ORIGINAL ARTICLE

Obstruction after alcohol septal ablation is associated with cardiovascular mortality events

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ABSTRACT

Background Left ventricular outflow tract obstruction (≥30 mm Hg at rest; LVOTO) is considered a possible risk of long-term outcomes in patients with hypertrophic cardiomyopathy (HCM). However, the influence of LVOTO on the occurrence of cardiovascular mortality events in patients after alcohol septal ablation (ASA) for obstructive HCM remains unresolved.

Methods We compared the outcomes of patients treated with ASA with residual LVOTO <30 mm Hg with those with residual LVOTO ≥30 mm Hg at the first postdischarge check-up (1–6 months after the procedure).

Results A total of 270 patients (60±12 years, median follow-up 5.1 years; 95% CI 4.5 to 5.9 years) treated with a single ASA were included; 208 (77%) and 62 (23%) patients had post-ASA LVOTO <30 and ≥30 mm Hg at the first postdischarge clinical check-up, respectively (LVOTO 13±6 vs 50±27 mm Hg; p<0.01). Freedom from cardiovascular mortality events at 1, 5 and 10 years were 99% (95% CI 96% to 100%) vs 94% (95% CI 85% to 98%), 95% (95% CI 89% to 97%) vs 80% (95% CI 66% to 89%) and 82% (95% CI 69% to 89%) vs 72% (95% CI 55% to 84%) (log-rank test, p<0.01), respectively. In multivariable analysis adjusted for age at ASA, sex, baseline LVOTO and baseline septum thickness, the independent predictors of cardiovascular mortality events were early postdischarge LVOTO ≥30 mm Hg (HR 2.95, 95% CI 1.26 to 6.91; p=0.01) and baseline septum thickness (HR 1.07, 95% CI 1.01 to 1.13; p=0.02).

Conclusions After ASA for obstructive HCM, LVOTO ≥30 mm Hg at the first postdischarge clinical check-up is associated with significantly higher occurrence of subsequent cardiovascular mortality events.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is an inherited myocardial disease characterised by cardiac hypertrophy in the absence of hypertension and aortic valve disease.[1 2] Left ventricular outflow tract obstruction (LVOTO) is present in approximately two-thirds of patients. In recent studies, alcohol septal ablation (ASA) was associated with excellent long-term survival,[3–9] even comparable with that of an age-matched and sex-matched general population.[7 8] However, some patients who have undergone ASA present residual LVOTO. Several studies have suggested that LVOTO in patients with HCM is a strong and independent predictor of progression to severe symptoms of heart failure or death.[10 11] However, the relationship between post-ASA residual obstruction and the occurrence of subsequent adverse cardiovascular events remains unresolved.

Therefore, we report here a multicentre comparison of the long-term occurrence of cardiovascular mortality events in patients treated with ASA and early postprocedural LVOTO of <30 mm Hg vs ≥30 mm Hg.

METHODS

The study design is based on a multicentre ASA registry in which patients were prospectively collected and retrospectively reviewed. A total of 270 patients (60±12 years, women 53%) were enrolled with highly symptomatic obstructive HCM treated with ASA at three centres during the period from 1998 to 2015. All patients had to undergo a single ASA and submit to long-term follow-up at the centre where ASA was performed. Patients who experienced the cardiovascular mortality event during the first postprocedural month were not enrolled. Written informed consent was obtained from each patient, and the local ethics committees approved the study.

The diagnosis of obstructive HCM was established by experienced cardiologists based on echocardiographic and/or cardiac magnetic resonance examinations, with wall thickness ≥15 mm, maximal (provocable) LVOTO ≥50 mm Hg and severe symptoms (New York Heart Association (NYHA) class III/IV and/or exercise syncopes). ASA was indicated after a detailed multidisciplinary evaluation based on local clinical experience and the patient's preference.

All interventional procedures were performed by interventional cardiologists at centres with special cardiomyopathy clinics. The technical details of the interventions were described previously. All centres used echocardiography-guided ASA and low doses of injected alcohol.[12–14]

All patients underwent routine clinical and echocardiographic check-ups 1–6 months after ASA and then every year, depending on the local customs of the HCM centre. Patients were assigned to one of two groups according to residual LVOTO at the first postdischarge clinical check-up after ASA (LVOTO <30 mm Hg and LVOTO ≥30 mm Hg).

Definitions

The primary endpoint was the occurrence of cardiovascular mortality events (cardiovascular death, the first appropriate implantable cardioverter-defibrillator (ICD) discharge and resuscitation) in patients treated with ASA and early postprocedural LVOTO of <30 mm Hg vs ≥30 mm Hg. Cardiovascular death was defined as death related to any cardiovascular disease, including stroke. In

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patients with an implanted ICD, device interventions triggered by ventricular fibrillation or ventricular tachycardia were considered as appropriate discharges.

Statistical analysis

All data were evaluated by two independent statisticians. Data were presented as means±SDs for continuous variables and proportions for categorical variables. Student's t test was used to assess the statistical significance of continuous variables. Cox proportional hazards regression was used to identify predictors of cardiovascular mortality events. Generalised Therneau and Grambsch test based on scaled Schoenfeld residuals was used to check the proportional hazard assumption in Cox's model. Neither the tests for individual covariates in univariate models nor the global test in multiple model showed any statistically significant violation of the assumption. Graphical assessment based on log–log plots gave the parallel curves. The following clinical and echocardiographic variables with potential impact on cardiovascular mortality events were evaluated, first in a univariate model: age at ASA, sex, LVOTO, septum thickness and left atrial diameter, both at baseline and at the last clinical check-up. Variables with values of $p<0.15$ were then entered into a multivariable analysis, which was performed using backward stepwise Cox regression. The long-term occurrence of cardiovascular mortality events was estimated using the Kaplan-Meier method, and differences between groups were assessed by the log-rank test. Kaplan-Meier curves of groups with LVOTO <30 mm Hg and LVOTO ≥30 mm Hg were adjusted for age at ASA (60 years), baseline septum thickness (20 mm), baseline LVOTO (70 mm Hg) and sex (50% women). A value of $p<0.05$ was considered statistically significant. The statistical software, GraphPad, release V.6.05 (GraphPad Software, La Jolla, California, USA) was used for statistical analysis.

RESULTS

A total of 310 patients with ASA were treated; 35 (11.3%) patients were excluded due to repeat septal reduction therapy; four (1.3%) patients died before the first post-ASA check-up; one patient moved abroad.

A total of 270 patients (86%, 60±12 years) treated with a single ASA were included; 208 (77%) and 62 (23%) patients had post-ASA LVOTO <30 mm Hg and ≥30 mm Hg at the time of the first postdischarge clinical check-up (2.3±1.5 months after ASA), respectively (LVOTO 13±6 vs 50±27 mm Hg; $p<0.01$). Both groups had similar baseline characteristics (table 1). No patient was lost to follow-up. The clinical and echocardiographic data at the time of the last clinical check-up are summarised in table 1. A total of 44 deaths (16%) occurred after the ASA procedure and before the last clinical check-up (1582 patient-years), yielding an all-cause mortality rate of 2.78% per year.

The incidence of cardiovascular mortality events is summarised in table 2.

Kaplan-Meier survival curves are shown in figures 1 and 2. Freedom from cardiovascular mortality events in LVOTO <30 mm Hg group versus LVOTO ≥30 mm Hg group at 1, 5 and 10 years were 99% (95% CI 96% to 100%) vs 94% (95% CI 85% to 98%), 95% (95% CI 89% to 97%) vs 80% (95% CI 66% to 89%) and 82% (95% CI 69% to 89%) vs 72% (95% CI 55% to 84%) (log-rank test, $p<0.01$), respectively. Unadjusted and adjusted freedom from cardiovascular mortality events are significantly different for both groups after stratification by early postdischarge LVOTO (log-rank, $p=0.002$; $p=0.019$ after adjustment).

Table 1 Clinical and echocardiographic characteristics at baseline, at early postdischarge clinical check-up and at the last check-up

	LVOTO <30 mm Hg N=208	LVOTO ≥30 mm Hg N=62	p Value
Age, years	58.9±11.9	57.9±14.1	0.559
Sex, females, %	109 (52.4)	34 (54.8)	0.773
Alcohol, mL	1.7±0.8	1.8±0.6	0.123
CKMB max, µkat/L	3.0±2.1	2.8±1.4	0.806
Dyspnoea, NYHA class			
Baseline	2.9±0.5	3.0±0.5	0.498
Early post-ASA check-up	1.6±0.7	1.9±0.7	0.003
Last clinical check-up	1.7±0.7	2.0±0.7	0.003
Angina, CCS class			
Baseline	1.5±1.2	1.4±1.3	0.356
Early post-ASA check-up	0.3±0.6	0.4±0.8	0.779
Last clinical check-up	0.2±0.5	0.3±0.6	0.727
Left ventricular outflow gradient, mm Hg			
Baseline	64.1±39.5	92.8±39.8	<0.001
Early post-ASA check-up	12.8±6.0	49.9±26.5	<0.001
Last clinical check-up	13.3±11.4	33.2±29.7	<0.001
Left ventricular diameter, mm			
Baseline	42.4±5.3	42.8±6.1	0.690
Early post-ASA check-up	45.4±5.1	45.7±5.8	0.684
Last clinical check-up	46.5±5.2	46.7±5.9	0.764
Left ventricular ejection fraction, %			
Baseline	73.2±9.9	71.3±9.9	0.169
Early post-ASA check-up	70.3±10.1	69.6±9.4	0.409
Last clinical check-up	68.5±8.7	67.3±10.2	0.303
Basal septum thickness, mm			
Baseline	20.5±4.1	22.4±5.9	0.009
Early post-ASA check-up	15.8±4.9	18.7±5.2	<0.001
Last clinical check-up	13.5±3.6	16.2±4.6	<0.001
Left atrium diameter, mm			
Baseline	46.2±6.0	48.1±7.4	0.043
Early post-ASA check-up	45.2±5.9	47.0±7.2	0.052
Last clinical check-up	46.4±6.7	48.2±7.4	0.075
Mean follow-up duration, years	5.8±4.1	5.2±4.0	

ASA, alcohol septal ablation; CCS, Canadian Cardiovascular Society; LVOTO, left ventricular outflow tract obstruction.

Table 2 Cardiovascular mortality events during follow-up

	LVOTO <30 mm Hg N=208	LVOTO ≥30 mm Hg N=62	p Value
Cardiovascular death	12 (5.8%)	6 (9.7%)	0.353
The first appropriate ICD discharge	2 (1.0%)	4 (6.5%)	0.007
Resuscitation	1 (0.5%)	3 (4.8%)	0.011

LVOTO, left ventricular outflow tract obstruction.

In multivariable analysis adjusted for age at ASA, sex, baseline LVOTO and baseline septum thickness, the independent predictors of cardiovascular mortality events were early postdischarge LVOTO ≥30 mm Hg (HR 2.95, 95% CI 1.26 to 6.91; $p=0.01$) and baseline septum thickness (HR 1.07, 95% CI 1.01 to 1.13; $p=0.02$).

DISCUSSION

In this study, the following principal findings are reported: (i) patients with obstructive HCM treated with a single ASA and

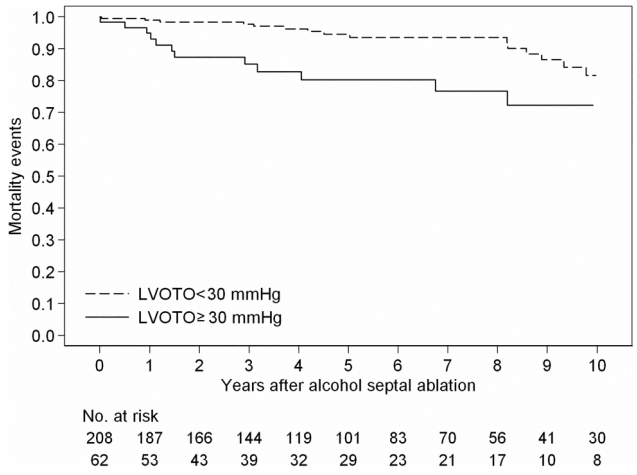

Figure 1 Kaplan-Meier curves describing freedom from cardiovascular mortality events in patients with residual left ventricular outflow tract obstruction (LVOTO) <30 mm Hg and ≥30 mm Hg.

subsequent residual LVOTO ≥30 mm Hg detected early after ASA have a higher rate of post-ASA cardiovascular mortality events than those with no or mild residual LVOTO (<30 mm Hg); (ii) the independent predictors of cardiovascular mortality events in these patients are early postdischarge LVOTO ≥30 mm Hg (HR 2.95) and baseline septum thickness (HR 1.07).

From the pathophysiological point of view, a variety of mechanisms are responsible for the negative clinical consequences of LVOTO. Myocardial ischaemia could be caused by increased LV work, increased oxygen consumption and simultaneous microvascular coronary artery disease. Also, a significant LVOTO results in increased LV wall stress. On the other hand, it has been demonstrated that the elimination of obstruction can lead to an acute decrease in oxygen myocardial consumption[15] and a continuous decrease in LV myocardial mass,[16] which might be essential mechanisms for the long-term improvement of a patient's prognosis.

Maron *et al*[10] described a deleterious effect of LVOTO defined as ≥30 mm Hg on the long-term outcomes of patients with HCM. Sorajja *et al*[17] found a strong correlation between the severity of LVOTO and outcome among patients with mildly symptomatic or asymptomatic obstructive HCM. Elliott *et al* demonstrated that LVOTO ≥30 mm Hg was an independent predictor of sudden cardiac death among an unselected population of obstructive patients with HCM. They also found that the relative risk of sudden cardiac death or ICD discharge increased by 1% for each 1 mm Hg of LVOTO.[18] Similarly, data from the Euro-ASA registry showed that each mm Hg increase in post-ASA LVOTO was associated with a 1% increase in the long-term risk of all-cause death.[6] In this study, early post-ASA LVOTO ≥30 mm Hg was associated with a threefold increase in the risk of cardiovascular mortality events during long-term follow-up. Thus, there is a growing body of evidence consistently suggesting that LVOTO in patients with HCM has negative clinical implications and that its elimination/reduction can be associated with reduced symptoms and improved prognoses. Similarly, the pre-ASA thickness of the basal septum is an independent risk factor affecting the occurrence of sudden cardiac death[1 2 11 19] and cardiovascular mortality events.

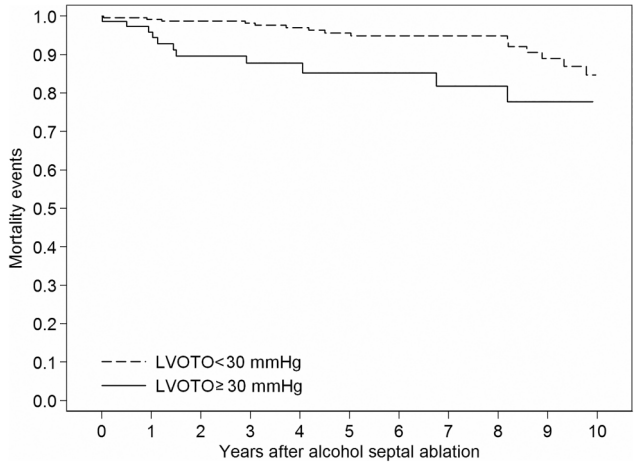

Figure 2 Kaplan-Meier curves describing freedom from cardiovascular mortality in patients with residual left ventricular outflow tract obstruction (LVOTO) <30 mm Hg and ≥30 mm Hg (adjustment for age, sex, baseline LVOTO and baseline septum thickness).

Notably, the present study has several limitations. First, some inherent limitations are associated with the retrospective and observational design of this study. Second, as was demonstrated in the past, some patients present with thicker basal septa and slower haemodynamic improvement after ASA. The ASA-related reduction of LVOTO may be determined by individual factors and can last 1–6 months.[20] Therefore, each participating centre had its own schedule for post-ASA clinical examinations. Thus, we cannot clearly recommend when patients should be examined post ASA to assess the long-term postprocedural prognosis. However, this limitation does not dispute the fact that the long-term effects of LVOTO are deleterious and negatively impact the occurrence of cardiovascular mortality events.

CONCLUSIONS

After ASA for obstructive HCM, residual obstruction ≥30 mm Hg at the early postdischarge clinical check-up is associated with a significantly higher occurrence of post-ASA cardiovascular mortality events.

Key messages

What is already known on this subject?
Left ventricular outflow tract obstruction is associated with increased mortality in patients with hypertrophic cardiomyopathy. There is a growing body of non-randomised evidence suggesting that reduction/elimination of the outflow gradient might be associated with better clinical outcomes.

What might this study add?
This study is the first to demonstrate that patients who have undergone alcohol septal ablation and then achieve outflow gradient <30 mm Hg soon after the procedure present a significantly lower occurrence of cardiovascular mortality events during long-term follow-up.

How might this impact on clinical practice?
The results of this study suggest that alcohol septal ablation with complete elimination of obstruction might be advantageous for symptomatic patients with hypertrophic obstructive cardiomyopathy. Additional studies supporting this data are needed.

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Contributors JV drafted the MS, performed statistical analysis, conceived and designed the research and acquired the data; JK, JJ, RA and PT made critical revision of the MS and acquired the data.

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