ORIGINAL ARTICLE

Age-related survival after alcohol septal ablation in hypertrophic obstructive cardiomyopathy

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Abstract

Aims   Since its introduction, alcohol septal ablation (PTSMA) was discussed as treatment option only in elderly symptomatic patients with hypertrophic obstructive cardiomyopathy (HOCM). We report on long-term follow-up after PTSMA with respect to patient's age.

Methods and results   Between May 2000 and June 2017, we treated 952 consecutive HOCM patients with PTSMA; 133 (14.0%) patients were <40 years of age (Group A; mean age 30.3 ± 7.6; 26.3% female), 422 (44.3%) patients were between ≥40 and <60 years of age (Group B; mean age 50.6 ± 5.8; 27.0% female), and 397 (41.7%) patients were ≥60 years of age (Group C; 69.7 ± 6.1; 60.2% female). After PTSMA, need of pacemaker implantation was lowest in Group A (3.8%, $P < 0.01$ each) compared with Group B (9.2%) and Group C (14.1%) during hospital stay. One patient in Groups A and C died during hospital stay, each. Follow-up was longer in Group A (7.4 ± 5.5 years) compared with Group C (5.6 ± 4.8 years; $P < 0.001$) and comparable with Group B (6.5 ± 5.1 years). Mortality was highest in Group C (13.1%; $P < 0.0001$ each) compared with Group A (1.5%) and Group B (4.3%). In Group A, no patient died from cardiac reason, whereas five patients died from cardiac reasons in Group B and seven patients in Group C. Sudden cardiac death was not observed in Group A, whereas three patients in Group B and one patient in Group C suffered sudden cardiac death.

Conclusions   Mortality after PTSMA is predominantly due to non-cardiac reasons and mainly observed in elderly patients. Survival in young patients is not affected by cardiac mortality. In experienced centres with careful patient selection, PTSMA is safe in young patients.

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiac disorder. Its prevalence is given with 0.2% in a cohort study of probands age 23–35 years.[1] About 70% of the patients develop left ventricular dynamic obstruction.[2,3] In symptomatic patients despite maximal medical tolerated therapy, surgical myectomy was introduced as successful treatment option for gradient reduction even in younger patients. Since its introduction by Sigwart in 1994, percutaneous alcohol septal ablation[4] achieved widespread acceptance,

especially if this interventional procedure is performed in experienced centres. Actual American guidelines reserve alcohol septal ablation to adult patients with increased surgical risk due to serious co-morbidities or advanced age.[5] The European guidelines underline the controversial standpoints regarding alcohol septal ablation due to the lack of long-term data on the late effects of a myocardial scar in children, adolescents, and young adults.[6] Therefore, we report on the long-term follow-up after alcohol septal ablation with respect to patient's age in a large single-centre cohort.

Methods

Patients

The study includes 952 consecutive patients with symptomatic hypertrophic obstructive cardiomyopathy who underwent first alcohol septal ablation (PTSMA) at Leopoldina Hospital Schweinfurt, Germany, between May 2000 and June 2017. Clinical indications were dyspnoea (New York Heart Association) and/or angina (Canadian Cardiovascular Society) Functional Class III or IV, and/or recurrent exercise-induced presyncope or syncope. Left ventricular gradients should be at least 30 mmHg at rest or 50 mmHg at provocation (Valsalva manoeuvre or post-extrasystolic beat).

We divided the cohort into three groups: young (<40 years; Group A), middle-aged (40 to <60 years; Group B), and older (≥60 years; Group C) patients. After intensive explanation of both septal reduction treatment options (surgical myectomy and PTSMA), all patients—and in all underage patients their parents—gave written consent. The study was in compliance with the Declaration of Helsinki.

Baseline examinations

All patients underwent medical history taking including family history with respect to HCM and sudden cardiac death (SCD). Baseline echocardiography was performed in each patient including outflow tract gradient measurement at rest and Valsalva manoeuvre. Electrocardiographic studies included ECG at rest and Holter monitoring in all patients. Ergospirometry could be performed in 81.7% of the patients. Invasive studies including coronary angiography, simultaneous LV gradient measurements at rest, Valsalva and post-extrasystolic beat, and LV angiography were mainly performed in one session with PTSMA.

Alcohol septal ablation technique

The technique of PTSMA was described before.[7,8] In brief, PTSMA was performed with local anaesthesia, with continuous simultaneous pressure recording of left ventricular and aortic pressure after exclusion of aortic valve gradient, and protection of a temporary pacemaker in patients without pre-implanted device [pacemaker or implantable cardioverter defibrillator (ICD)]. Intraprocedural echocardiographic monitoring and angiographic exclusion of intraseptal collateralization were mandatory. After alcohol injection, monitoring on the intensive care unit for at least 48 h or until definitive decision on the necessity of device implantation due to permanent total heart block was standard. The type of device was chosen according to the currently valid recommendations. Hospital discharge was earliest 1 week after PTSMA.

Follow-up

The patients underwent a first non-invasive follow-up control after 3 months. Subsequent cardiac examinations had been annually performed either in our institution or by the referring cardiologists. Vital status, cardiac or other clinical events, and symptomatic status compared with the pre-interventional time had been evaluated by a questionnaire. Direct telephone contact to the patients or general practitioner or referring cardiologist was performed in doubtful answers and non-returned questionnaires.

Definitions

Echocardiographic measurements were obtained following the current guidelines of the American Society of Echocardiography. Wall thickness of interventricular septum and posterior wall as well as left atrial dimension in parasternal long axis was indexed by body surface area. Left ventricular outflow tract gradients were assessed by continuous wave Doppler echocardiography at rest and at Valsalva manoeuvre.

Holter monitoring was taken for at least 24 h before ablation. According to risk stratification models, a non-sustained ventricular tachycardia (NSVT) was defined as three consecutive ventricular beats at a rate of 120 b.p.m. and <30 s in duration. Ergospirometry was performed using a ramp protocol with measurement of absolute and indexed maximal workload (watts and watts per BSA), peak O_2 consumption (mL/min), and O_2 consumption at anaerobic threshold (mL/min).

All-cause mortality was defined as death due to any cause. Cardiovascular death was defined as death related to any cardiovascular disease, including stroke. Cardiac death was defined as death related to any cardiac disease including SCD. SCD 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.

Statistics

All data were collected in an SQL database. Statistical analysis was performed using Stata 15 (StataCorp, College Station, TX). Continuous variables were expressed as mean ± standard deviation and in addition median and inter-quartile range in case of non-normal distribution (body weight, body mass index, left atrial diameter, and left ventricular end-systolic diameter). Frequencies were given

for discrete variables. Comparison of continuous variables was carried out using ANOVA or Kruskal–Wallis test. Continuous variables of two groups were compared with the unpaired Student's t-test. Paired Student's t-test was used for comparison of continuous variables at different times within one group. Categorical variables were compared using χ^2 test. A P-value <0.05 was considered statistically significant. Survival estimations were analysed with Kaplan–Meier curves. Differences in survival were assessed using the log-rank test.

Results

Baseline characteristics

We subdivided our study cohort of 952 patients (range 14.9–85.1 years) with first PTSMA at our centre in three age groups (*Table 1*). *Figure 1* shows age distribution of the cohort in decades; 133 (14.0%) patients were <40 years of age at the time of PTSMA (Group A, mean age 30.3 ± 7.6 years), 422 (44.3%) patients were between 40 and <60 years

Table 1 Baseline characteristics of 952 patients with alcohol septal ablation (PTSMA) with respect to age groups

	Group A <40 years	Group B 40 to <60 years	Group C ≥60 years	*P*-value
Patients	133 (14.0)	422 (44.3)	397 (41.7)	
Women	35 (26.3)	114 (27.0)	239 (60.2)*	*P < 0.00001 (C vs. A and B)
Age (years)	30.3 ± 7.6	50.6 ± 5.8	69.7 ± 6.1	
Height (cm)	175.4 ± 10.2	173.9 ± 9.6	166.6 ± 10.1*	*P < 0.00001 (C vs. A and B)
Weight (kg)	81.7 ± 17.4	87.1 ± 16.0	78.2 ± 14.8	P < 0.00001
Median (range)	82.0 (70–92)	86 (77–98)	76 (68–88)	
BMI (kg/m^2)	26.5 ± 4.9*	28.8 ± 4.6	28.2 ± 4.7	P < 0.001
Median (IQR)	26.3 (22.9–29.9)	28.2 (25.6–31.3)	27.3 (24.8–30.6)	
BSA (m^2)	1.96 ± 0.23	2.00 ± 0.21	1.85 ± 0.20	P < 0.001
Symptoms				
NYHA III/IV	91 (68.4)	286 (67.8)	321 (80.9)	P < 0.001
Angina pectoris	59 (44.3)	215 (50.9)	217 (54.8)	n.s.
Syncope				
Unexplained	13 (9.8)	37 (8.8)	43 (10.8)	n.s.
Effort induced	59 (44.3)	155 (36.8)	174 (33.8)	n.s.
Palpitations	45 (33.8)	135 (32.0)	113 (28.5)	n.s.
Family history				
Hypertrophic CM	67 (50.4)*	107 (25.4)	53 (13.4)	*P < 0.00001 (A vs. B and C)
Sudden cardiac death	23 (17.3)*	47 (11.1)	28 (7.0)*	*P < 0.01 (A vs. B and C)
Smoker	47 (35.3)	142 (33.7)	65 (16.4)*	*P < 0.0001 (C vs. A and B)
Cardiac diseases				
Hypertension	19 (14.3)*	213 (50.6)	284 (71.5)	*P < 0.00001 (A vs. B and C)
Coronary artery disease	1 (0.8)	39 (9.3)	83 (20.9)	P < 0.00001
Atrial fibrillation	4 (3.0)	56 (13.3)	73 (18.4)	P < 0.001
Paroxysmal	4 (3.0)	49 (11.6)	60 (15.1)	
Permanent	0 (0)	7 (1.7)	13 (3.3)	
Medication				n.s.
Beta-blocker	94 (70.7)	280 (66.4)	264 (66.5)	
Verapamil	36 (27.1)	94 (22.3)	115 (29.0)	
Disopyramide	4 (3.0)	6 (1.4)	3 (0.8)	
Prior septal reduction				
Alcohol septal ablation	8 (6.3)	17 (4.1)	16 (4.2)	n.s.
Myectomy	3 (2.4)	7 (1.7)	10 (2.6)	n.s.
Prior device therapy				
Pacemaker	6 (4.7)	16 (3.9)	30 (7.8)	n.s.
ICD	25 (19.7)	42 (10.1)	23 (6.0)	P < 0.0001
Holter				
Sinus rhythm	122 (96.1)	392 (94.5)	352 (90.0)	P < 0.01
Atrial fibrillation	0 (0)	11 (2.7)	29 (7.5)	P < 0.001
SV tachycardia	6 (4.7)	42 (10.1)	65 (16.6)	P < 0.01
Non-sustained VT	10 (7.9)	47 (11.3)	41 (10.5)	n.s.
Ergospirometry				
Work capacity (W)	134.7 ± 44.3	124.4 ± 44.1	92.6 ± 36.5	P < 0.00001
Work capacity (W/kg)	1.7 ± 0.5	1.5 ± 0.5	1.2 ± 0.4	P < 0.00001
Peak VO$_2$ (mL/min/kg)	23.0 ± 6.2	20.7 ± 5.5	17.6 ± 4.6	P < 0.00001
VO$_2$ at AT (mL/min/kg)	15.3 ± 4.7	13.7 ± 4.2	13.0 ± 3.9	P < 0.00001

AT, anaerobic threshold; BMI, body mass index; BSA, body surface area; CM, cardiomyopathy; ICD, implantable cardioverter defibrillator; IQR, inter-quartile range; NYHA, New York Heart Association; SD, standard deviation; SV, supraventricular; VO$_2$, oxygen consumption; VT, ventricular tachycardia.
Values are given in mean ± SD, median and IQR (in non-normal distribution), and n (%).

Figure 1 Distribution of age (in decades) in 952 patients at the time of alcohol septal ablation (PTSMA).
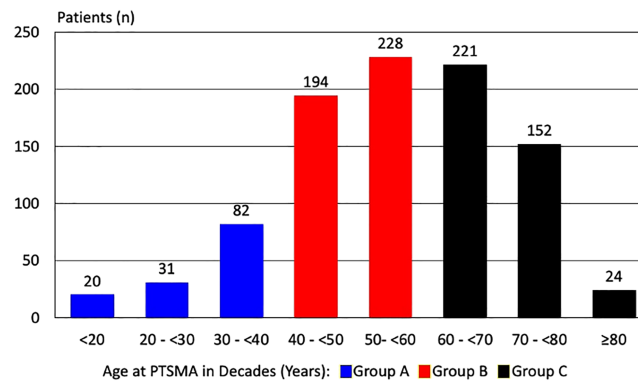
(Group B, mean age 50.6 ± 5.8 years), whereas 397 (41.7%) patients were ≥60 years of age (Group C, mean age 69.7 ± 6.1 years). The small number of patients with prior septal reduction treatment either by PTSMA or myectomy was comparable.

The old patients suffered more often from dyspnoea New York Heart Association Class III/IV (80.9%; $P < 0.001$ each) compared with patients of Group A (68.4%) and Group B (67.8%). Differences in other cardiac symptoms like angina and exercise-induced as well as unexplained syncope were not found.

Young patients reported more often family history of HCM (50.4%; $P < 0.00001$, each) and SCD (17.3%; $P < 0.01$, each) compared with patients of Group B (HCM 25.4% and SCD 11.1%) and Group C (HCM 13.4% and SCD 7.0%). In contrast to comparable number of pre-interventional pacemaker implantation in all groups, young patients had more often a pre-implanted ICD (19.7%, $P < 0.0001$ each) compared with patients of Group B (10.1%) and Group C (6.0%). Pre-interventional Holter monitoring showed no differences in incidence of NSVT. A history of atrial fibrillation was less commonly reported by young patients (3.0%; $P < 0.001$, each) compared with patients in Group B (13.3%) and Group C (18.4%).

Not unexpected, the incidences of systemic hypertension (Group A 14.3% vs. Group B 50.6% vs. Group C 71.5%; $P < 0.00001$ between all age groups) and coronary artery disease (Group A 0.8% vs. Group B 9.3% vs. Group C 20.9%; $P < 0.00001$ between all age groups) were significantly higher with increasing age. Comparable number of patients reported on smoking in Group A (35.3%) and Group B (33.7%), whereas smoking was less often seen in Group C (16.4%; $P < 0.0001$, each).

Acute results and hospital course

According to larger maximal septal thickness (*Table 2*), we injected a larger amount of alcohol in younger patients of Group A (2.4 ± 0.7 mL; $P < 0.00001$, each) compared with patients of Group B (2.0 ± 0.4 mL) and Group C (2.0 ± 0.3 mL). Older patients of Group C had less maximal CK rise (820 ± 394 U/L; $P < 0.05$, each) compared with patients of Group A (916 ± 446 U/L) and Group B (908 ± 574 U/L).

Echocardiographic gradient reduction at hospital discharge (*Table 3*) was less in young patients of Group A [45.3 ± 30.7 mmHg at rest ($P < 0.001$ each) and 68.3 ± 38.0 mmHg at Valsalva ($P < 0.001$ each)] compared with patients of Group B (31.7 ± 28.2 mmHg at rest and 54.5 ± 39.3 mmHg at Valsalva) as well as Group C (31.6 ± 30.3 mmHg at rest and 54.8 ± 43.0 mmHg at Valsalva).

One patient of Group A died at Day 3 after PTSMA due to pulmonary embolism, and one patient of Group C died at Day 33 due to pneumonia. A 47-year-old woman got a dissection of the left main coronary artery at the first attempt, which could be fixed with a stent followed by successful PTSMA 6 months later.

Conduction abnormalities were less often observed in younger patients of Group A (*Table 2*). Furthermore, temporary total heart blocks during PTSMA were more often seen in patients of Group C (43.6%) and Group B (39.3%) compared with the young patients (28.6%; $P < 0.05$, each). Consequently, young patients required less often implantation of a permanent pacemaker due to ongoing total heart block (3.8%; $P < 0.01$, each) compared with patients of Group B (9.2%) and Group C (14.1%).

Follow-up results

Follow-up was longer in younger patients (7.4 ± 5.5 years) and patients in Group B (6.5 ± 5.1 years) compared with Group C (5.6 ± 4.8 years; $P < 0.001$, each) (*Table 4*). The proportions of living patients who reported clinical improvement were comparable in all groups (94% in Group A vs. 93.8% in Group B vs. 95.0% in Group C).

Table 2 Baseline echocardiographic measurements of 952 patients with alcohol septal ablation (PTSMA) with respect to age groups

	Group A <40 years	Group B 40 to <60 years	Group C ≥60 years	P-value
Patients	133 (14.0)	422 (44.3)	397 (41.7)	
Maximal IVS thickness (mm)	23.9 ± 5.6*	20.9 ± 4.0	20.1 ± 3.5	*P < 0.00001 (A vs. B and C)
Maximal IVS/BSA (mm/m^2)	12.4 ± 3.5*	10.5 ± 2.3	10.9 ± 2.2	*P < 0.00001 (A vs. B and C)
Subaortic IVS thickness (mm)	21.2 ± 4.8	19.8 ± 3.8	18.9 ± 3.5	P < 0.00001
Subaortic IVS/BSA (mm/m^2)	11.0 ± 2.8	9.9 ± 2.1	10.3 ± 2.1	P < 0.001
LVPW thickness (mm)	13.6 ± 3.7	13.4 ± 2.8	12.9 ± 2.7*	*P < 0.05 (C vs. A and B)
LVPW/BSA (mm/m^2)	7.1 ± 2.1	6.7 ± 1.5	7.0 ± 1.6	P < 0.05
LVEDD (mm)	42.1 ± 5.7	44.3 ± 6.7	43.0 ± 6.4	P < 0.01
LVEDD/BSA (mm/m^2)	21.6 ± 3.2	22.3 ± 3.5	23.3 ± 3.8	P < 0.001
LVESD (mm)	22.1 ± 5.4	23.7 ± 5.7	23.3 ± 5.8	n.s.
Median (IQR)	22 (19–26)	23 (19–27)	23 (19–27)	
LVESD/BSA (mm/m^2)	11.3 ± 2.8	11.9 ± 2.9	12.6 ± 3.2*	P < 0.001 (C vs. A and B)
LA diameter (mm)	46.0 ± 7.5	46.6 ± 6.6	45.5 ± 6.7	n.s
Median (IQR)	46 (41–51)	47 (42–51)	45 (41–49)	
LA/BSA (mm/m^2)	23.5 ± 4.1	23.5 ± 3.6	24.6 ± 4.0*	P < 0.001 (C vs. A and B)
LVOT Doppler gradients				
Rest (mmHg)	69.7 ± 34.7	59.5 ± 35.3	66.5 ± 41.7	P < 0.01
Valsalva (mmHg)	98.8 ± 40.1*	102.8 ± 40.1	108.5 ± 48.6	*P < 0.05 (A vs. C)

BSA, body surface area; IQR, inter-quartile range; IVS, intraventricular septum; LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVOT, left ventricular outflow tract; LVPW, left ventricular posterior wall; SD, standard deviation.
Values are given in mean ± SD, median and IQR (in non-normal distribution), and n (%).

Reduction of outflow tract gradients at rest and Valsalva in young patients was delayed (*Figure 2*). Because of our staged procedure of interventional gradient reduction that takes into consideration the potential remodelling within the first year after PTSMA, re-PTSMA in survivors was more often observed in younger patients of Group A (23.3%; P < 0.001) compared with patients in Group B (13.3%) and Group C (10.6%), whereas the numbers of necessary myectomies, observed atrial fibrillation, and necessary pacemaker were comparable (*Table 4*). Differences between the groups (P < 0.05)

were found in the number of ICD implantations during follow-up. Holter monitoring at follow-up showed no differences in patients with NSVT (*Table 4*) and no significant increase compared with baseline evaluation.

Overall mortality was highest in old patients of Group C (52 patients (13.1%); P < 0.0001, each), whereas 2 patients of Group A (1.5%) and 18 patients of Group B (4.3%) died during follow-up. *Figure 3* shows that no young patient died because of cardiovascular cause. Cardiac deaths due to heart failure were seen in 5 (1.18%) patients of Group B and 7 (1.76%)

Table 3 Hospital course of 952 patients with PTSMA with respect to age groups

	Group A <40 years	Group B 40 to <60 years	Group C ≥60 years	P-value
Patients	133 (14.0)	422 (44.3)	397 (41.7)	
Angiographic LVEF (%)	71.4 ± 10.5	73.1 ± 8.4	72.4 ± 10.0	n.s.
Invasive LV gradients				
Rest (mmHg)	62.2 ± 34.5*	49.3 ± 38.0	49.7 ± 38.8	*P < 0.001 (A vs. B and C)
Valsalva (mmHg)	87.4 ± 37.9*	92.7 ± 36.1	99.9 ± 40.8	*P < 0.001 (C vs. A and B)
Post-extrasystole (mmHg)	128.3 ± 42.5*	132.8 ± 47.3	139.1 ± 51.9	*P < 0.05 (A vs. C)
More than 1 branch treated	5 (3.8)*	5 (0.9)	2 (0.5)	*P < 0.05 (A vs. B and C)
Alcohol injected (mL)	2.4 ± 0.7*	2.0 ± 0.4	2.0 ± 0.3	*P < 0.00001 (A vs. B and C)
Maximal CK rise (U/L)	916 ± 446	908 ± 574	820 ± 394*	*P < 0.05 (C vs. A and B)
Third-degree AV block at any time	38 (28.6)*	166 (39.3)	173 (43.6)	*P < 0.05 (A vs. B and C)
Echo gradients at discharge				
Rest (mmHg)	45.3 ± 30.7*	31.7 ± 28.2	31.6 ± 30.3	*P < 0.001 (A vs. B and C)
Valsalva (mmHg)	68.3 ± 38.0*	54.5 ± 39.3	54.8 ± 43.0	*P < 0.01 (A vs. B and C)
Complications				
Death	1 (0.8)	0	1 (0.3)	n.s.
Permanent pacemaker	5 (3.8)*	39 (9.2)	56 (14.1)	*P < 0.01 (A vs. B and C)
Pericardial effusion	1 (0.8)	6 (1.4)	17 (4.3)	n.s.

AV, atrioventricular; CK, creatine kinase; LV, left ventricular; LVEF, left ventricular ejection fraction; SD, standard deviation.
Values are given in mean ± SD and n (%).

Table 4 Follow-up of 952 patients with PTSMA with respect to age groups

	Group A <40 years	Group B 40 to <60 years	Group C ≥60 years	P-value
Patients	133 (14.0)	422 (44.3)	397 (41.7)	
Follow-up (years)	7.4 ± 5.5	6.5 ± 5.1	5.6 ± 4.8[*]	[*]P < 0.001 (C vs. A and B)
Clinical symptoms				n.s.
Improvement	125 (94.0)	396 (93.8)	377 (95.0)	
No change	6 (4.5)	18 (4.3)	10 (2.5)	
Worsening	1 (0.8)	5 (1.2)	2 (0.5)	
Echo gradients at last follow-up				
Rest (mmHg)	23.7 ± 24.9[*]	16.4 ± 18.1	17.7 ± 21.4	[*]P < 0.001 (A vs. B and C)
Valsalva (mmHg)	34.3 ± 33.5	30.9 ± 30.6	33.5 ± 36.4	n.s.
Maximal IVS thickness (mm)	21.1 ± 5.4[*]	18.2 ± 4.0	17.5 ± 3.6	[*]P < 0.001 (A vs. B and C)
Holter NSVT	11 (10.9)	30 (9.0)	24 (8.3)	n.s.
Complications				
Death	2 (1.5)	18 (4.3)	52 (13.1)[*]	P < 0.0001 (C vs. A and B)
Myectomy	5 (3.8)	9 (2.1)	5 (1.3)	n.s.
Re-PTSMA	31 (23.3)	56 (13.3)	42 (10.6)	<0.001
Atrial fibrillation	10 (7.5)	31 (7.3)	16 (4.0)	n.s.
Pacemaker implantation	1 (0.8)	12 (2.8)	12 (3.0)	n.s.
ICD implantation	11 (8.3)	26 (6.2)	13 (3.3)	P < 0.05

ICD, implantable cardioverter defibrillator; IVS, intraventricular septum; NSVT, non-sustained ventricular tachycardia; SD, standard deviation.
Values are given in mean ± SD and *n* (%).

patients of Group C. Furthermore, non-cardiovascular causes were the predominant reason of mortality in all age groups. Survival (*Figure 4*) was highest in young patients (P < 0.0001). At 5 years, Kaplan–Meier estimated survival was 0.993 (Group A) compared with 0.981 (Group B) and 0.919 (Group C). After 10 years, estimated survival was 0.980 in Group A, 0.956 in Group B, and 0.762 in Group C. After 15 years, estimated survival was 0.980 in Group A, 0.902 in Group B, and 0.608 in Group C.

Discussion

Despite the initial and still persistent scepticism about the negative effects of an induced myocardial infarction,[9,10] alcohol septal ablation could be established as accepted treatment option in symptomatic patients with hypertrophic obstructive cardiomyopathy—especially after the introduction of echocardiographic guidance to identify the appropriate target vessel.[2,4,7,11–13] But actual European Society of
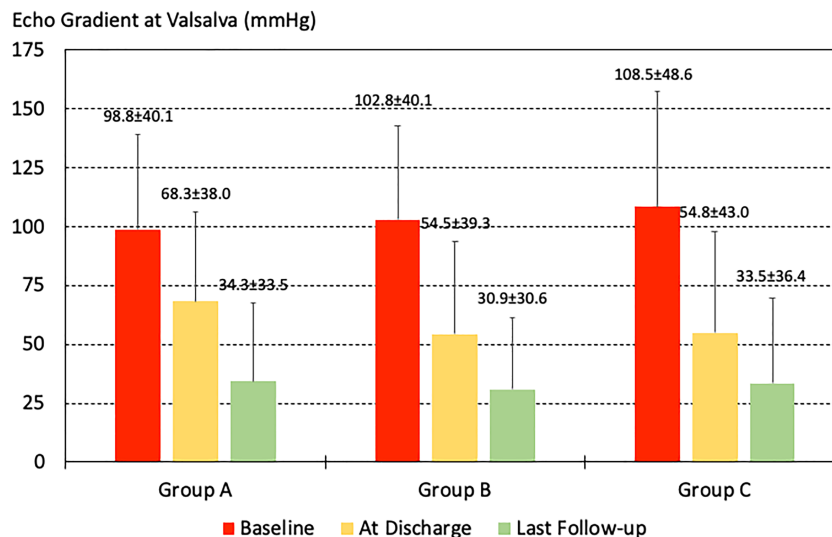
Figure 2 Reduction of echocardiographic gradients at Valsalva after alcohol septal ablation (PTSMA) with respect to age groups (Group A = patients <40 years of age; Group B = patients >40 to <60 years of age; and Group C = patients ≥60 years of age).

Figure 3 Reasons of death after alcohol septal ablation (PTSMA) with respect to age groups (Group A = patients <40 years of age; Group B = patients >40 to <60 years of age; and Group C = patients ≥60 years of age).
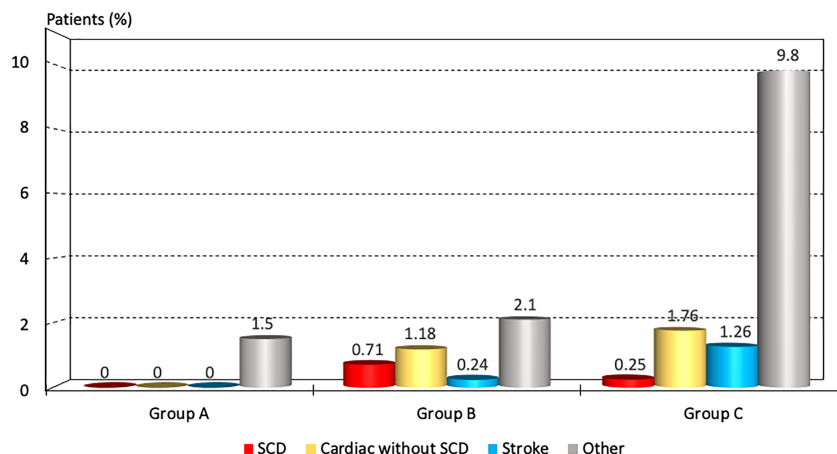

Cardiology (ESC) guidelines of HCM discuss alcohol septal ablation controversial in adolescents and young adults because of lack of data on the long-term effects of myocardial scar.[6] Therefore, we report on long-term follow-up after PTSMA in a large single-centre cohort with respect to patient's age at the time of gradient reduction therapy. Our study did not intend to show superiority of PTSMA in any age group, but only to describe follow-up with respect to patient's age at the time of intervention.

In contrast to other studies,[14–17] we chose different age groups taking into account actual risk stratification models[18,19] and mortality causes in HCM.[20,21] ESC risk stratification defines history of SCD in one or more first-degree relatives under 40 years of age as risk factor for SCD. Therefore, we used this age as cut-off to define young patients. As the main cause of death in HCM patients >60 years of age was non-HCM related,[21] we chose this threshold to define the group of older patients. Consequently, patients

Figure 4 Kaplan–Meier estimated overall survival after alcohol septal ablation (PTSMA) with respect to age groups (Group A = patients <40 years of age; Group B = patients >40 to <60 years of age; and Group C = patients ≥60 years of age).
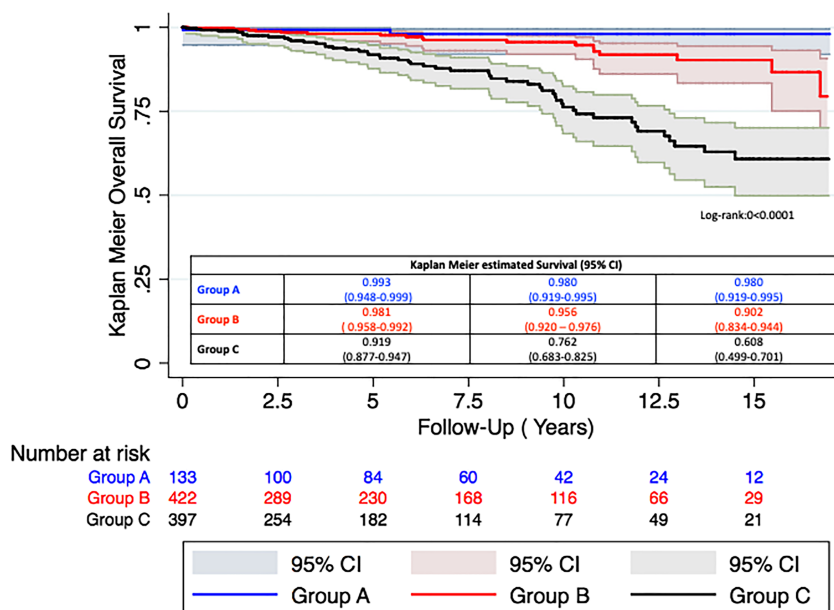
between 40 and 60 years of age were defined as middle-aged group.

The most important finding was the absence of sudden and cardiac death in the young age group, which supports previous reports that therapeutic alcohol-induced infarction did not increase the risk of SCD. This absence was not caused by the higher number of ICD implantation before and after PTSMA. Only one female patient with successful PTSMA at the age of 15 years required the ICD for secondary prevention of SCD 11 years later—she had no adequate or inadequate ICD intervention during 8 years follow-up after implantation. All other patients got their ICD implanted for primary prevention due to changing risk stratification models during the study period.

Not surprisingly, mortality increased with age. In agreement with the observations of Maron *et al*.,[20] the main cause of death in elderly patients was non-cardiac death, whereas in middle-aged patients, cardiac and non-cardiac causes of death were balanced. These findings support previous data that alcohol septal ablation does not harm survival due to the induced scar irrespectively of patient's age.[14,15,17]

Our interventional procedure with staged echo-guided ablation that takes into account the previously reported remodelling with continuous gradient reduction during the first post-interventional year[8] resulted in higher number of young patients requiring re-intervention. Although not proven by randomized trials, it can be speculated that our careful method intending to create a scar as small as possible and as big as necessary may cause the excellent acute and follow-up results. Therefore, we do not rate a re-PTSMA as complication but integral part of the treatment.

Comparable with previous reports, patients showed an age-independent clinical improvement at last follow-up.[14,15,17] This important finding is in accordance with the last measured stress gradients that showed no age-related differences, whereas the gradients at discharge showed higher values in young patients. These findings also support our previous observation of remodelling with further gradient reduction during follow-up.

Besides the discussed positive long-term survival, our analysis showed some interesting and important points with respect to age-related baseline characteristics and acute results. Despite autosomal dominant inheritance, age-related gender distribution supports general findings of male dominance in younger age groups. Previous own analysis discussed delayed diagnosis of HCM in women due to lack of BSA indexed, but use of non-indexed echocardiographic thresholds of left ventricular wall thickness on the one hand and reduced disease awareness of cardiologists and affected women on the other hand.[22] Therefore, Tome Esteban concluded the need of an age-appropriate and gender-appropriate approach definition.[23]

As expected, family history of HCM as well as SCD was more often observed in the young age group. Consequently,

and in accordance with the current risk stratification models, an ICD for primary prevention of SCD was more often implanted in young patients. A direct comparison of the frequency of pre-interventional ICD implantation rates with other surgical and interventional cohorts is neither possible nor useful because of the different age groups selected in the studies.

Like in other reports,[14,15,17] left ventricular hypertrophy was more pronounced in young patients both taking into account absolute and indexed echocardiographic measurements. As we inject 1 cc of alcohol per cm absolute septal thickness, the quantity of injected alcohol was highest in young age group. In agreement with the experience of a European multicentre study,[24] which describes the 30 day course after alcohol septal ablation, the larger amount of alcohol also had no negative influence on acute results and long-term survival after PTSMA.

As the result of longer lasting disease, old patients suffered more often from atrial fibrillation, which could also be caused by the age-dependent increase of incidence of hypertension. Not unexpected is the consequently seen higher incidence of ischaemic stroke in the old patient group. Even reports on causes of HCM-related deaths in a post-mortem observation had described advanced age as main reason of stroke due to atrial fibrillation.[21]

Estimated by increase of maximal CK rise after PTSMA, the septal scar was smaller in the old-aged group. In-hospital overall mortality was very low with 0.21% without age-related differences. This is in contrast to the results of the Euro-ASA group who reported an increase of in-hospital mortality with advancing age.[14] The numerically most significant complication of PTSMA is the occurrence of total heart block resulting in the need of permanent pacemaker implantation. Not only the occurrence of heart block at any time of the intervention increased with age, but also the recovery to normal AV conduction during hospital stay decreased with age and was highest in the young age group resulting in lower need of permanent pacemaker implantation. This finding was also reported by Liebregts *et al*.[14] But direct comparisons of absolute numbers are not possible because of chosen age groups and different timing for indication for permanent pacemaker implantation with respect operator's experience[25,26] and patient's requirements.

The positive results of this large observational study in our experienced single-centre cohort should stimulate the discussion about actual ESC guideline statements, which recommend alcohol septal ablation primarily to elderly patients due to unknown effects of the induced myocardial scar.[6] However, decision-making process with respect to indication and method of gradient reduction should be limited to an HCM team. This team ideally includes colleagues with special experience in diagnosis, surgical myectomy, and alcohol septal ablation.[27] Only under this scenario morphological and clinical parameters can be properly considered as basis of a

personalized decision about the optimal treatment in an individual patient.

Limitations

This large single-centre observational study reports on the age-dependent results of alcohol septal ablation. A major limitation of observational studies can be the selection bias of treated patients. Therefore, the important question about clinical and morphological criteria favouring PTSMA in each age group cannot be answered. Prospective registries or randomized trials maybe helpful in order to identify these criteria. Furthermore, comparison with surgical myectomy cannot be performed. This can only be performed in a randomized trial. Because of the time span of this study, we did not perform genetic testing in a larger proportion of the patients. Finally, values of BNP and/or NT-proBNP cannot be shown sufficiently because of the long duration of the study and that the values cannot be shown reliably because of the change from BNP to NT-proBNP during the study period.

Conflict of interest

All authors declare no conflicts of interest connected to this paper.

Funding information

No funding was used while completing this study.

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