International Journal of Cardiology 273 (2018) 155–161

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Timing of invasive septal reduction therapies and outcome of patients with obstructive hypertrophic cardiomyopathy

Luna Cavigli [a,1,2], Carlo Fumagalli [a,*,1,2], Niccolò Maurizi [a,2], Alessandra Rossi [a,2,3], Anna Arretini [a,2], Mattia Targetti [a,2], Silvia Passantino [a,2], Francesca Girolami [b,2], Benedetta Tomberli [a,2], Katia Baldini [a,2], Alessia Tomberli [a,2], David Antoniucci [a,2], Magdi H. Yacoub [c,2], Niccolò Marchionni [a,2], Pier Luigi Stefano [a,2], Franco Cecchi [d,2], Iacopo Olivotto [a,2]

[a] Cardiothoracic and Vascular Department, Careggi University Hospital, Florence, Italy
[b] Genetic Diagnostics Unit, Careggi University Hospital, Florence, Italy
[c] Harefield Heart Science Centre, National Heart & Lung Institute, Imperial College, London, UK
[d] Istituto Auxologico, Milan, Italy

ARTICLE INFO

Article history:
Received 30 January 2018
Received in revised form 30 August 2018
Accepted 3 September 2018
Available online 5 September 2018

Keywords:
Timing
Surgical myectomy
Alcohol septal ablation
Septal reduction therapies
Hypertrophic obstructive cardiomyopathy
Outcome

ABSTRACT

Background: Whether early vs. delayed referral to septal reduction therapies (SRT, alcohol septal ablation or surgical myectomy) bears prognostic relevance in hypertrophic obstructive cardiomyopathy (HOCM) is unresolved. We analyzed the impact of SRT timing on the outcome of HOCM patients.

Methods: We followed 126 patients for 5 ± 4 years after SRT (mean age 53 ± 15 years; 55 post-ASA and 71 post-SM). Based on time-to-treatment (TTT; from HOCM diagnosis to SRT), patients were divided into three groups: "<3" years, N = 50; "3–5" years, N = 25; ">5" years, N = 51.

Results: Patients with TTT > 5 years were younger at diagnosis and more often had atrial fibrillation (AF). Left ventricular outflow tract (LVOT) gradients were comparable in the 3 TTT groups. Two patients died peri-operatively, all with TTT > 5. Long-term, 8 patients died (3 suddenly and 5 due to heart failure). Mortality increased progressively with TTT (2% vs. 4% vs. 12% for TTT "<3", "3–5", and ">5" years, p for trend = 0.039). Independent predictors of disease progression (new-onset AF, worsening to NYHA III/IV symptoms, re-intervention or death) were TTT ("3–5" vs. "<3" years: HR: 4.988, 95%CI: 1.394–17.843; ">5" vs. "<3" years: HR: 3.420, 95%CI: 1.258–9.293, overall p-value = 0.025), AF at baseline (HR: 1.896, 95%CI: 1.002–3.589, p = 0.036) and LVOT gradient (HR per mm Hg increase: 1.022, 95%CI: 1.007–1.024, p = 0.023).

Conclusions: Delay in SRT referral has significant impact on long-term outcome of patients with HOCM, particularly when >5 years from first detection of gradient, even when successful relief of symptoms and gradient is achieved. Earlier interventions are associated with lower complication rates and better prognosis, suggesting the importance of timely SRT to maximize treatment benefit and prevent late HOCM-related complications.

1. Introduction

Dynamic left ventricular outflow tract obstruction (LVOTO) is a key determinant of symptoms and prognosis in patients with hypertrophic obstructive cardiomyopathy (HOCM) [1–3]. Septal reduction therapies (SRT) for severe, drug-refractory symptoms associated with LVOTO, include surgical septal myectomy (SM) and alcohol septal ablation (ASA). In experienced centers, both procedures can provide substantial and durable symptom relief in HOCM patients, and are believed to improve outcome [4–6]. Long-term, however, a sizeable subset of patients experiences adverse cardiovascular events or die from cardiovascular causes despite successful SRT [7–9]. Notably, enlarged left atrial diameter (LAD) and prior history of atrial fibrillation (AF) are the main predictors of post-SRT adverse outcome [10]. These features reflect time-related

Abbreviations: ASA, alcohol septal ablation; CV, cardiovascular; HOCM, hypertrophic obstructive cardiomyopathy; LAD, left atrial diameter; LVOT, Left ventricular outflow tract; LVOTO, Left ventricular outflow tract obstruction; NYHA, New York Heart Association functional class; SAM, systolic anterior motion; SM, septal myectomy; SRT, septal reduction therapies; TTT, time-to-treatment.

* Corresponding author at: Cardiomyopathy Unit, Department of Clinical and Experimental Medicine, University of Florence and AOU Careggi, Largo Brambilla, 3, 50134 Florence, Italy.
E-mail address: 00.carlo@gmail.com (C. Fumagalli).

[1] The two authors contributed equally to this work.
[2] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
[3] Dr. Alessandra Rossi, who provided fundamental contribution to the perioperative care of our patients and to this paper, died on August 9, 2017.

https://doi.org/10.1016/j.ijcard.2018.09.004
0167-5273/

atrial remodeling associated with long-standing LVOTO, and generally reflect delayed timing of intervention, raising the possibility that earlier SRT might translate into more favourable long-term prognosis. However, the question whether early vs. delayed SRT is relevant to outcome in HOCM, has not been previously addressed in the literature.

We here report the experience of a tertiary referral center in which a resident SRT program for HOCM was established since the mid-90s, initially based mainly on ASA and subsequently moving towards SM. Before the establishment of local expertise, patients with HOCM were treated conservatively and only seldom referred to external institutions for SRT [4]. Such conservative approach also reflected lack of clear evidence showing prognostic impact of LVOT obstruction before 2003 [1]. Following the introduction of ASA and SM, referral to SRT at our Center occurred more frequently and earlier, leading to considerable variation in time-to-treatment (TTT). Whether TTT influences the outcome of SRT in HOCM was specifically assessed in the present study, focusing on post-operative results and long-term survival.

2. Patients and methods

2.1. Patient selection

We retrospectively reviewed the clinical records of 1644 consecutive patients with hypertrophic cardiomyopathy (defined by the presence of an increased asymmetric left ventricular wall thickness ≥15 mm in the absence of abnormal loading conditions) [11,12], seen at the Florence Cardiomyopathy Unit from January 1980 to December 2015. Phenocopies (such as Anderson-Fabry disease or other storage or infiltrative conditions) were carefully excluded. Of these, 489 (30%) presented LVOT obstruction, defined by a gradient ≥30 mm Hg at rest and/or >50 mm Hg during exercise, as measured by echocardiography [11]. A total of 216 patients (44% of all obstructive), with drug-refractory symptoms, were treated with SRT, namely ASA or SM. Of these, 126 (58%) were treated at our Institution and constitute our study population; of the remaining 90, 76 were excluded because they had been referred for SRT elsewhere, often before being seen at our center - with considerable variability in operative techniques and results - and 14 had no follow-up data.

All patients were evaluated following a protocol standardized at our center, including baseline 12-lead ECG, 24-hour Holter recordings, and comprehensive two-dimensional (2D) and Doppler echocardiography. Peak instantaneous LVOT gradient, due to mitral valve systolic anterior motion (SAM) and mitral septal contact, was assessed with continuous wave Doppler under standard conditions (11). Exercise echocardiography was routinely performed since 2003 [13]. Pre- and post-operative echocardiograms were performed within 30 days and at 6 months after surgery.

2.2. Septal reduction strategies

SRT (i.e. SM or ASA) were offered to patients with a LVOT gradient ≥50 mm Hg (at rest or exercise-induced) who remained symptomatic for dyspnea, angina and/or presyncope or syncope despite maximal tolerated treatment with betablockers or verapamil, often combined with disopyramide [11,14]. In the period 1999–2004, ASA was the preferred option at our center, because of rapidly developing expertise by the interventional team (led by DA) and lack of local surgical experience. Conversely, after 2005, a dedicated surgical program was established (by MHY and PLS) and SM with LVOT remodeling became the gold standard, with ASA limited to selected patients judged at high surgical risk. In addition, the choice between the two techniques was driven by a series of technical considerations (including the need for additional surgical procedures) and individual patients' preference.

ASA was performed according to standard protocols, as previously described [15]. Briefly, a temporary pacemaker lead was inserted in all patients without permanent pacing devices. A coronary angioplasty balloon catheter was introduced over a wire into the target septal perforating artery. After balloon inflation, contrast was injected through the catheter to identify the course of the septal artery and confirm the absence of reflux proximal to balloon. Subsequently, a small volume (typically ≈3 cc) of ethanol was injected slowly through the balloon catheter, followed by normal saline flush. Ten minutes after ethanol injection, the balloon was deflated and removed. Coronary angiography was then performed to exclude left anterior descending artery damage and confirm occlusion of the septal branch.

SM was performed as previously described, in order to achieve an individually tailored remodeling of the outflow tract [15]. Through a trans-aortic approach, an extended septal myectomy guided by pre-operative imaging of the depth, width and length of muscle hypertrophy, was performed. The left and right fibrous trigones were then explored and mobilized by removing the fibrous tissue from the trigones angles, thus restoring the normal mobility of the subaortic curtain. To correct anterior displacement of the papillary muscles or their attachment to the lateral LV wall, they were thinned or mobilized from the LV free wall, and abnormal chords limiting their mobility were cut. In addition, any obstructive accessory chord or mitral valve tissue was removed.

2.3. Definition of time-to-treatment and study endpoints

The time-to-treatment (TTT) was defined as the interval from first echocardiographic detection of LVOT obstruction to SRT. Patients were then divided into three groups according to TTT: within 3 years ("<3 years"), between 3 and 5 years ("3–5 years") and >5 years (">5 years").

All patients were evaluated within 30 days after SRT, at 6 months and at further follow-up visits scheduled annually or more often if required. Assessment at each visit included 12-lead ECG, 24-hour ECG Holter recording and echocardiography. Cardiovascular mortality, defined as the occurrence of sudden cardiac death, heart failure-related death, aborted cardiac arrest or heart transplant, was the primary endpoint of the study. Secondary endpoints were: 1. a combination of cardiovascular mortality and re-intervention; 2. overall disease progression defined as cardiovascular mortality, re-intervention, new-onset AF, or progression to NYHA class III-IV.

2.4. Statistical analysis

Continuous variables, reported as mean ± SD or as median and interquartile range (IQR; for non-normal distributions), were compared between groups with Student's *t*-test or non-parametric tests, as appropriate. Categorical variables, reported as percentages were compared between groups with chi-squared test (or a Fisher's exact test when any expected cell count was <5). The Kaplan-Meier curves for the secondary endpoint (CV mortality or re-intervention) were plotted according to interventional strategy (ASA vs. SM) and survival distributions were compared using the log-rank test. Cox multivariable regression analysis (variable selection method: backward stepwise elimination) was performed including all candidate variables ($p < 0.10$ in univariate analysis). A two-sided p-value < 0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics for Macintosh, Version 24.0 (Armonk, NY: IBM Corp., USA).

3. Results

3.1. Pre-operative characteristics

The 126 study patients (67% men) were referred to SRT (ASA/SM: 55/71; 44 vs. 56%) at a mean age of 53 ± 15 years; 77 (61%) were in New York Heart Association (NYHA) functional class III–IV at the time of the procedure, whereas the remaining 49 (39%) were in class II, often symptomatic with angina or pre-syncope/syncope (Table 1). None of the patients had received prior treatment for LVOTO such as pacing or ASA.

The two SRT options were similarly distributed in each of the three TTT groups: prevalence in the "<3 years", "3–5 years" and ">5 years" groups was 32%, 48% and 53% for ASA and 68%, 52% and 47% for SM, respectively ($p = 0.091$). Despite comparable LA diameters and magnitude of LVOT gradients, patients with TTT >5 years were older and had greater prevalence of AF (Table 1). Of note, patients in this group underwent SRT after a median of 13 years (95% CI: 9–24) from initial detection of LVOT obstruction.

3.2. Interventions and peri-procedural outcomes

Of the 55 patients who underwent ASA, 35 had alcoholization of the first septal branch, 15 of the second, and 5 of the third; average ethanol dosage injected was 3.02 ± 0.85 ml. Peak rise in total creatinine kinase (CK) was 1377 ± 974 IU/l. No additional coronary procedures were performed. All 71 patients who underwent surgery were treated following the classical trans-aortic approach. A combined approach via the apex (through a "fish-mouth" incision) was necessary in three patients due to midventricular obstruction, and apical aneurysmectomy was performed in one patient. Eleven patients (15%) underwent additional surgical procedures including mitral replacement for degeneration of the leaflets ($n = 4$), mitral valve repair ($n = 2$), plasty of bicuspid aortic valve ($n = 2$) and coronary bypass graft ($n = 3$).

Peri-procedural outcomes, defined as events occurring up to 30 days after SRT, are summarized in Supplementary Table A. In patients with TTT <3 and 3–5 years, peri-operative course was largely uneventful (94% or $n = 67$ without major complications). Among those with TTT >5 years, 1 (2%) experienced sustained ventricular tachycardia and 2 (4%) died during or immediately after the procedure (1 ASA and 1 SM). Both patients had a history of obstructive disease dating more than a decade and were in NYHA class III. Specifically, the SM patient

Table 1
Baseline clinical characteristics of 126 HOCM patients referred for septal reduction therapy.

	Overall	Type of procedure			Time from gradient detection to septal reduction therapy (TTT)			
		Alcohol septal ablation	Surgical myectomy	p value	<3 years	3–5 years	>5 years	p value
	N = 126	N = 55	N = 71		N = 50	N = 25	N = 51	
Population								
Demographic data								
Male sex, n (%)	67 (53)	23 (42)	44 (62)	0.030	28 (56)	11 (44)	28 (55)	0.842
Age at diagnosis	47 ± 17	49 ± 14	42 ± 16	0.010	49 ± 15	43 ± 15	40 ± 16	0.015
Age at invasive procedure	53 ± 15	58 ± 13	48 ± 15	<0.001	50 ± 14	47 ± 16	56 ± 15	0.032
Time-to-treatment median (IQ range)	4.0 (1−12)	9.0 (3–15)	2.5 (1–7)	0.034	0 (0–1)	4 (3–4)	13 (9–24)	<0.001
Clinical status								
NYHA								
II, n (%)	49 (39)	12 (22)	37 (53)	0.003	21 (42)	9 (36)	19 (37)	0.511
III + IV, n (%)	77 (61)	43 (78)	34 (48)		29 (58)	16 (64)	32 (63)	
Atrial fibrillation, n (%)	34 (27)	23 (42)	11 (16)	<0.001	9 (18)	4 (16)	21 (41)	0.003
Paroxysmal, n (%)	30 (24)	21 (39)	9 (12.7)		9 (18)	3 (12)	18 (35)	
Persistent/permanent, n (%)	4 (3.1)	2 (3.6)	2 (2.8)		0	1 (4.0)	3 (5.8)	
Syncope, n (%)	17 (14)	5 (9.3)	12 (17)	0.731	6 (12)	4 (16)	7 (14)	0.902
Angina, n (%)	41 (33)	10 (18)	31 (44)	0.069	20 (40)	6 (24)	15 (29)	0.199
PM, n (%)	3 (2.4)	1 (1.9)	2 (2.8)	0.561	1 (2.0)	1 (4.0)	1 (2.0)	0.961
ICD, n (%)	7 (5.6)	1 (1.9)	6 (8.5)	0.712	0	3 (12)	4 (8)	0.043
Cardiac arrest, n (%)	1 (0.8)	1 (1.9)	0	0.163	0	0	1 (2)	0.493
Pre-operative echocardiographic data								
Left atrial diameter, mm	50 ± 9	51 ± 7	50 ± 10	0.291	49 ± 10	52 ± 12	50 ± 8	0.641
Septal wall thickness, mm	25 ± 5	26 ± 6	24 ± 5	0.202	24 ± 5	24 ± 5	26 ± 5	0.322
Moderate or severe mitral valve regurgitation, n (%)	41 (31)	23 (42)	18 (25)	<0.001	16 (32)	9 (36)	16 (31)	0.798
Resting LVOT gradient (mm Hg)	60 ± 32	70 ± 33	52 ± 31	0.004	63 ± 36	58 ± 32	55 ± 30	0.444
Resting LVOT gradient >30 mm Hg, n (%)	100 (79)	49 (89)	51 (72)	0.025	39 (78)	21 (84)	40 (78)	0.882
Resting LVOT gradient >50 mm Hg, n (%)	68 (54)	36 (67)	32 (45)	0.033	27 (54)	14 (56)	27 (53)	0.07
Ejection fraction, (%)	67 ± 9	66 ± 10	67 ± 9	0.475	66 ± 9	66 ± 8	68 ± 10	0.701
Pre-op treatment								
B-blockers, n (%)	95 (76)	34 (62)	61 (86)	0.071				
Amiodarone, n (%)	14 (11)	7 (13)	7 (10)	0.523				
Verapamil/diltiazem, n (%)	14 (11)	7 (13)	7 (10)	0.922				
Disopyramide, n (%)	41 (33)	12 (22)	29 (41)	0.190				

Legend: NYHA: New York Heart Association, PM: Pacemaker, ICD: Implantable cardioverter defibrillator, LVOT: left ventricle outflow tract obstruction.

was a 62-year old man, with moderate pre-operative mitral regurgitation due to SAM, an ex-smoker with no evidence of coronary artery disease, operated 25 years following HOCM diagnosis. He died perioperatively having gone back on-pump due to residual mitral regurgitation after myectomy. The ASA patient was a 54-year old woman who suffered electromechanical dissociation during LAD catheterization, before alcohol injection, presumably due to severe microvascular dysfunction exacerbated by perturbed LAD flow. Autopsy report showed diffuse endomyocardial ischemia.

Of note, no peri-operative deaths occurred after 2003. Overall, 15 patients (12%) developed post-operative permanent A-V block requiring pacemaker implantation (9 post ASA and 6 post SM) (Supplementary Table A).

3.3. Efficacy of SRT and need for re-intervention

Average follow-up for the 124 patients discharged alive was 5 ± 4 years. Overall, efficacy of SRT treatments was similar in the three TTT groups (Table 2). At last visit, 103 (83%) patients were in NYHA Class I/II, and 76 (61%) had sustained improved of at least 1 NYHA class. Marked gradient reduction and symptomatic improvement was obtained by both SRT procedures and comparable for all TTT groups, although residual gradient was slightly higher after ASA (Fig. 1, Panel A). The three TTT groups were also similar in terms of re-intervention rates (6% vs. 12% vs. 14%, respectively, p = 0.171): a total of 13 (10%) patients were referred to a second procedure (surgical in all cases) after a median of 3 (95% CI: 2–4) years, despite a successful initial result, due to relapsing symptoms and dynamic gradients particularly at the mid-ventricular level. A second procedure was required more frequently following ASA than SM (22% vs. 1.4%, p = 0.001); of note, only one patient who had undergone SM required a redo, 5 years after the initial operation, as compared to 12 following ASA (Table 2).

3.4. Long-term outcome

At end of follow up, 106 of 124 initially discharged patients were alive (85%): of the remaining 18, 8 died of cardiac causes (3 sudden deaths and 5 related to heart failure) and 10 of non-cardiac causes (the single most common being cancer). Cardiovascular mortality was significantly lower after SM than after ASA (0.3%/year vs. 2.3%/years; p = 0.03; Fig. 1, Panel B). The difference between the two intervention approaches was even larger when CV mortality and re-intervention were combined as a single outcome, with event rates of 0.7% and 5.5%/year for SM and ASA, respectively (p < 0.001; Fig. 1, Panel B).

3.5. Impact of TTT on cardiovascular mortality and disease progression

Overall cardiovascular mortality showed a significant incremental trend with increasing TTT, and was maximal for a TTT >5 years (2% vs. 4% vs. 12%, respectively, p for trend = 0.039), with annual mortality rates of 0.4%, 1.2% and 2.3% for TTT <3, 3–5 and >5 years, respectively (p = 0.020, Table 2). Consistently, the secondary end-point (reflecting disease progression) occurred with increasing frequency for longer TTTs and peaked in patients with TTT >5-years (26% vs. 36% vs. 49%, respectively, p for trend = 0.018; Fig. 1, Panel C). Of note, the secondary end-point occurred in 49% of patients with TTT >5 years, with a 29% prevalence of AF, an 18% progression to NYHA III/IV, a 14% rate of re-intervention and a 12% cardiovascular mortality (Fig. 1, Panel C).

Table 2
Long-term outcomes.

	Overall	Type of procedure			Time from gradient detection to septal reduction therapy (TTT)			
		Alcohol septal ablation	Surgical myectomy	p value	<3 years	3–5 years	>5 years	p value
	N = 124[a]	N = 54	N = 70		N = 50	N = 25	N = 49	
Population								
Demographic data								
Follow-up, years	5 ± 4	5.7 ± 4.1	4.2 ± 3.0	0.030	5.0 ± 3.5	4.1 ± 3.2	5.3 ± 3.9	0.435
Death, n (%)	18 (15)	15 (28)	3 (4.3)	0.001	4 (8)	3 (12)	11 (22)	0.087
Cardiovascular death, n (%)	8 (6.4)	7 (12.9)	1 (1.4)	0.010	1 (2)	1 (4)	6 (12)	0.039
SCD n (%)	3 (2.4)	3 (5.5)	0		0	0	3 (6.1)	
HF n (%)	5 (4.0)	4 (7.4)	1 (1.4)		1 (2)	1 (4)	3 (6.1)	
Cardiovascular death, (%)/year	1.3	2.3	0.3	0.032	0.40	1.23	2.29	0.020
Re-intervention	13 (10)	12 (22)	1 (1.4)	<0.001	3 (6)	3 (12)	7 (14)	0.171
Disease progression	46 (37)	15 (57)	15 (21)	<0.001	13 (26)	9 (36)	24 (49)	0.018
Clinical status at final evaluation								
NYHA CLASS								
I + II, n (%)	103(83)	38 (70)	65 (93)	<0.001	45 (90)	18 (72)	40 (82)	0.173
III + IV, n (%)	21 (17)	16 (30)	5 (7.1)		5 (10)	7 (28)	9 (18)	
Atrial fibrillation, n (%)	27 (22)	16 (30)	11 (16)	0.002	9 (18)	4 (16)	14 (29)	0.208
Paroxysmal, n (%)	16 (13)	7 (13)	9 (13)		5 (10)	3 (12)	8 (16)	
Persistent, permanent, n (%)	11 (8.8)	9 (17)	2 (2.8)		4 (8)	1 (4)	6 (12)	
Syncope, n (%)	10 (8)	5 (9.3)	5 (7.1)	0.730	2 (4)	5 (20)	3 (6.1)	0.017
Angina, n (%)	17 (14)	10 (19)	7 (10)	0.069	8 (16)	2 (8)	7 (14)	0.645
Stroke, n (%)	5 (4.0)	4 (7.4)	1 (1.4)	0.037	0	2 (8)	3 (6.1)	0.160
Cardiac arrest, n (%)	3 (2.4)	3 (5.5)	0	0.047	0	0	3 (6.1)	0.055
ICD, n (%)	18 (15)	13 (24)	5 (7.1)	0.01	4 (8)	5 (20)	9 (18)	0.234
PM, n (%)	8 (6.4)	3 (5.5)	5 (7.1)	0.990	2 (4)	2(8)	4 (8.2)	0.667
Post-operative echocardiographic data								
Left atrial diameter, mm	47 ± 7	49 ± 7	46 ± 7	0.027	46 ± 8	49 ± 6	47 ± 6	0.474
Septal LV Wall thickness, mm	21 ± 5	22 ± 5	20 ± 5	0.029	20 ± 5	21 ± 4	22 ± 5	0.023
Resting LVOT gradient, mm Hg	15 ± 16	22 ± 21	11 ± 10	<0.001	13 ± 12	19 ± 13	16 ± 20	0.264
Resting LVOT gradient >30 mm Hg, n (%)	12 (10)	10 (19)	2 (2.8)	0.009	4 (8)	3 (12)	5 (10)	0.570
Moderate or severe mitral valve regurgitation, n (%)	22 (18)	7 (13)	15 (21)	0.310	14 (28)	2 (8)	6 (12)	0.333
Ejection fraction (%)	63 ± 9	61 ± 11	65 ± 7	0.030	62 ± 9	64 ± 6	64 ± 11	0.588
Treatment								
B-Blockers, n (%)	90 (74)	31 (57)	59 (84)	0.847	37 (74)	17 (68)	36 (73)	0.927
Amiodarone, n (%)	16 (13)	5 (9.3)	11 (16)	0.073	8 (16)	3 (12.0)	5 (10)	0.662
Verapamil/diltiazem, n (%)	3 (2.4)	0	3 (4.3)	0.258	2 (4)	1 (4.0)	0	0197
Disopiramide, n (%)	1 (0.8)	1 (1.9)	0	0.378	0	0	1 (2.0)	0.475

Legend: SCD: Sudden cardiac death, HF: Heart Failure, LVOT: left ventricle outflow tract, PM: Pacemaker, ICD: Implantable cardioverter defibrillator. Disease Progression: new-onset AF, worsening to NYHA III/IV symptoms, re-intervention or death.
[a] 2 of the 126 original patients died in hospital following SRT.

At Cox multivariable regression analysis, TTT ("3–5" vs "<3" years: HR: 4.988, 95%CI: 1.394–17.843; ">5" vs "<3" years: HR: 3.420, 95%CI: 1.258–9.293, overall p-value = 0.025), presence of atrial fibrillation at baseline (HR: 1.896, 95%CI: 1.002–3.589, p = 0.036) and LVOT gradient (HR per mm Hg increase: 1.022, 95%CI: 1.007–1.024, p = 0.023) were independent baseline predictors of disease progression after SRT (Table 3). When patients who had undergone additional surgical procedures on the mitral valve (plasty or replacement) were excluded, results were unaffected and TTT remained an independent predictor of disease progression at multivariable analysis (HR = 2.009, p = 0.027). Conversely, the variable "Treatment Strategy" (i.e. SM vs. ASA) failed to achieve significance when entered in the multivariable model (HR: 0.881, 95% C.I. 0.384–1.019, p = 0.765). When ASA and SM patients were analyzed separately, TTT was confirmed as the only predictor of outcome in the ASA cohort (overall p = 0.01), whereas no model could be constructed in the SM cohort due to paucity of events.

4. Discussion

4.1. Time-to-treatment and outcome in HOCM

Despite an impressive number of studies addressing every aspect of SRT (and largely focusing on the comparison between SM and ASA), none have previously addressed the impact of timing of intervention and, as a result, HCM guidelines do not provide recommendations on this important issue [11,12]. In this single-center experience extending over two decades, a prolonged delay from first diagnosis of LVOT obstruction to intervention had an adverse impact on long-term prognosis, which became considerable when exceeding 5 years. Notably, about 50% of patients with late SRT referral developed evidence of disease progression at 5-year follow-up, largely driven by heart failure symptoms and AF, but also comprising increased rates of cardiovascular mortality. The proportion of patients reaching the combined study end-point increased from 26% to 36% to 49%, for TTT <3, 3–5 and >5 years, respectively (p for trend = 0.018), while annual mortality rates increased from 0.4% to 1.2% to 2.3% (p = 0.020). At multivariable analysis, a TTT >5 years doubled the risk of disease progression, irrespective of other well-known predictors including left atrial size and magnitude of outflow gradient [7,9]. Importantly, these differences occurred despite largely similar baseline clinical profiles in the 3 TTT groups. However, patients with TTT >5 were significantly older at the time of the SRT and had higher prevalence of atrial fibrillation, plausibly reflecting the longer exposure to LVOTO and its associated structural remodeling.

In addition, differences in outcome related to TTT were observed despite successful abolition of the gradient in the vast majority of patients. Even though one fifth of ASA patients required late re-interventions – a proportion exceeding 15-fold that of SM - these were equally distributed across the three TTT categories.

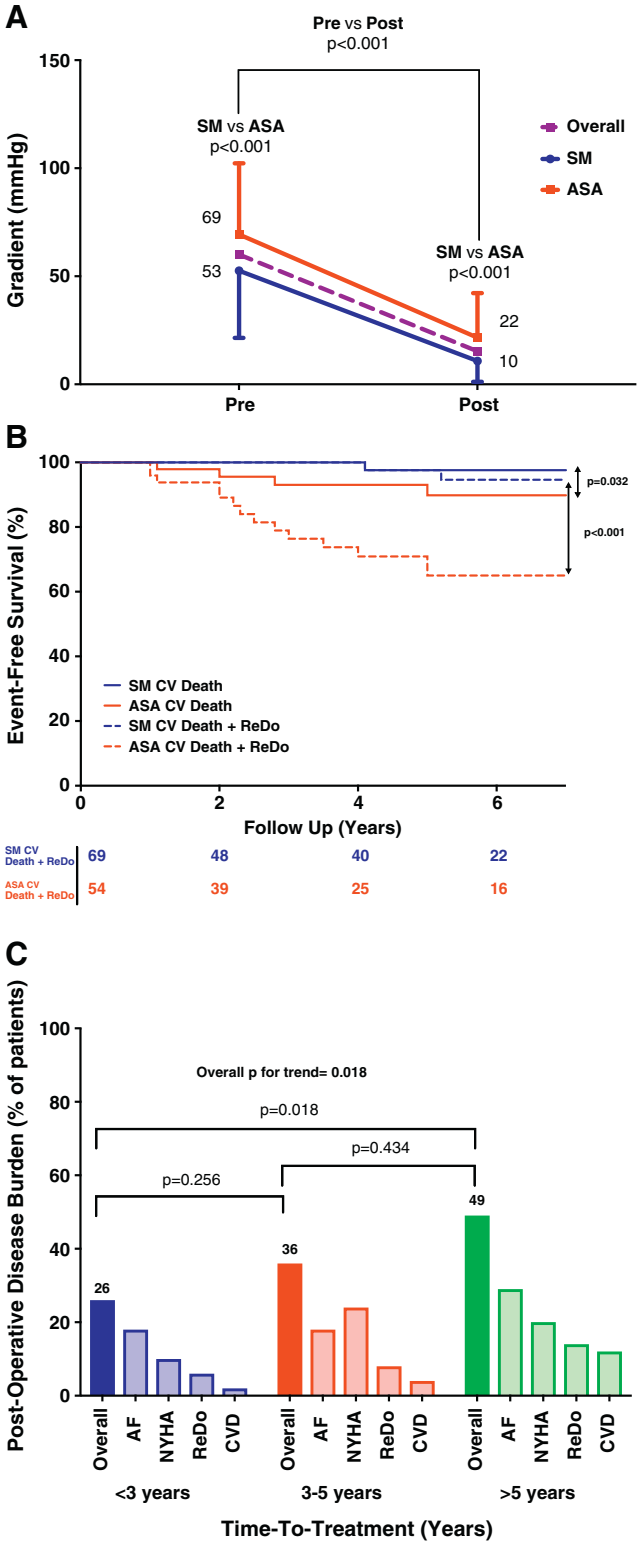

Fig. 1. Panel A. Left ventricular outflow tract gradient reduction by septal reduction therapies. Baseline (Pre) versus Follow-Up (Post) values are shown. Panel B. Outcome of SRT in 124 patients with HOCM. Kaplan-Meier curves depicting event-free survival for cardiovascular mortality following SRT (continuous lines) and a combination of cardiovascular mortality and re-intervention (dashed lines) by septal reduction treatment. Panel C. Occurrence of the secondary endpoint according to TTT classes. Patients were divided into three groups according to time from detection of outflow obstruction to SRT (TTT, "<3" years, "3–5" years and ">5" years) irrespective of treatment strategy (surgical vs. percutaneous). [Legend: Subgroups are not mutually exclusive. AF: New Onset Atrial Fibrillation, NYHA: Progression to NYHA III/IV, ReDo: Re-intervention, CVD: Cardiovascular death].

Our data support the view that, in a disease requiring extended patient care over decades, deciding when to intervene is important. From a pathophysiological standpoint, an association between delay in gradient relief and increased clinical risk is fully consistent with the negative impact of prolonged exposure to afterload mismatch, elevated filling pressures and diastolic dysfunction in HOCM patients, highlighting the need for individual tailoring of SRT timing based on evaluation of risks and benefits in a truly long-term perspective [1,4].

4.2. Implications for management

Even though optimal *individual* timing for SRT is challenging, given the heterogeneity of HOCM, our data suggest that a delayed intervention results in increased risk of disease progression and cardiovascular events even when reasonable control of symptoms is achieved by pharmacological therapy and lifestyle adaptation [16]. As a result, it is important to monitor the clinical stability of HOCM patients (or lack thereof) by a multimodality approach including serial assessment of NT-proBNP and cardiopulmonary testing or exercise echocardiography [17]. In the presence of early signs of hemodynamic and structural deterioration, SRT should be discussed with the patient, ideally in an experienced and multidisciplinary setting [18].

Further studies are warranted to resolve two issues particularly relevant to management. The first is the potential indication for SRT in HOCM patients with severe gradients who are asymptomatic or mildly symptomatic, in view of a potential survival benefit measured against the small interventional risk reported by experienced referral (but not shared by low-flow) centers [4,5,18–22]. Useful considerations may be drawn from the setting of valvular heart disease: recent evidence in asymptomatic patients with severe aortic stenosis and mitral regurgitation shows that an early elective surgical approach as opposed to watchful waiting may lower arrhythmic and heart failure-related events and reduce long-term complications [23–26].

The second, closely related issue regards the identification of the truly stable obstructive patients, in whom SRT can be safely delayed or withheld. In HOCM, unlike nonobstructive disease, prediction of adverse long-term outcome cannot be based for example on the extent of late gadolinium enhancement at cardiac magnetic resonance, as myocardial fibrosis is generally mild or absent in obstructive patients [27]. Rather, red flags for long-term risk might be represented by left atrial remodeling, onset of AF [7,20], and progression in left ventricular diastolic dysfunction [28].

Novel pharmacological approaches might soon provide further therapeutic opportunities for HOCM patients. A newly developed allosteric myosin inhibitor suppressed the development of ventricular hypertrophy, cardiomyocyte disarray, and myocardial fibrosis in a mouse HCM model [29] and, in a recently completed Phase 2, open-label human study (PIONEER-HCM; https://clinicaltrials.gov/ct2/show/NCT02842242) showed promising results in HOCM patients in term of LVOT gradient reduction and improved exercise tolerance. Despite these promising, future perspectives, to date the interventional SRT still appear as a cornerstone in the management of HOCM patients who are refractory to more conventional pharmacological approaches.

4.3. Comparison of SM versus ASA

Both SM and ASA proved safe and effective in reducing obstruction: 90% of patients had post-operative LVOT gradients <30 mm Hg and optimal symptom control was achieved in most cases. At follow up, patients had a remarkable decrease in the occurrence of syncope, angina and NYHA III/IV symptoms (from 61% at baseline to 17% at 5 years, $p < 0.001$). ASA was associated with slightly but significantly greater residual LVOT gradients (22 ± 10 mm Hg vs. 11 ± 10 mm Hg for SM, $p < 0.001$) and greater need for re-intervention (22 vs. 1.4%, respectively, $p < 0.001$). These results are largely consistent with those reported by major European and North American centers, reflecting known

Table 3
Predictors of disease progression in HCM patients undergoing septal reduction therapies.

	Univariate analysis			Multivariate analysis[a]		
	Hazard ratio	95% C.I.	p value	Hazard ratio	95% C.I.	p Value
Variables						
Age at diagnosis	1.009	0.992–1.027	0.288			
Age at SRT	1.031	1.008–1.005	0.011	1.019	0.988–1.051	0.234
Sex (men)	0.621	0.343–1.126	0.117			
Treatment strategy (SM vs. ASA)	0.334	0.183–0.647	0.009	0.881	0.384–1.019	0.765
Time-to-treatment			0.041			0.025
3–5 years vs. <3 years	2.463	1.007–6.023		4.988	1.394–17.843	
>5 years vs. <3 years	2.231	1.134–4.388		3.420	1.258–9.293	
Atrial fibrillation (yes vs. no)[a]	2.803	1.481–5.307	0.002	1.896	1.002–3.589	0.036
Septal LV wall thickness (per mm increase)[a]	1.026	0.959–1.099	0.455			
Ejection fraction (per unit increase)[a]	1.037	0.987–1.078	0.102			
LVOT gradient (per mm Hg increase)[a]	1.010	1.001–1.020	0.022	1.022	1.007–1.024	0.023

Legend: NYHA: New York Heart Association, LVOT: Left ventricle outflow tract, SRT = Septal reduction therapy.
[a] At time of SRT.

technical limitations of ASA [30,31]. However, in the present cohort, the under-performance of ASA may have been exaggerated by its slight overrepresentation in patients with TTT >5 years. ASA was indeed more prevalent (albeit not significantly as an overall trend) in the TTT >5 group, because it was the first-line option at our center before 2003. Due to the conservative approach often adopted in the same period, this resulted in the fact that most of the patients with extended medical management of obstruction were ultimately treated percutaneously rather than surgically. This bias may also explain the older age and partly account for the higher mortality in the ASA group.

Our SM program, as others developed in the context of high-flow surgical centers, benefitted substantially from the recent technical advances, progressively leading to a quasi-elimination of the concept of "inoperable" HOCM patients and, accordingly, to a reduction in the absolute indications to ASA [18,30,32]. While ASA may still have a role in a limited number of patients at extremely high risk, the more tailored and radical elimination of LVOT obstruction guaranteed by SM in expert hands support the gold standard role of surgery in HOCM: a concept clearly stated in the ACC/AHA, but not in the ESC guidelines [11].

4.4. Study limitations

This is a retrospective non-randomized study, with inherent limitations due to lack of matching in the TTT populations object of the comparison. Further studies based on larger HOCM populations are needed to explore the role of SRT timing on long-term outcome, ideally using Propensity Score Matching analysis to reduce the impact of potential sources of bias. Nevertheless, the three TTT subsets in our cohort were well balanced for most baseline features (except age and prevalence of atrial fibrillation), and the two therapeutic strategies were balanced across these groups.

TTT was defined from first LVOTO detection rather than symptom onset, i.e. the true target of SRT: while this is unavoidably arbitrary, the choice was based on the difficulty to retrospectively define the onset of symptoms in HOCM, potentially an even more arbitrary approach. Use of disopyramide was limited in our cohort, especially among ASA patients treated before 2005, when disopyramide was still not widely used and data on the safety of the drug were limited. Data on heart failure hospitalization were not available. Finally, our cohort was not powered to show whether the impact of TTT differs based on the type of procedure. Therefore, we cannot exclude that the higher prevalence of ASA in the TTT >5 year group may have contributed to its worse prognosis However, the key player in dictating outcome seems to be the time interval from gradient detection to the procedure, rather than the procedure itself. Thus, it is plausible to speculate that the relevance of TTT should be comparable between SM and ASA. However, this issue also requires larger dedicated studies.

5. Conclusions

Delay in SRT referral has significant impact on long-term outcome of patients with HOCM, particularly when >5 years from first detection of gradient, and in patients undergoing ASA, even when successful relief of symptoms and gradient is achieved. Earlier interventions are associated with lower complication rates and better prognosis, suggesting the importance of timely SRT to maximize treatment benefit and prevent late HOCM-related complications.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.004.

Acknowledgments

Dr. I. Olivotto is supported by the Italian Ministry of Health: RF-2013-02356787 (Left ventricular hypertrophy in aortic valve disease and hypertrophic cardiomyopathy: genetic basis, biophysical correlates and viral therapy models), NET-2011-02347173 (Mechanisms and treatment of coronary microvascular dysfunction in patients with genetic or secondary left ventricular hypertrophy) and "Monitoraggio e prevenzione delle morti improvvise cardiache giovanili in Regione Toscana" - ToRSADE - Tuscany Registry of Sudden cArdiac DEath (Bando FAS Salute 2014). We are grateful to Prof. Gianni Virgili (Department of Translational and Clinical Medicine, University of Florence, Italy) for the valuable statistical advice.

Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

References

[1] M.S. Maron, I. Olivotto, S. Betocchi, S.A. Casey, J.R. Lesser, M.A. Losi, et al., Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy, N. Engl. J. Med. 348 (4) (2003) 295–303.
[2] P.M. Elliott, J.R. Gimeno, M.T. Tome, J. Shah, D. Ward, R. Thaman, et al., Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy, Eur. Heart J. 27 (16) (2006) 1933–1941.
[3] P. Sorajja, R.A. Nishimura, B.J. Gersh, J.A. Dearani, D.O. Hodge, H.J. Wiste, et al., Outcome of mildly symptomatic or asymptomatic obstructive hypertrophic cardiomyopathy: a long-term follow-up study, J. Am. Coll. Cardiol. 54 (3) (2009) 234–241.
[4] S.R. Ommen, B.J. Maron, I. Olivotto, M.S. Maron, F. Cecchi, S. Betocchi, et al., Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy, J. Am. Coll. Cardiol. 46 (3) (2005) 470–476.
[5] A. Iacovoni, P. Spirito, C. Simon, M. Iascone, G. Di Dedda, P. De Filippo, et al., A contemporary European experience with surgical septal myectomy in hypertrophic cardiomyopathy, Eur. Heart J. 33 (16) (2012) 2080–2087.
[6] M. Liebregts, P.A. Vriesendorp, B.K. Mahmoodi, A.F. Schinkel, M. Michels, J.M. ten Berg, A systematic review and meta-analysis of long-term outcomes after septal reduction therapy in patients with hypertrophic cardiomyopathy, JACC Heart Fail. 3 (11) (2015) 896–905.

[7] A. Woo, W.G. Williams, R. Choi, E.D. Wigle, E. Rozenblyum, K. Fedwick, et al., Clinical and echocardiographic determinants of long-term survival after surgical myectomy in obstructive hypertrophic cardiomyopathy, Circulation 111 (2005) 2033–2041.
[8] D.H. Kwon, S.R. Kapadia, E.M. Tuzcu, C.M. Halley, E.Z. Gorodeski, R.J. Curtin, et al., Long-term outcomes in high-risk symptomatic patients with hypertrophic cardiomyopathy undergoing alcohol septal ablation, JACC Cardiovasc. Interv. 1 (4) (2008) 432–438.
[9] M.L. Brown, H.V. Schaff, J.A. Dearani, Z. Li, R.A. Nishimura, S.R. Ommen, Relationship between left ventricular mass, wall thickness, and survival after subaortic septal myectomy for hypertrophic obstructive cardiomyopathy, J. Thorac. Cardiovasc. Surg. 141 (2) (2011) 439–443.
[10] G. Finocchiaro, F. Haddad, A. Pavlovic, G. Sinagra, I. Schnittger, J.W. Knowles, et al., Latent Obstruction and Left Atrial Size Are Predictors of Clinical Deterioration Leading to Septal Reduction in Hypertrophic Cardiomyopathy, 2014 1532–8414 (Electronic).
[11] P.M. Elliott, A. Anastasakis, M.A. Borger, M. Borggrefe, F. Cecchi, P. Charron, et al., 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathyThe Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC), Eur. Heart J. 35 (39) (2014) 2733–2779.
[12] B.J. Gersh, B.J. Maron, R.O. Bonow, J.A. Dearani, M.A. Fifer, M.S. Link, et al., 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, Circulation 124 (24) (2011) e783–e831.
[13] M.S. Maron, I. Olivotto, A.G. Zenovich, M.S. Link, N.G. Pandian, J.T. Kuvin, et al., Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction, Circulation 114 (21) (2006) 2232–2239.
[14] E. Ammirati, R. Contri, R. Coppini, F. Cecchi, M. Frigerio, I. Olivotto, Pharmacological treatment of hypertrophic cardiomyopathy: current practice and novel perspectives, Eur. J. Heart Fail. 18 (9) (2016) 1106–1118.
[15] I. El-Hamamsy, K. Lekadir, I. Olivotto, A. El Guindy, R. Merrifield, L. Rega, et al., Pattern and degree of left ventricular remodeling following a tailored surgical approach for hypertrophic obstructive cardiomyopathy, Glob. Cardiol. Sci. Pract. 2012 (1) (2012) 9.
[16] M.V. Sherrid, I. Barac, W.J. McKenna, P.M. Elliott, S. Dickie, L. Chojnowska, et al., Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy, J. Am. Coll. Cardiol. 45 (8) (2005) 1251–1258.
[17] J.B. Geske, T. Konecny, S.R. Ommen, R.A. Nishimura, P. Sorajja, H.V. Schaff, et al., Surgical myectomy improves pulmonary hypertension in obstructive hypertrophic cardiomyopathy, Eur. Heart J. 35 (30) (2014) 2032–2039.
[18] L.K. Kim, R.V. Swaminathan, P. Looser, R.M. Minutello, S.C. Wong, G. Bergman, et al., Hospital volume outcomes after septal myectomy and alcohol septal ablation for treatment of obstructive hypertrophic cardiomyopathy: US nationwide inpatient database, 2003–2011, JAMA Cardiol. 1 (3) (2016) 324–332.
[19] J. Veselka, M.K. Jensen, M. Liebregts, J. Januska, J. Krejci, T. Bartel, et al., Long-term clinical outcome after alcohol septal ablation for obstructive hypertrophic cardiomyopathy: results from the Euro-ASA registry, Eur. Heart J. 37 (19) (2016) 1517–1523.
[20] L.K. Williams, H. Rakowski, Surgical myectomy for hypertrophic obstructive cardiomyopathy: the cut that heals, Circulation 128 (3) (2013) 193–197.
[21] H. Rastegar, G. Boll, E.J. Rowin, N. Dolan, C. Carroll, J.E. Udelson, et al., Results of surgical septal myectomy for obstructive hypertrophic cardiomyopathy: the Tufts experience, Ann. Cardiothorac. Surg. 6 (4) (2017) 353–363.
[22] B.J. Maron, E.J. Rowin, S.A. Casey, M.S. Maron, How hypertrophic cardiomyopathy became a contemporary treatable genetic disease with low mortality: shaped by 50 years of clinical research and practice, JAMA Cardiol. 1 (1) (2016) 98–105.
[23] R.M. Suri, J.L. Vanoverschelde, F. Grigioni, H.V. Schaff, C. Tribouilloy, J.F. Avierinos, et al., Association between early surgical intervention vs watchful waiting and outcomes for mitral regurgitation due to flail mitral valve leaflets, JAMA 310 (6) (2013) 609–616.
[24] R. Zilberszac, H. Gabriel, M. Schemper, G. Laufer, G. Maurer, R. Rosenhek, Asymptomatic severe aortic stenosis in the elderly, JACC Cardiovasc. Imaging 10 (1) (2017) 43–50.
[25] R.M. Suri, H.V. Schaff, M. Enriquez-Sarano, Mitral valve repair in asymptomatic patients with severe mitral regurgitation: pushing past the tipping point, Semin. Thorac. Cardiovasc. Surg. 26 (2) (2014) 95–101.
[26] M. Banovic, B. Iung, J. Bartunek, M. Asanin, B. Beleslin, B. Biocina, et al., Rationale and design of the Aortic Valve replAcemenT versus conservative treatment in Asymptomatic seveRe aortic stenosis (AVATAR trial): a randomized multicenter controlled event-driven trial, Am. Heart J. 174 (2016) 147–153.
[27] I. Olivotto, B.J. Maron, E. Appelbaum, C.J. Harrigan, C. Salton, C.M. Gibson, et al., Spectrum and clinical significance of systolic function and myocardial fibrosis assessed by cardiovascular magnetic resonance in hypertrophic cardiomyopathy, Am. J. Cardiol. 106 (2) (2010) 261–267.
[28] P. Debonnaire, E. Joyce, Y. Hiemstra, B.J. Mertens, D.E. Atsma, M.J. Schalij, et al., Left atrial size and function in hypertrophic cardiomyopathy patients and risk of new-onset atrial fibrillation, Circ. Arrhythm. Electrophysiol. 10 (2) (2017).
[29] E.M. Green, H. Wakimoto, R.L. Anderson, M.J. Evanchik, J.M. Gorham, B.C. Harrison, et al., A small-molecule inhibitor of sarcomere contractility suppresses hypertrophic cardiomyopathy in mice, Science 351 (6273) (2016) 617–621.
[30] M. Liebregts, P.A. Vriesendorp, J.M. Ten Berg, Alcohol septal ablation for obstructive hypertrophic cardiomyopathy: a word of endorsement, J. Am. Coll. Cardiol. 70 (4) (2017) 481–488.
[31] M. Liebregts, R.C. Steggerda, P.A. Vriesendorp, H. van Velzen, A.F. Schinkel, R. Willems, et al., Long-term outcome of alcohol septal ablation for obstructive hypertrophic cardiomyopathy in the young and the elderly, JACC Cardiovasc. Interv. 9 (5) (2016) 463–469.
[32] M.H. Yacoub, A. Afifi, H. Saad, H. Aguib, A. ElGuindy, Current state of the art and future of myectomy, Ann. Cardiothorac. Surg. 6 (4) (2017) 307–317.