3%) patients primarily treated by ASA subsequently underwent surgical myectomy. Of 110 (9%) patients with an implanted ICD, 58 (5%) underwent implantation after ASA.

Survival after alcohol septal ablation

The median of follow-up time for the survival analyses was 5.7 years. Five (0.4%) patients were lost to long-term follow-up. Overall, 171 (13%) patients died during 7057 patient-years of follow-up, corresponding to a post-ASA all-cause mortality rate of 2.42 (95% CI 2.07–2.82) deaths per 100 patient-years (*Figure 3*). Survival rates are summarized in *Table 2* and *Figures 3–5*. According to multivariable analysis, independent predictors of all-cause mortality were higher age at ASA (HR 1.06, 95% CI 1.05–1.08; $P < 0.001$), septum thickness before ASA (HR 1.05, 95% CI 1.01–1.09; $P < 0.001$), NYHA class before ASA (HR 1.5, 95% CI 1.00–2.10; $P = 0.047$), and LV outflow tract gradient at the last clinical check-up (HR 1.01, 95% CI 1.00–1.01; $P = 0.048$).

A total of 197 (15%) patients experienced all-cause death or appropriate ICD discharge during 7055 patient-years of follow-up, corresponding to a rate of mortality events of 2.84 (95% CI 2.46–3.27)

Table 1 Clinical and echocardiographic characteristics at baseline and last clinical check-up

	Baseline (*N* = 1275)	Follow-up >30 days (*N* = 1254)
Age, years	58 ± 14	63 ± 13
Dyspnoea, NYHA class	2.9 ± 0.5	1.6 ± 0.7
Angina, CCS class	1.3 ± 1.2	0.7 ± 0.8
Episodes of syncope, %	22	7
Left ventricular outflow tract gradient, mmHg	67 ± 36	16 ± 21
Left ventricular end-diastolic diameter, mm	43 ± 6	46 ± 6
Left ventricular ejection fraction, %	70 ± 10	66 ± 10
Basal septum thickness, mm	20 ± 4	15 ± 4

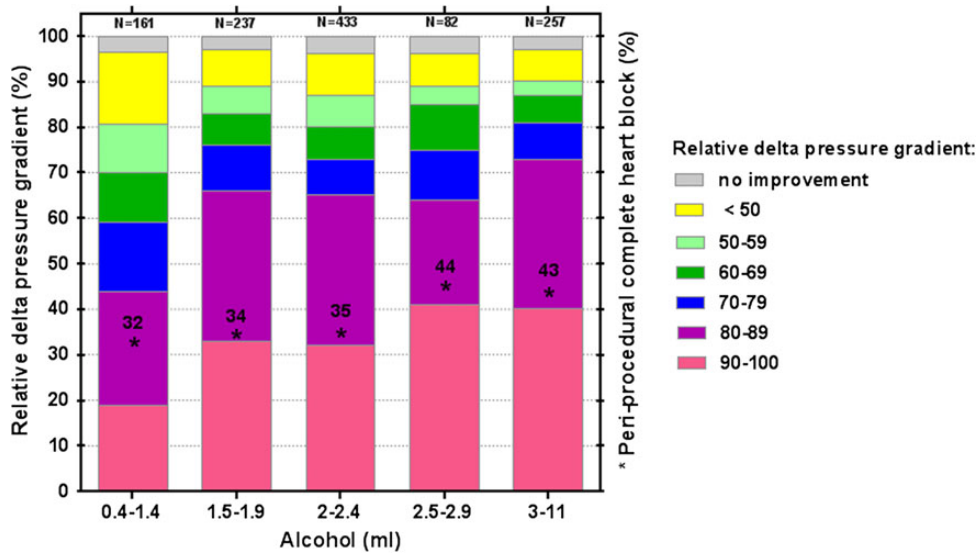

Figure 1 Relationship between alcohol dose, relative delta pressure gradient, and complete heart block.

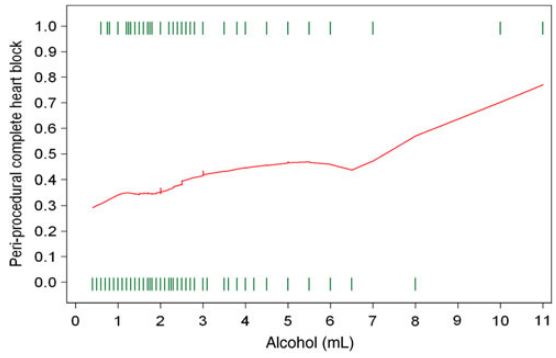

Figure 2 Locally weighted scatterplot smoothing curve describing relationship between alcohol dose and the occurrence of peri-procedural complete heart block. The hash markings represent observed values for the occurrence (top) and absence (bottom) of complete heart block.

Figure 3 Kaplan–Meier survival curve describing all-cause mortality with 95% confidence intervals.

per 100 patient-years (*Figure 4*). In multivariable analysis, independent predictors of mortality events were higher age at ASA (HR 1.05, 95% CI 1.04–1.07; $P < 0.001$), septum thickness before ASA (HR 1.06, 95% CI 1.03–1.10; $P = 0.001$), and LV outflow gradient at the last check-up (HR 1.01, 95% CI 1.00–1.01; $P = 0.020$). *Table 3* summarizes the causes of death after ASA.

Sudden mortality events (sudden death and first appropriate ICD discharge or successful resuscitation) occurred in 68 (5.3%) patients, corresponding to an event rate of 0.98 (95% CI 0.76–1.12) per 100 patient-years (*Figure 5*). Of these, 29 (43%) patients survived the first event. The only independent predictor of sudden mortality events was the septum thickness before ASA (HR 1.07, 95% CI 1.01–1.12; $P = 0.014$).

Sudden or cardiovascular death occurred in 82 (6.4%) patients, corresponding to an annual mortality rate of 1.16 (95% CI 0.92–1.44) per 100 patient-years. Mortality events at least partially attributable to HCM (peri-procedural events and sudden mortality events or cardiovascular death) occurred in 108 (8.5%) patients, corresponding to an annual mortality rate of 1.58 (95% CI 1.29–1.90) per 100 patient-years.

Discussion

The Euro-ASA registry was designed as a large, multinational European registry aimed at identifying long-term outcomes and their predictors in patients after ASA for highly symptomatic obstructive HCM. Two decades after the introduction of ASA, we here report the following principal findings: (i) a larger volume of alcohol is more effective in decreasing LV outflow tract gradient, but is also associated with a higher occurrence of peri-procedural complete heart

Table 2 Event-free survival rates after alcohol septal ablation

	Survival rates (95% CI)			
	1 year	3 years	5 years	10 years
All-cause death	98% (96–98%)	94% (93–95%)	89% (87–91%)	77% (73–80%)
All-cause death or appropriate implanted cardioverter-defibrillator discharge	97% (96–98%)	92% (90–94%)	87% (85–89%)	73% (69–77%)
Sudden mortality event	99% (98–99%)	97% (95–98%)	95% (93–96%)	90% (88–93%)

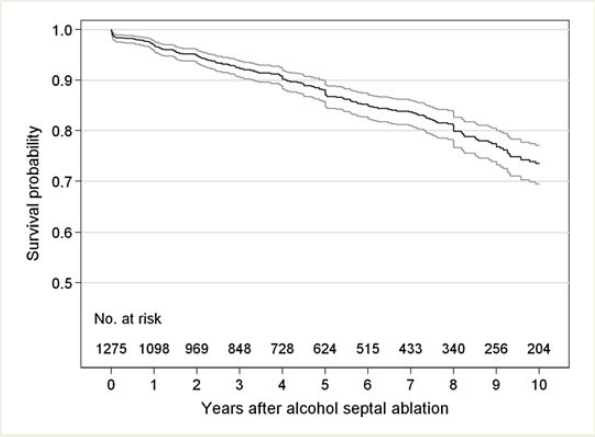

Figure 4 Kaplan–Meier survival curve describing all mortality events including appropriate implanted cardioverter-defibrillator discharges and resuscitations with 95% confidence intervals.

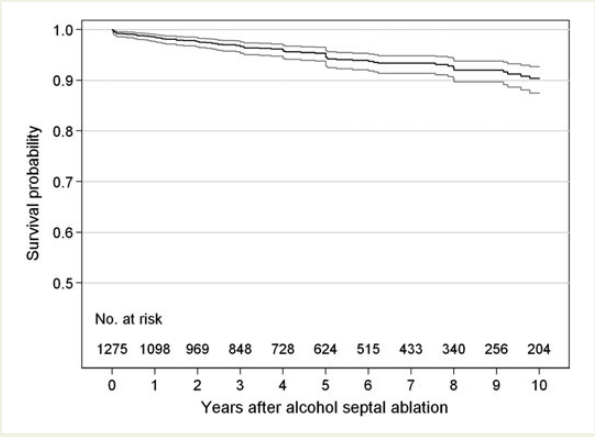

Figure 5 Kaplan–Meier survival curve describing all sudden mortality events including appropriate implanted cardioverter-defibrillator discharges and resuscitations with 95% confidence intervals.

block; (ii) LV outflow tract gradient is lowered by 76, and 86% of patients' experience improvement of ≥1 class of NYHA; (iii) a more pronounced reduction of LV outflow tract gradient is associated with a lower resultant NYHA class; (iv) the 30-day post-procedural mortality is 1%, and 12% of treated patients require an early post-procedural pacemaker implantation; (v) the annual post-ASA mortality rate is 2.4% and the risk of a sudden mortality event is 1% per year; and (vi) the all-cause mortality is independently associated with the residual LV outflow tract gradient.

Table 3 Causes of death after alcohol septal ablation

Cardiovascular death	21%
Sudden death	19%
Implanted cardioverter-defibrillator discharge or defibrillation	17%
Non-cardiovascular death	34%
Unknown cause of death	9%

Based on data from smaller studies describing similar haemodynamic results with the use of low or high doses of intracoronary alcohol during ASA,[19,20] the low doses (1–2 mL) have become standard in most ASA centres. The current registry suggests that higher doses of alcohol are slightly more effective in decreasing LV outflow tract gradient. This has significant clinical consequences, because lower LV outflow tract gradient was associated both with better functional class and survival. On the other hand, this advantage of higher alcohol doses was balanced by a higher risk of peri-procedural complete heart block. Based on our findings, we believe that ASA doses of alcohol ranging between 1.5 and 2.5 mL are well balanced in terms of efficacy and safety for most patients. Nevertheless, the optimal dose of alcohol can vary for each individual patient depending on the severity of their symptoms, acceptability of procedural risk, and LV morphology.

Our results suggest that besides the proper selection of patients suitable for ASA, it is of a crucial importance to achieve a sufficient thinning of the basal septum, which is independently associated with the resultant delta pressure gradient. In other words, limited ablation, even in the correct location, might lead to an insufficient haemodynamic result.

Procedure-related mortality was believed to be low even in the first decade after ASA introduction, with a reported mean value of ~1.5%.[21] In this registry, we found the 30-day post-ASA all-cause mortality to be even lower (1%) including non-cardiovascular mortality. On the other hand, the complication rate related to ASA is still not negligible and it is notable that 1/10 of patients will subsequently undergo pacemaker implantation, and a few (1.6%) patients experience early post-procedural ventricular arrhythmias. Fortunately, the initial fears of late LV dysfunction and arrhythmias, or an increased

rate of sudden death,[15,16] were not observed in our current study. In this registry, with a follow-up exceeding 7000 patient-years, the rate of sudden mortality events was 1% per year, including 0.6% of sudden deaths, which is lower or similar to results presented from HCM registries containing patients without previous ASA.[22–24] The combined rate of sudden and cardiovascular mortality reported here (1.2%) was also relatively low and not even entirely attributable to HCM.

In the arena of HCM prognostication and choosing the optimal septal reduction therapy, there is still a knowledge gap with regard to post-procedural mortality and risk/benefit of ASA compared with surgical myectomy. Long-term survival in the current study was comparable with similar reports of patients treated by myectomy. In this study ($n = 1275$, mean age at ASA 58 years), 10-year survival was 77%, compared with two surgical Mayo Clinic studies[25,26] with survival rates of 77% (Schaff *et al.*, 749 patients, mean age at surgery 52 years) and 83% (Ommen *et al.*, 289 patients, mean age at surgery 45 years). Similar to our data, the North American ASA Registry (874 patients, mean age at ASA 55 years) demonstrated a 9-year survival rate of 74%,[5] but their patients were younger than those included in our registry. An identical 10-year survival rate of 77% was also reported by Sorajja *et al.*[27] in 544 consecutive patients with obstructive HCM (mean age 59 years), who were mildly symptomatic or asymptomatic and did not require septal reduction therapy. All these data, albeit reported from cohorts with a lower number of patients, seem to be consistent with our results and suggest that the long-term survival of patients treated by both techniques for septal reduction therapy is similar. Indeed, this view has also been confirmed by several meta-analyses.[28,29]

Prediction of post-ASA clinical outcome is challenging because of the marked heterogeneity of the treated HCM cohort. In this study, the independent predictors of all-cause mortality were higher age, septum thickness, and NYHA class before ASA, and the only predictor of sudden mortality events was septum thickness before ASA. In the context of the known risk factors for long-term mortality in HCM patients, these results are not surprising.[1,2] However, the residual LV outflow tract gradient at the last clinical check-up was also independently associated with all-cause mortality, and all-cause mortality and risk of appropriate ICD discharge, respectively. Our results suggest that each mmHg increase in residual LV obstruction was associated with ~1% increase in long-term risk of all-cause death. It is also worth noting that in post-surgical myectomy patients, an association of incomplete relief of the LV outflow obstruction with worse survival has also been demonstrated.[30] Nagueh *et al.*[5] demonstrated in the North American ASA registry that mortality after ASA was predicted by the baseline LV ejection fraction, pre-procedural functional class, the number of septal arteries injected with ethanol, post-ablation septal thickness, beta-blocker use, and the number of ablation procedures. In line with this evidence, our data emphasize the importance of the LV outflow obstruction elimination and inherent patient's characteristics including the age at ASA, baseline functional status, and baseline septum thickness.

Based on the summary of evidence, we speculate that with the exception of ICD implantation for prevention of sudden cardiac death, reduction of LV outflow gradient is the most important therapeutic procedure affecting long-term survival of highly symptomatic patients with obstructive HCM, and that the means used to accomplish this reduction are less important. In other words, it matters less whether the LV outflow obstruction is eliminated by means of myectomy or ASA; the most important considerations are the safety of the procedure and the final haemodynamic result.

The present study was observational and the current results may not be entirely generalizable, since the patients were treated at tertiary centres that had great experience with HCM. Also, a key factor influencing the results of ASA is probably the optimal selection of HCM patients who are appropriate for this therapy. Typically, patients with less basal hypertrophy, long mitral leaflets, and marked hypertrophy of (bifid) papillary muscles are good candidates for septal myectomy and simultaneous surgical procedures on mitral valve and/or papillary muscles.[3] On the other hand, patients with hypertrophy localized mainly in the basal part of the septum without elongated mitral leaflets are effectively and safely treated by ASA.

Conclusion

Patients with obstructive HCM treated at tertiary centres have both low peri-procedural and long-term mortality after ASA. Higher doses of alcohol are slightly more effective in reducing LV obstruction and result in a higher incidence of peri-procedural complete heart block. Since the post-procedural LV outflow tract obstruction is independently associated with both worse functional status and prognosis, the choice of optimal therapy in these patients should be focused on elimination of LV outflow tract gradient.

Authors' contributions

J. V.: performed statistical analysis; J.V., L.F., M.K.J., M.L.: handled funding and supervision; J.V., M.K.J., M.L. J.J., J.K., T.B., M.D., P.R.H., V.M.A., H.S., D.H., P.T., R.A., H.B., R.S., J.t.B., L.F.: acquired the data; J.V.: conceived and designed the research; J.V.: drafted the manuscript; J.V., M.K.J., M.L., J.J., J.K., T.B., M.D., P.R.H., V.M.A., H.S., D.H., P.T., R.A., H.B., R.S., J.t.B., L.F.: made critical revision of the manuscript for key intellectual content.

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