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A New Perspective in the Evaluation of Hypertrophic Obstructive Cardiomyopathy Patients after Percutaneous Transluminal Septal Myocardial Ablation

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1. Abstract

1.1. Objective: In clinical practice, an indicator that could be used to identify suitable patients for PTSMA and assess their long-term prognosis, is important for the cardiologists. In this retrospective study, we aimed to investigate the association between TG index and acute- or long-term outcomes of HOCM patients after PTSMA, and further investigate the interaction effects of LVOTG and IVST.

1.2. Methods: The study design is based on four tertiary centers from Mid-China, and a total of 284 HOCM patients (132 males, average age 54.80±11.98 years) were treated with PTSMA. A new clinic index(TG= IVS thickness×LVOT gradient) was designed. Both 30-day major cardiovascular adverse events and all-cause mortality of the HOCM patients were analyzed. Cox proportional hazards regression model adjusting for potential risk factors was applied to explore the hazard ratio (HR) for all-cause mortality.

1.3. Results: With a normal procedure of injection alcohol (2.201± 1.025 ml) in patients, Echo-Doppler LVOTG and IVST were reduced to 40.11±24.44 mmHg and 17.68±4.07 mm at the last clinical check-up, respectively. Patients with the IVST≤20mm or the TG index≤1683 had a higher incidence of PTSMA-contributable complications and a needing for a permanent pacemaker. A total of 21(9.8%) deaths occurred in 903 patient-years, representing 0.65 deaths and 4.06 deaths per 100 patient-years in the TG index>1683 group and TG index ≤1683 group. The confounder-adjusted estimate for 8-years survival from all-cause death were 16.53% (95% CI=9.12%-20.76%) vs. 84.18% (95% CI =76.54%-88.21%) (log-rank P<0.001) in the TG>1683 group and TG≤1683 group, respectively. Subgroup analysis showed that patients with LVOTG>82 mmHg and IVST>20mm group presented a higher risk of all-cause mortality as compared to those LVOTG≤82 mmHg (HR: 18.63, 95%CI=1.09~319.15).

1.4. Conclusions: Patients with a smaller TG index showed a huge advantage in long-term survival (8 years survival from all-cause death 16.53% in TG index≤1683 group Vs. 84.18% in TG index>1683 group). Thus, the TG index should be a perfect indicator in the evaluation of HOCM patients whether suitable for the PTSMA and to be used to predict long-term survival.

2. Introduction

Hypertrophic Cardiomyopathy (HCM) is the most common genetic heart disease and is characterized by left ventricular hypertrophy in the absence of aortic valve stenosis or chronic hypertension [1, 2]. The morphology of HCM can be divided into basal, mid-ventricular, apical, and diffuse types according to its position of hypertrophic myocardium [3]. HCM patients with Left Ventricular Outflow Tract (LVOT) obstruction are associated with symptoms of severe heart failure, angina, syncope, and increased risk of sudden cardiac death [4].

Percutaneous Transluminal Septal Myocardial Ablation (PTSMA) has been introduced for more than two decades in some experienced centers and became a full-fledged therapeutic option for HCM obstructive patients (HOCM) with a limited groin approach,

less invasive treatment, effective elimination of gradient of LVOT, and improvement of the diastolic function. ESC and AHA guidelines recommended that PTSMA can be considered on HOCM patients with resting LVOT gradient (LVOTG) ≥30 mmHg or provocation (≥50 mmHg) [5, 6]. Euro-ASA registry study has proved that HOCM patients with an IVST≤16mm had a high rate of early complications after PTSMA [7], and another study found patients with an IVST>30 mm associated with poor long-term survival [8]. In addition, Josef Veselka HOCM patients with an LVOTG≥30 mmHg (post-PTSMA) had a significantly higher incidence of cardiovascular mortality events [9]. In summary, previous studies or recommendations have considered the prognostic impact of LVOTG or IVST on PTSMA patients alone, and the results are controversial.

In clinical practice, most cardiologists believed that HOCM patients with thick IVST should be accompanied by higher LVOTG. Actually, the small difference in the position of the interventricular septum can lead to a big variance LVOT gradient despite the same IVST. Thus, it is essential to design a new indicator, which could combine both IVST and LVOTG, to identify the suitable HOCM patients and evaluate their long-term prognosis after PTSMA. However, till now, no systemic research investigated the relationship between clinic outcome of HOCM after-PTSMA and IVST combined LVOTG [10].

Herein, we designed a new clinic index(TG (Thickness Gradient)= IVS thickness×LVOT gradient). In this retrospective study, we aimed to investigate the association between TG index and acute- or long-term outcomes of HOCM patients after PTSMA, and further investigate the interaction effects of LVOTG and IVST, and analyze whether PTSMA is an adequate management option in HOCM patients.

3. Method

3.1. Patients Selection

The study design is based on four tertiary centers from Mid-China (The First Affiliated Hospital of University of Science and Technology of China; The first affiliated hospital of Anhui Medical University; The Second affiliated hospital of Anhui Medical University; The fourth affiliated hospital of Anhui Medical University), in which patients were prospectively collected and retrospectively reviewed. Between 2008 and 2018, A total of 284 patients (54.80±11.98 years, women 53.5%) were enrolled. The clinical inclusion criteria were as follows: dyspnea of New York Heart Association, presense of angina, recurrent exercise-induced presyncope or syncope, and LVOT gradient≥30 mm Hg at rest or≥50 mm Hg at provocation (Valsalva maneuver or post-extra systolic potentiation). All patients had to undergo a single PTSMA and submit to long-term follow-up at the center where PTSMA was performed.

3.2. Alcohol Septal Ablation Technique

All interventional procedures regarding PTSMA were made after a detailed multidisciplinary evaluation and performed by experienced cardiologists. PTSMA technique procedures were nearly same and guided by the current Chinese guidelines in this study [11, 12]. Blood was drawn for a test of the cardiac infarction of creatine kinase (CK-MB) and troponin-I in the 24 hours post-ASA.

3.3. Endpoints and Definitions

Both acute complications and long-term survival of the HOCM patients were analyzed in this study: (i) 30-day major cardiovascular adverse events consist of permanent pacemaker implantation, electrical defibrillation for Ventricular Tachycardia (VT) /ventricular fibrillation (VF), or cardiac tamponade and an appropriate ICD discharge; (ii) long term all-cause mortality rate (All-cause mortality was defined as death due to any cause); (iii) long-term LVOT gradient (the reduction of LVOT gradient was defined as follows: pressure gradient at baseline-pressure gradient at the last clinical check-up); (iv) severity of dyspnea (NYHA class).

3.4. Follow up

The HOCM patients underwent a first noninvasive follow-up control and finished cardiac echocardiography in 3-6 months post-PTSMA. Afterward, normal cardiac examination were performed either in our hospital or by the other cardiologists. The survival of patients was communicated through clinical visits or telephone calls, and the information was updated in 2020–2021. For lost or deceased patients who lost communication or died outside with the general doctor or next of kin was performed to ascertain the cause of death.

3.5. Statistical Analysis

The R software and SPSS 17.0 software were used for statistical analysis. Means ± standard deviation were calculated for continuous variables and numbers with frequency for categorical variables. All descriptive statistics were dichotomized by the median level of LVOTG, IVST, and TG. Univariate analyses were performed using the Student's t-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables for intergroup comparisons. Cox proportional hazards regression model adjusting for potential risk factors (including sex, age, BMI, alcohol drinking, smoking, intraoperative alcohol dose, preoperative NYHA grade) was applied to explore the Hazard Ratio (HR) of the Echocardiographic index for all-cause mortality, And the risk estimates with 95% CI was calculated. The adjusted survival curves were plotted by inverse probability weights method using RISCA statistical package of R software. Subgroup analysis was conducted to further explore the interaction effects of LVOTG and IVST.

4. Results

4.1. Baseline characteristics

A total of 284 adult HOCM patients (152 females) were treated with PTSMA, and the average population age was 54.80±11.98 years (Range 26-80). In this cohort, echocardiography estimated

the mean basal IVST and LVOTG at rest was 20.75±4.56 mm and 78.58±22.30 mmHg, respectively (Table 1).

The comparison of baseline clinical and echocardiographic characteristics in the study cohort was shown in table 1. There was a higher incidence of AF (atrial fibrillation) in HOCM patients with higher LVOTG (P=0.019). When stripped group by either LVOTG or IVST, no difference was found in the prevalence of angina, syncope, NYHA class, and LVEF. When stripped by TG index, also no significant difference was observed in the prevalence of angina, syncope, NYHA class, and LVEF, while a significant difference showed in both LVOTG (64.25±21.9 mmHg Vs 93.31±9.38 mmHg; P<0.001) and IVST (18.44±4.17 mm Vs 23.11±3.66 mm; P<0.001). Interestingly, patients with thicker IVST or bigger TG index were accompanied by smaller LVED.

Comparison of clinical and echocardiographic characteristics at the last clinical check-up post-PTSMA

With a normal procedure of injection alcohol (average volume 2.201± 1.025 ml) in patients (Table 2), Echo-Doppler LVOTG and IVST (at rest) were reduced to 40.11±24.44 mmHg (P<0.001 Vs. before PTSMA) and 17.68±4.07 mm (P<0.001 Vs. before PTSMA) at the last clinical check-up, respectively. There was no significant difference in the usage of total alcohol dose among different groups. Also, a similar up-regulated serum CKMB level was detected after PTSMA operation (check-up at the first 24 hours) in different separate groups.

In the LVOTG subgroup, there was a parallel decrease in the IVS thickness and LVOT gradient. However, a higher reduction of IVS thickness (4.45±3.87mm Vs 1.58±1.65mm, P= 0.017) in the IVST>20 mm group but less decrease of LVOT gradient (33.88±25.65 mmHg Vs 43.36±30.87 mmHg, P <0.001) was observed in the IVST≤20mm group. In the TG index subgroup, still, there was a parallel reduction in the IVS thickness and LVOT gradient (4.29±3.77 mm and 46.86±25.19 mmHg, each) after PTSMA.

Table 1: Comparative analysis of preoperative baseline characteristics of HOCM patients

Factors	LVOTG group		t/χ^2	*P* value	IVST group		t/χ^2	*P* value	TG index		t/χ^2	*P* value	Overall
	⩽82	>82			⩽20	>20			⩽1683	>1683			
Age, y	53.72±12.12	55.91±11.79	-1.338	0.182	55.86±11.54	53.71±12.37	1.31	0.192	53.81±11.75	55.83±12.18	-1.234	0.219	54.80±11.98
Sex, Male	68(47.89)	64(45.07)	0.226	0.634	60(42.25)	72(50.70)	2.038	0.153	64(45.07)	68(47.89)	0.226	0.634	132(46.50)
Smoking history	12(8.45)	20(14.08)	2.254	0.133	16(11.27)	16(11.27)	0	1	8(5.63)	24(16.90)	7.15	0.007	32(11.30)
Drinking history	8(5.63)	12(8.45)	0.861	0.354	8(5.63)	12(8.45)	0.861	0.354	4(2.82)	16(11.27)	7.745	0.005	20 (7.00)
Hypertension	56(39.44)	60(42.25)	0.233	0.629	68(47.89)	48(33.80)	4.535	0.033	60(42.25)	56(39.44)	0.233	0.629	116(40.80)
Diabetes	20(14.08)	8(5.63)	5.705	0.017	12(8.45)	16(11.27)	0.634	0.426	20(14.08)	8(5.63)	5.705	0.017	28(9.90)
BMI, kg/m^2	25.59±4.33	24.43±3.65	2.117	0.035	25.49±4.43	24.53±3.57	1.748	0.082	25.67±3.98	24.35±4.02	2.41	0.017	25.02±4.04
Atrial fibrillation	16(11.27)	4(2.82)	7.745	0.005	12(8.45)	8(5.63)	0.861	0.354	12(8.45)	8(5.63)	0.861	0.354	20(7.00)
Chest pain	31(21.30)	32(22.86)	0.02	0.886	35(24.76)	28(20.00)	0.999	0.317	37(25.93)	26(18.10)	2.468	0.116	63(20.07)
NYHA class II	12(8.45)	16(11.43)	2.167	0.338	12(8.45)	16(11.43)	2.167	0.338	12(8.45)	16(11.43)	2.167	0.338	28(9.86)
III	126(88.73)	118(83.10)			126(88.73)	118(83.10)			126(88.73)	118(83.10)			244(85.92)
IV	4(2.82)	8(5.63)			4(2.82)	8(5.63)			4(2.82)	8(5.63)			12(4.23)
Syncope (%)	28(19.44)	16(11.43)	3.873	0.049	28(19.44)	16(11.43)	3.873	0.049	20(13.89)	24(17.14)	0.43	0.512	44 (15.50)
Basal LVOTG at rest (mmHg)	60.31±16.97	97.37±3.74	-22.14	<0.01	76.64±22.17	80.57±22.37	-1.289	0.199	64.25±21.9	93.31±9.38	-12.65	<0.001	78.58±22.30
Basal IVST (mm)	20.39±4.39	21.11±4.72	-1.161	0.247	17.31±2.89	24.29±2.99	-17.34	<0.001	18.44±4.17	23.11±3.66	-8.678	<0.001	20.75±4.56
LAD (mm)	46.03±7.18	47.03±6.24	-1.083	0.28	44.76±6.16	48.33±6.86	-3.989	<0.001	45.81±6.82	47.26±6.6	-1.576	0.116	46.52±6.74
LVED (mm)	45.28±4.95	45.94±4.53	-1.013	0.312	47.16±4.44	44.02±4.54	5.101	<0.001	46.45±5.17	44.74±4.12	2.662	0.008	45.61±4.75
LVEF (%)	68.01±7.09	66.91±8.56	1.021	0.308	68.08±6.51	66.84±9.01	1.155	0.25	67.71±6.62	67.23±8.96	0.444	0.657	67.47±7.85
Follow-up (years)	4.39±2.24	4.10±2.10	0.967	0.335	4.25±2.30	4.24±2.04	0.05	0.96	4.26±2.18	4.23±2.18	0.115	0.909	4.24±2.17

Table 2: Comparative analysis of last clinical check-up characteristics of patients post-PTSMA

Factors	LVOTG group		t/χ^2	*P* value	IVST group		t/χ^2	*P* value	TG index		t/χ^2	*P* value	Overall
	≤82	>82			≤20	>20			≤1683	>1683			
NYHA class I	4(2.82)	0(0)	9.27	0.026	4(2.82)	0(0)	18.815	<0.001	4(2.82)	0(0)	26.277	<0.001	4(1.41)
II	117(82.39)	113(79.58)			126(88.73)	106(74.65)			129(90.84)	103(72.53)			232(81.69)
III	21(14.79)	24(16.90)			12(8.45)	32(22.53)			9(6.34)	35(24.65)			44(15.49)
IV	0(0)	5(3.52)			0(0)	4(2.82)			0(0)	4(2.82)			4(1.41)
LVOTG at rest (mmHg)	34.66±23.51	45.57±24.24	3.312	0.001	33.28±25.58	47.35±20.98	4.346	<0.001	33.77±22.9	46.46±24.39	3.885	<0.001	40.11±24.44
IVS thickness (mm)	17.79±3.65	17.57±4.46	0.393	0.695	15.72±2.78	19.82±4.19	8.215	<0.001	16.5±3.67	18.83±4.13	4.286	<0.001	17.68±4.07
LAD (mm)	43.11±7.84	42.69±6.48	0.432	0.666	41.33±6.41	44.56±7.6	3.332	0.001	42.54±7.27	43.26±7.1	0.72	0.472	42.90±7.18
LVED (mm)	44.86±3.97	44.63±3.78	0.427	0.67	45.75±4.1	43.68±3.31	4.019	<0.001	45.54±4.25	43.94±3.28	3.055	0.003	44.74±3.87
LVEF (%)	69.24±6.07	71.83±5.56	3.206	0.002	70.22±5.13	70.91±6.73	0.829	0.408	69.65±5.55	71.43±6.21	2.174	0.031	70.55±5.95
Alchohol volume	2.186±1.148	2.217±0.886	-0.22	0.825	2.258±1.193	2.143±0.819	0.826	0.41	2.033±1.116	2.374±0.894	-2.456	0.015	2.201±1.025
Decrease of LVOTG (mmHg)	25.71±26.58	51.8±24.8	7.353	<0.001	43.36±30.87	33.88±25.65	2.412	0.017	30.66±29.97	46.86±25.19	4.24	<0.001	38.76±28.78
Reduction of IVST (mm)	2.35±3.02	3.54±3.37	2.674	0.008	1.58±1.65	4.45±3.87	6.843	<0.001	1.59±1.79	4.29±3.77	6.601	<0.001	2.96±3.25
CKMB	140.69±86.34	126.03±59.18	1.435	0.153	124.53±82.55	142.71±63.27	1.797	0.074	137.49±87.19	129.23±58.56	0.806	0.422	133.36±74.21
Tropolin I	10.67±5.74	13.53±5.45	3.003	0.003	12±5.91	12.2±5.66	0.212	0.832	10.88±5.78	13.23±5.54	2.44	0.016	12.10±5.76

4.2. Early Complications Post-PTSMA

Short-term major adverse events were summarized and shown in table 3. No significant difference was found in the early occurrences of sudden cardiac death (P>0.05) and other types of complications (electrical defibrillation, cardiac tamponade, and ICD discharge) (P>0.05). However, patients with the IVST≤20mm or the TG index≤1683 had a higher incidence of PTSMA-contributable complications, which were driven by a higher rate of heart conduction problem with subsequent need of a permanent pacemaker.

4.3. Long-term Outcomes

None of the patients was lost to follow-up. The mean follow-up time in the entire cohort was 4.24±2.17 years, and a total of 21(9.8%) deaths occurred in the course of 903 patients years, representing 1.27 deaths and 3.49 deaths per 100 patients-years in the LVOTG>82mmHg group and the LVOTG≤82mmHg group, 1.97 deaths and 2.59 deaths per 100 patients-years in the IVST≥20 mm group and the IVST≤20 mm group, 0.65 deaths and 4.06 deaths per 100 patients-years in the TG index>1683 group and TG index≤1683 group.

The confounder adjusted Kaplan-Meier curves of all-cause death rates were shown in figure 1. The survival free of all-cause death in LVOTG >82mmHg group and LVOTG ≤82mmHg group at 5years and 8years were 98.54% (95% CI=93.24%-99.86%) vs. 99.37% (95% CI=96.79%-99.86%) (log rank P = 0.578), and 59.12% (95% CI= 50.15%-68.72%) vs. 32.18% (95% CI=22.12%-40.98%) (log rank P < 0.001). Patients in IVST >20 mm group tend to exhibit lower survival as compared to IVST≤20 mm group (HR=2.82, 95% CI=0.90~8.85). Of importantly, the confounder-adjusted estimate for 5- and 8-years survival from all-cause death were 92.33% (95% CI= 89.38%-96.23%) vs. 96.88% (95% CI= 94.32%-98.67%) (log rank P = 0.134), and 16.53% (95% CI=9.12%-20.76%) vs. 84.18% (95% CI =76.54%-88.21%) (log rank P < 0.001) in the TG>1683 group and TG≤1683 group, respectively.

In multivariable analysis, the predictor of all-cause mortality at which PTSMA was performed was patients' NYHA class (HR=4.804, 95% CI:1.064–21.689; P =0.041), baseline LVOTG before PTSMA (HR= 5.607, 95% CI:1.206–26.054; P =0.028), and TG index (HR= 5.725, 95% CI:1.551–21.128; P =0.009).

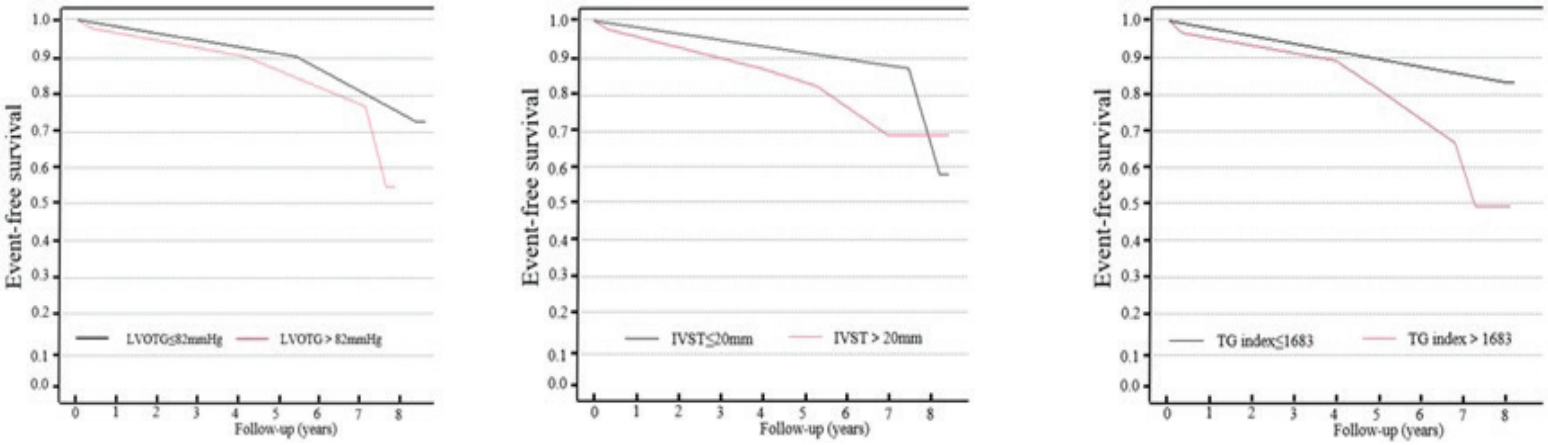

Figure 1: Kaplan-Meier curves describing survival from cardiovascular mortality events in patients with residual left ventricular outflow tract gradient (LVOTG), interventricular septum thickness, TG index. (adjustment for age, sex, baseline LVOTO and baseline septum thickness)

Table 3: In-hospital cardiac events after PTSMA.

Factors	LVOTG group		t/χ^2	*P* value	IVST group		t/χ^2	*P* value	TG index		t/χ^2	*P* value
	≤82	>82			≤20	>20			≤1683	>1683		
Pacemaker implantation	13(9.15)	8(5.63)	1.286	0.257	20(14.08)	1(0.70)	18.563	<0.001	17(11.97)	4(2.82)	8.69	0.003
Other complications	2(1.41)	4(2.82)	0.17	0.68	3(2.11)	3(2.11)	<0.001	1	2(1.41)	4(2.82)	0.17	0.68
Sudden cardiac death	3(2.11)	1(0.70)	0.254	0.615	3(2.11)	1(0.70)	0.254	0.615	3(2.11)	1(0.70)	0.254	0.615

PTSMA, Percutaneous transluminal septal myocardial ablation, LVOTG, left ventricular obstruction tract gradient; IVST, interventricular septum thickness; other complications (electrical defibrillation for VT/VF, cardiac tamponade, and ICD discharge).

4.4. Subgroup Analysis

In IVST>20mm group, patients with LVOTG>82 mmHg presented a higher risk of all-cause mortality as compared to those LVOTG≤82 mmHg (HR: 18.63, 95%CI=1.09~319.15). However, the statistic was insignificant in IVST≤20mm group. Similarly, in LVOTG>82 mmHg group, the risk of mortality was 15.31 (95%CI=2.12-110.75) in patients with IVST>20mm as compared to patients with IVST≤20mm, and the HR showed insignificant in LVOTG≤82 mmHg group (As shown in table 4 and 5).

Table 4: Cox proportional harzard regression analysis on the association of LVOTG with all-cause mortality in IVST subgroups.

Factor	IVST≤20mm		IVST>20mm	
	HR(95%*CI*)	*P* value	*HR*(95%*CI*)	*P* value
LVOTG≤82	reference		reference	
>82	1.11(0.20~6.19)	0.904	18.63(1.09~319.15)	0.044

Adjusted factors:age, sex, BMI, alcohol drinking, smoking,total alcohol dose,NYHA classification.

Table 5: Cox proportional harzard regression analysis on the association of IVST with all-cause mortality in LVOTG subgroups.

Factor	LVOTG≤82mm		LVOTG>82mm	
	HR(95%*CI*)	*P* value	*HR*(95%*CI*)	*P* value
IVST≤20	reference		reference	
>20	0.91(0.04~21.35)	0.955	15.31(2.12~110.75)	0.007

Adjusted factors:age, sex, BMI, alcohol drinking, smoking,total alcohol dose,NYHA classification.

5. Discussion

As all we know, after the first successful case of alcohol septal ablation [13], great advances have been made on PTSMA over the past several decades and standardized procedures have been proposed [14-16]. However, the type of HOCM patients who were the best candidates for PTSMA was still controversial, and the acute- and long-term prognosis post-PTSMA still attracted our attention [17].

To our knowledge, this is the first study to use the TG index, which is a new index that can combine both baseline IVS thickness and LVOT gradient (at rest), to evaluate acute- and long-term outcomes of HOCM patients. We designed this study to re-consider the statement in the current ESC/AHA guidelines and gave more detail in choosing PTSAM treatment for HOCM patients. Here, we reported the following important findings: (i) PTSMA remained an effective and less invasive treatment opportunity in alleviating LVOTG (pre-operative 78.58±22.30 mmHg Vs post-PTSMA 40.11±24.44 mmHg; P<0.001) and improving cardiac function (NYHA class pre-operative 2.94±0.37 Vs post-PTSMA 2.17±0.45; P<0.001). (ii) patients with thinner IVST (≤20mm) had a better performance in alleviating LOVTG, but more acute complete conduction block (13.89% Vs 0.95%, P <0.001). (iii) The reduction of total alcohol injection could not reduce the needing for pacemaker implantation in TG index subgroups. (iv) There was no statistically significant difference in long-term outcomes regardless of IVS thickness in this study. (v) Patients with a lower TG index showed better long-term event-free survival. (vi) Subgroup analysis showed that HOCM patients with both IVST>20mm and LVOTG>82 mmHg had the worst long-term survival performance.

The median preoperative IVST and LVOTG from our study patients were 20 mm and 82mmHg (baseline at rest), respectively, which was similar to Angelika's [18] study and the Euro-ASA registry [19]. We reported the first check-up LVOTG post-PTSMA was around 40.11±24.44 mmHg, which was also close to other European studies [18, 20-23]. The short-term cardiac sudden death post-PTSMA was very low (<1%) regardless of LVOGT, IVST, and TG index, and similar with other reports [19]. Notably, our study found that IVST≤20mm groups had a higher complete conduction complication rate (13.89% Vs 0.95%; P<0.001) and further needed pacemaker implantation, this result was similar with Euro-ASA registry but the cutoff of IVST was thicker (20mm) in our study [19]. That data may remind us to put more attention on the HOCM patients with IVST≤20mm when we choose PTSMA.

Past researchers thought that injection dose of alcohol-associated with the early complications such as conduction problems, cardiac sudden death, and ventricular septal defect [6, 19, 24-26], and they had proposed that reduced alcohol dose may be an effective approach to reduce the high rate of complete heart block during PTSMA. Unfortunately, Josef Veselkas and his colleague did not find any association between alcohol dose and short- or long-term outcomes through analyzing 1440 HOCM patients [20]. The total injection of alcohol volume (2.201±1.025ml) in our study was almost the same as in other studies [18, 20]. Our research showed a significant reduction in the injection of desiccated alcohol in patients with a smaller TG index group (2.033±1.116 Vs 2.374±0.894; P<0.015), while they still had a high rate of needing pacemaker implantation which was driven by complete heart block (12.04% Vs 2.86%; P<0.011). And in terms of long-term prognostic impact, the multivariable analysis has included alcohol usage to decrease its confounding effect. Further matching studies are essential if we want more accurate results on the correlation between alcohol dose and prognosis.

The main purpose of conducting PTSMA is to alleviate the LVOT obstruction and improve cardiac function for the change of patient long-term prognosis and quality of life. Still, our study proved that PTSMA was one of the most effective treatments in alleviating LVOTG (pre-operation 78.58±22.30 mmHg Vs 40.11±24.44 mmHg; P<0.001) and improving cardiac function (NYHA class pre-operation 2.94±0.37 Vs post-PTSMA 2.17±0.45; P<0.001). In the Euro-ASA registry study, they reported that patients with mild hypertrophy had a better long-term survival[19]. Also, Jensen found that patients with baseline IVST >25 mm had a 5-fold increased risk in all-cause mortality compared with patients with baseline IVST ≤20 mm [27]. In our study, we also found a lower

survival trend forward in the patients with baseline IVST >20 mm, while after 5years later, all-cause mortality was similar regardless of baseline IVST. Two reasons could be used to explain that difference: first, through subgroups analysis, we found that patients with IVST>20mm had a higher reduction of IVST but less decrease of LVOTG in the same injection of total dose alcohol. Second, the cutoff IVST was 20mm in our study, which is thicker than others.

To our surprise, patients with a smaller TG index showed a huge advantage in long-term survival (8 years survival from all-cause death 16.53% in TG index≤1683 group Vs. 84.18% in TG index>1683 group). Further detailed analysis proved that TG also was a better index in reflecting the alleviation of LVOT gradient and IVS thickness. In Josef Veselka's study, they found that the first post-discharge check-up LVOTG≥30 mmHg was a strong predictor for the occurrence of subsequent cardiovascular mortality events [9]. Thus, baseline IVST should not be considered as the only factor to evaluate the long-term outcomes in the HOCM patients post-PTSMA. According to these results, the TG index should be a better indicator in the evaluation of HOCM patients whether suitable for the PTSMA and to be used to predict long-term survival.

6. Limitations

This retrospective, observational and multicenter study has its inherent limitations that should be considered before the generalization of the results. First, the total number of HOCM patients would be the biggest limitation of our study. Plus, the TG index was a new indicator and designed by ourselves, which need to be more widely used and accepted in other multi-center studies with larger sample size. Second, even though part of the results of this study are consistent with the published results, a prospective, randomized, and controlled trial would be essential for the future. Third, we have to be aware of some diversity that exists in the interpretation and implementation of the existing evidence on PTSMA, e.g. patient selection, myectomy as an alternative method, and these patients were treated by tertiary center cardiologists specializing in HOCM [28]. Therefore, multicenter, multinational randomized trials would be essential to ultimately determine whether patients with different IVST and LVOTG could be treated with PTSMA or not. However, limitations does not dispute the result that the long-term effects of a higher TG index were deleterious and negatively impact the occurrence of cardiovascular mortality events.

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