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ORIGINAL ARTICLE

Percutaneous transluminal septal myocardial ablation for hypertrophic obstructive cardiomyopathy through non-left anterior descending septal perforators

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Abstract

Percutaneous transluminal septal myocardial ablation (PTSMA) has become a significant treatment for symptomatic patients with hypertrophic obstructive cardiomyopathy (HOCM) despite maximal medical therapy. The target septal arteries usually arise from the left anterior descending artery (LAD). However, when septal perforators do not originate from the LAD, non-LAD septal perforators should be included as candidate-target septal branches that feed the hypertrophic septal myocardium, causing left ventricular outflow tract (LVOT) obstruction. Data pertaining to the procedure remain limited. We aimed to investigate PTSMA through the non-LAD septal perforators in patients with HOCM. In this case series review, we evaluated the baseline characteristics, echocardiographic features, and angiographic features, as well as symptoms and pressure gradient before and after PTSMA through the non-LAD septal perforators. Among 202 consecutive patients who underwent PTSMA for HOCM with LVOT obstruction, 21 had non-LAD septal branches that fed the hypertrophic septal myocardium and received alcohol ablation. Non-LAD septal perforators could be used as an alternative route for PTSMA in patients who experienced ineffective ablation of the septal branch that arises from the LAD. This unique procedure may improve response rates and overall outcomes of patients with HOCM.

Keywords Hypertrophic cardiomyopathy · Cardiomyopathy · Structure heart disease · Alcohol septal ablation

Introduction

Percutaneous transluminal septal myocardial ablation (PTSMA) has been performed for symptomatic patients with hypertrophic obstructive cardiomyopathy (HOCM) despite maximal medical therapy [1–6]. PTSMA is a less invasive approach than surgical myomectomy. Therefore, after a well-organized heart team discussion, PTSMA is performed particularly in patients who are of a relatively advanced age or have serious comorbidities. In this procedure, absolute ethanol is administered into the septal branch via a percutaneous approach to induce localized myocardial necrosis of the left ventricular septum, reducing the intraventricular pressure gradient [7–10]. Thus, searching for the appropriate septal branch that feeds the hypertrophic septal myocardium, causing left ventricular outflow tract (LVOT) obstruction, is potentially required to localize the optimal area of ablation. In most cases, the target septal branches arise from the left anterior descending artery (LAD). However, the target septal artery sometimes arises not from the LAD but from the diagonal branch, intermediate artery, left main trunk, or right coronary artery (RCA) [11–13].

A number of case reports have described the treatment of PTSMA through the non-LAD septal perforators [14–17]. However, data pertaining to the procedure remain limited.

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Thus, in this case review series, we aimed to investigate PTSMA through the non-LAD septal perforators in patients with HOCM.

Materials and methods

A total of 202 consecutive patients with LVOT obstruction who underwent PTSMA for drug-refractory HOCM at our Department of Cardiovascular Medicine between January 1998 and December 2018 were enrolled. At the initial presentation, we reviewed and optimized the medications prescribed to the patients. Symptomatic patients with HOCM were typically given β-blockers. Subsequently, class Ia antiarrhythmic agents were administered to the patients with residual symptoms. Patients were considered PTSMA candidates if their symptoms were lifestyle-limiting after optimization of medication and if a resting or provoked pressure gradient > 50 mmHg was confirmed by at least one method. We excluded those who received PTSMA for isolated mid-ventricular obstruction. Furthermore, we carefully selected the indication of PTSMA for patients with LVOT obstruction and mid-ventricular obstruction, in which muscular obstruction was thought to be the cause of their symptoms. All patients who underwent PTSMA were consecutively recorded in our institutional registry database. Written informed consent was obtained from all patients and ethical approval was obtained from the review committee of Nippon Medical School (Approval no. 28-07-615).

A diagnosis of hypertrophic cardiomyopathy (HCM) was established by transthoracic echocardiography (TTE) and cardiac magnetic resonance imaging (MRI). HCM was diagnosed based on the presence of a maximal LV wall thickness ≥ 15 mm and the absence of other conditions that may explain left ventricular hypertrophy (LVH) during the clinical course [8]. LV cavity size, LV wall thickness, and left atrial diameter were measured in accordance with the American Society of Echocardiography's recommendations. In this study, genetic findings consistent with HCM were not mandatory to make a clinical diagnosis of HCM. In patients suspected of having secondary cardiomyopathy, endomyocardial biopsy was undertaken from the LV or interventricular septum of the right ventricle for histological assessment.

We diagnosed HOCM in patients with defined HCM and an intraventricular velocity ≥ 2.7 m/s on TTE (or a gradient ≥ 30 mmHg on direct simultaneous recording) at rest or on provocation. The hemodynamic state of intraventricular obstruction was determined according to the guidelines of the American College of Cardiology Foundation/American Heart Association [8].

We confirmed the obstruction level of HOCM by TTE and MRI. Patients in New York Heart Association (NYHA) functional class II were stratified into two groups: those with slight limitation (class IIs) and those with moderate limitation (class IIm) in physical activity [18].

Routine coronary angiography, left ventriculography, right-sided catheterization, and pressure studies were performed. All invasive evaluations were performed under medication. Target septal artery candidates were chosen based on the presence of septal branch perfusion to the hypertrophic septal myocardium causing LVOT obstruction on coronary angiography. The gradient was calculated as a peak-to-peak difference in pressures between the ascending aorta and LV apex using a retrograde approach. Pressure recordings were acquired with a fluid-filled catheter system from specially designed pigtail catheters (Type MTaka; Medikit, Tokyo, Japan) at the LV apex and a catheter placed in the ascending aorta [19]. Simultaneous pressure recordings were obtained at baseline and after provocation by intravenous nitroglycerin, the Valsalva maneuver, and premature ventricular contraction induced by pigtail catheter manipulation.

A temporary pacemaker was placed into the right ventricle to prepare for any atrio-ventricular block during the procedure. A 0.014-inch normal percutaneous coronary intervention (PCI) guidewire and a small over-the-wire PCI balloon were inserted with low pressure (2–6 atm) dilatation into the target branch using a 6 Fr or 7 Fr PCI guiding catheter and a 4 Fr or 5 Fr specially designed pigtail catheter. Selective angiography was performed to confirm the isolation of the LAD and vessel distribution in the proximal septum. Super-selective myocardial contrast echocardiography was performed for confirmation of the expected ablation site during all procedures. A small amount (1.0–2.0 ml for a single branch) of ethanol was slowly injected (0.3 ml/min) through the lumen of the over-the-wire PCI balloon. Morphine chloride was used as an analgesic before ethanol injection, and general anesthesia was not administered. After the procedure, all patients were admitted to the cardiac care unit fitted with a temporary pacemaker for at least 48 h as a prophylactic measure against late-onset heart block.

Continuous variables are presented as means ± standard deviation or medians with interquartile ranges and categorical variables are presented as prevalence rates (%). Continuous variables were compared using Student's *t* test or the Mann–Whitney *U* test. Categorical variables were assessed using the Chi-squared test or Fisher's exact test. When we evaluated the changes before and after the procedure, categorical variables were compared using McNemar's test and continuous variables were compared using the paired *t* test or Wilcoxon's signed-rank test, as appropriate. All statistical analyses were performed using SPSS Statistics 23.0 (IBM Corp., Armonk, NY, USA), and a two-sided p value < 0.05 was considered statistically significant.

Results

Overall, 202 patients (239 procedures) with LVOT obstruction underwent PTSMA during the study period. Among these, 21 (10%) patients had non-LAD septal branches that fed the target septal myocardium responsible for LVOT obstruction. The baseline patient characteristics, echocardiography, as well as symptoms and echocardiographic pressure gradient before the procedure, are shown in Table 1. Among patients who underwent PTSMA of a non-LAD perforator, 38% ($n=8$) previously underwent PTSMA compared with only 13% ($n=24$) of those who previously underwent PTSMA of LAD culprit ($p=0.08$). Procedural, in-hospital, and 6-month outcome data are presented in Table 2. In our population of patients with non-LAD septal perforators as the target arteries for PTSMA, 11 (52%) non-LAD septal target arteries originated from the diagonal branches, followed by 4 (19%) intermediate arteries, 2 (10%) left main trunks, 2 (10%) obtuse marginal branches, and 2 (10%) RCAs. Although one case failed, the rest of the 20 cases were successful, with a demonstrably sufficient decrease in the pressure gradient (from 106 ± 50 to 35 ± 39 mmHg, $p<0.05$) and brain natriuretic peptide level (from 569 ± 652 to 237 ± 203 pg/ml, $p<0.05$), and an improvement in the NYHA functional class ($p<0.05$) during the 6-month follow-up (Figs. 1, 2). Treating non-LAD perforators was associated with a greater number of septal branches treated during the procedure, but there was no difference in the volume of

Table 1 Baseline characteristics of patients who underwent PTSMA through LAD and non-LAD septal perforators

	Non-LAD ($n=21$)	LAD ($n=181$)	p value
Age (years)	69 ± 12	63 ± 14	0.09
Sex (male:female)	7 (23):14 (67)	52 (29):129 (71)	0.62
Repeated PTSMA	8 (38)	24 (13)	0.08
Reason for repeated PTSMA			
Residual symptoms	4 (19)	–	
Recurrence of symptoms	3 (14)	–	
Staged ablation	1 (5)	–	
Family history of sudden cardiac death	4 (19)	23 (13)	0.49
Ventricular tachycardia/Fibrillation	0 (0)	6 (3)	1.00
Non-sustained ventricular tachycardia	2 (10)	16 (9)	1.00
Atrial fibrillation	3 (14)	42 (23)	0.42
Prior pacemaker implantation	0 (0)	2 (1)	1.00
Prior ICD implantation	0 (0)	19 (11)	0.23
Medication at PTSMA			
B-blocker	21(100)	169 (94)	0.61
Class Ia agents	16 (76)	132 (73)	1.00
Class III agents	2 (10)	8 (4)	0.28
Ca-channel blockers	8 (38)	44 (24)	0.19
Diuretics	8 (38)	37 (20)	0.09
ACEI/ARB	2 (1)	24 (13)	1.00
Height (cm)	156 ± 10	155 ± 10	0.62
Weight (kg)	60 ± 12	58 ± 13	0.55
BMI (kg/m^2)	24 ± 4	24 ± 4	0.67
Measurement of the left-sided heart			
Interventricular septum thickness (mm)	17 ± 3	17 ± 4	0.5
Posterior wall thickness (mm)	12 ± 3	12 ± 3	0.78
Left atrial diameter (mm)	44 ± 6	44 ± 8	0.99
Left ventricular end-diastolic diameter (mm)	43 ± 6	42 ± 6	0.33
Left ventricular end-systolic diameter (mm)	24 ± 6	23 ± 5	0.71
Pressure gradient (mmHg)	106 ± 50	91 ± 56	0.24
Brain natriuretic peptide (pg/ml)	569 ± 652	615 ± 604	0.77

ACE-I angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *ICD* implanted cardioverter-defibrillator, *LAD* left anterior descending artery, *LMT* left main trunk, *LVOT* left ventricular outflow tract, *PTSMA* percutaneous transluminal septal myocardial ablation, *RCA* right coronary artery

Table 2 Procedural and 6-month outcomes of patients who underwent PTSMA through LAD and non-LAD septal perforators

	Non-LAD ($n=21$)	LAD ($n=181$)	p value
Number of septal perforator			0.004
1	3 (14)	91 (50)	
2	9 (43)	56 (31)	
3	4 (19)	23 (13)	
4	5 (24)	10 (6)	
5	0 (0)	1 (1)	
Origin of the non-LAD septal perforator			
LMT	2 (10)	–	
RCA	2 (10)	–	
Intermediate	4 (19)	–	
Diagonal	11 (52)	–	
Obtuse marginal	2 (10)	–	
Volume of injected ethanol (ml)	3.5 ± 2.3	2.8 ± 1.5	0.15
Permanent pacemaker/ICD	2 (10)	9 (14)	1.00
In-hospital death	0 (0)	0 (0)	1.00
Death at 6-month follow-up	0 (0)	0 (0)	1.00

ICD implanted cardioverter-defibrillator, *LAD* left anterior descending artery, *LMT* left main trunk, *LVOT* left ventricular outflow tract, *PTSMA* percutaneous transluminal septal myocardial ablation, *RCA* right coronary artery

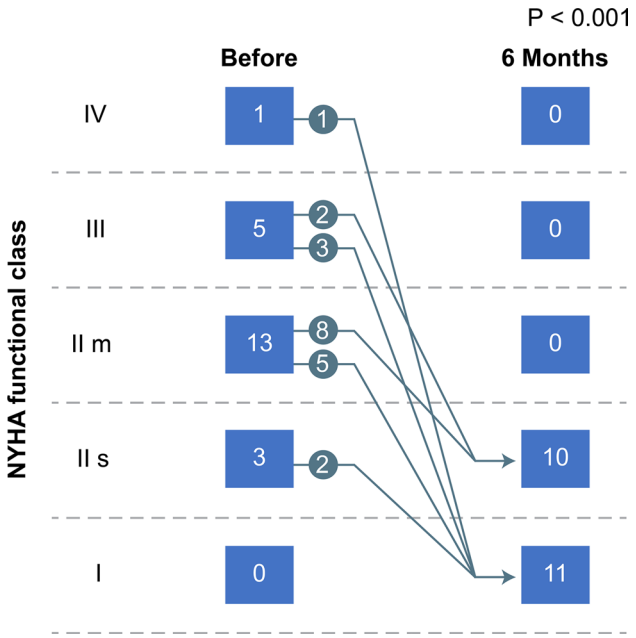

Fig. 1 Improvement in NYHA functional class at the 6-month follow-up. Improvement of symptoms was observed over the first 6 months. *NYHA* New York Heart Association

injected ethanol between the two groups (Table 2). There was no impact on periprocedural outcomes, including the need for a permanent pacemaker or implantable cardioverter-defibrillator, and mortality.

Figure 3 illustrates the procedural steps leading to the identification and treatment of a non-LAD perforator from the intermediate artery of a patient undergoing their first alcohol septal ablation. In this case, septal ablation through the intermediate artery, in addition to the first and second septal branches of the LAD, was necessary because this intermediate artery was found to supply the basal septum on contrast echocardiography. The microcatheter and perfusion balloon method was performed because insertion of the over-the-wire balloon catheter into a small non-LAD perforator was difficult.

First, we performed coronary angiography, which showed a basal septal branch that arises from the intermediate artery. Second, we placed and inflated the perfusion balloon (Ryusei® 3.0/13 mm: KANEKA Medix, Japan) into the LAD and injected 1.5 ml ethanol into the intermediate artery through a micro-catheter (Caravel®; Asahi Intecc, Japan). Finally, we inflated the balloon in the proximal segment of the first septal branch, injected ethanol into it, and repeated the exact procedure in the second septal branch.

Discussion

The present study provides new insights into PTSMA for HOCM, showing how effective septal myocardial ablations can be performed through non-LAD septal perforators. We showed the clinical importance of non-LAD septal perforators as an alternative route of PTSMA, in addition to describing a routine workflow for the procedure and illustrating some novel technical points. In general, anterior and posterior septal penetrating coronary branches supply the

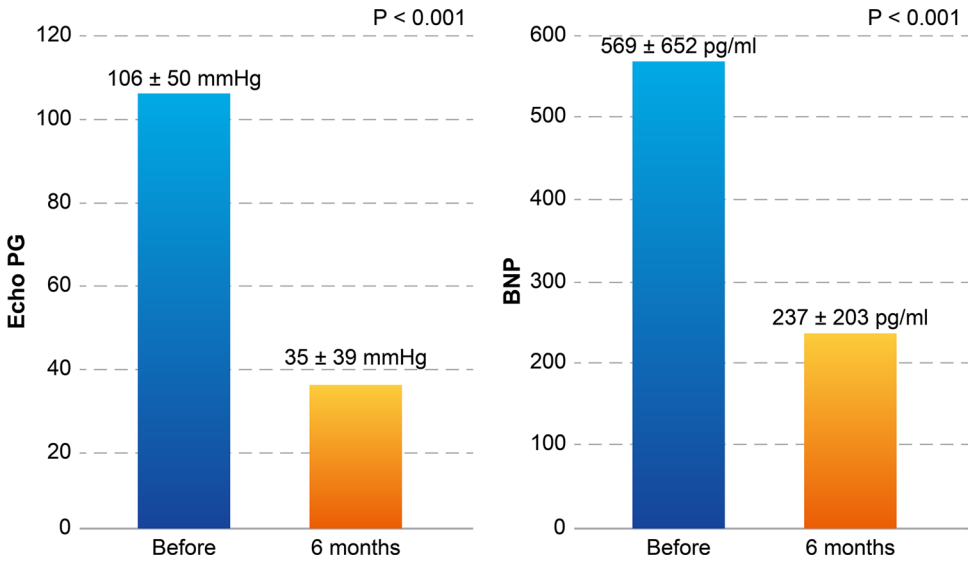

Fig. 2 Echo pressure gradient and brain natriuretic peptide before and 6 months after the procedure. A sufficient decrease in the PG and BNP level is observed at the 6-month follow-up. *BNP* brain natriuretic peptide, *PG* pressure gradient

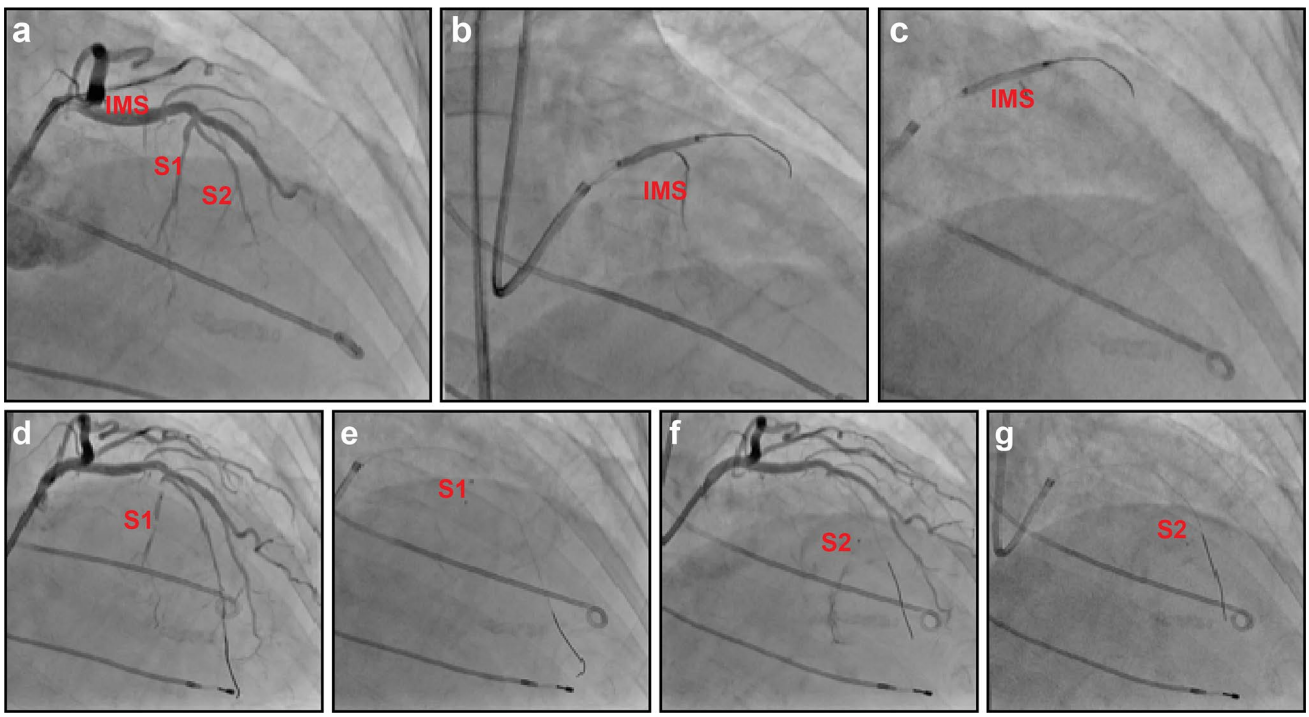

Fig. 3 Cine angiography images from a patient who underwent PTSMA of the intermediate artery as a non-LAD perforator. **a** Coronary angiography showed a basal septal branch that arise from the intermediate artery. This branch was believed to partially supply the basal septum on contrast echocardiography. In addition, the first and second septal branches were targeted during the procedure (RAO cranial view). **b** We placed and inflated the perfusion balloon (Ryusei® 3.0/13 mm; KANEKA Medix, Japan) into the intermediate artery and performed a tip injection from the micro-catheter (Caravel®; Asahi Intecc, Japan) placed in the basal septal branch from intermediate artery (RAO cranial view). Staining of the basal septum was demonstrated by contrast echocardiography during the alcohol septal ablation of this branch, confirming that this branch supplies the basal septum. **c** We injected 1.5 ml ethanol into the basal septal branch from intermediate artery through the micro-catheter (RAO cranial view). **f** We inflated an over-the-wire balloon in the proximal segment of S1 and a performed tip injection into it (RAO cranial view). **g** We inflated the balloon in the proximal segment of S1 and injected 2.2 ml ethanol (RAO cranial view). **g** We inflated an over-the-wire balloon in the proximal segment of S2 and performed a tip injection (RAO cranial view). **h** We inflated the balloon in the proximal segment of S2 and injected 1.8 ml ethanol (RAO cranial view). *PTSMA* percutaneous transluminal septal myocardial ablation, *IMS* septal branch from intermediate artery, *S1* first septal branch, *S2* second septal branch, *RAO* right anterior oblique, *LAD* left anterior descending artery

Table 3 The points we discuss to determine which procedure to be selected, PTSMA or surgical myectomy, in our heart team

	PTSMA preferred	Surgical myectomy preferred
Age	Over 40 years	40 years or younger
Surgical risk	Moderate or high	Low
Concomitant heart disease requiring surgery	No	Yes
Appropriate target branch	Yes	No
Abnormal papillary muscle	No	Yes
Apical aneurysm	No	Yes
Target myocardium to be ablated or resected	LVOT and/or mid ventricle	Including apical portion

PTSMA percutaneous transluminal septal myocardial ablation, *LVOT* left ventricular outflow tract

ventricular septal myocardium. Two-thirds of the septal myocardium (the anterior portion) is normally supplied by the anterior septal branch arteries arising from the proximal LAD, while the remaining septal myocardium (the posterior portion) is supplied by the posterior descending artery (which arises from the right coronary or circumflex artery, depending on the dominance pattern) [20, 21]. However, highly variable septal branch anatomy is sometimes observed in HOCM patients. In such a scenario, although septal branches from the diagonal branch are frequent, a number of case reports described the treatment of PTSMA through other septal branches [14–16]. Among the patients who underwent PTSMA through the non-LAD septal perforator in our study, one was treated with a staged procedure, whereas seven (33%) underwent previous PTSMA through the LAD in a routine manner before requiring additional procedures for residual or recurrent symptoms (Table 1). Moreover, in patients in whom PTSMA from a dual septal perforator blood supply was successful, no further PTSMA was performed. However, one patient who underwent PTSMA from a single septal perforator blood supply (diagonal branch) underwent repeated PTSMA through the LAD, 28 months later. This implies the difficulty in recognizing the non-LAD septal perforators as target arteries during the initial procedure. Recently, we have tended to perform PTSMA through non-LAD septal perforators with septal branches through the LAD during the same session after initial systematic screening using coronary angiography and cardiac computed tomography (CT) angiography. A previous study on PTSMA through non-LAD septal perforators also reported that a significant number of patients had undergone at least one previous unsuccessful PTSMA, and mentioned the importance of systematic screening for the ideal target septal branch to avoid incomplete PTSMA [22]. There are several key points that can be learned from this case review. First, we need to consider non-LAD septal perforators in addition to those from the main LAD as target arteries, when residual symptoms and a pressure gradient are present. The lack of a significant first septal branch from the main LAD can also be a sign of a non-LAD septal supply. Second, the target branch should be searched for again when significant staining is not visible on superselective myocardial contrast echocardiography. Myocardial contrast echocardiography is useful not only as a routine procedure, but also for identifying non-LAD septal perforators as appropriate target arteries [23–25]. Specifically, the branch from the intermediate artery or left main trunk should be identified, if there is no significant stain at the most basal segment of the LVOT (Fig. 3). Moreover, with the continued advances in imaging technology, CT angiography has been utilized to identify the target vessels when planning PTSMA [26]. Third, when a wire was placed into a non-LAD septal perforator, a more delicate technique using a micro-catheter was necessary, because of the tortuosity or acute angle of the branch and, in such scenario, dual-lumen microcatheter-facilitated reverse wire technique may be useful. In fact, in one patient, we were unable to place the wire into the target branch, because the target artery was tortuous at an acute angle and extremely small; therefore, the procedure was unsuccessful. Forth, we implemented the microcatheter and perfusion balloon method when insertion of the over-the-wire balloon catheter into a small non-LAD perforator was difficult (Fig. 3). Using the microcatheter and perfusion balloon method, we were also able to avoid leakage into untargeted vessels, which is one of the most critical complications of alcohol septal ablation. Finally, considerable attention should be given to complete heart block, while ablating a branch more proximal than the first septal branch of the LAD, because this branch often supplies the area between the upper proximal interventricular septum and the anterior segments. This area potentially contains the left bundle branch and a previous study reported that damage to this area by surgical septal myectomy led to left bundle branch block, although right bundle branch block often develops after routine PTSMA [27].

Finally, the well-organized heart team approach, including cardiologist, imaging specialist, and surgeon, is definitely important to provide HOCM patient optimal septal reduction therapy [7, 8]. We should have the appropriate discussion before the procedure (either percutaneously or surgically). The points which we discuss to determine which to choose in our heart team are summarized in Table 3. After

checking each point, we finally determine the procedure in a comprehensive manner.

The present study has some limitations. First, this was a retrospective analysis performed at a single institute and the number of patients was relatively small. Second, we only selected patients who received PTSMA for non-LAD septal arteries. Patients who had non-LAD septal perforators that could be potential target arteries might have been overlooked.

In conclusion, a non-negligible number of patients with HOCM were found to have non-LAD septal perforators, which could be used as an alternative route for PTSMA in patients who were not treated effectively with ablation of the septal branches that arise from the main LAD. This procedure may improve response rates and overall outcomes of patients with HOCM.

Author contributions All the authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by YI and MK. The first draft of the manuscript was written by YI and all the authors commented on previous versions of the manuscript. All the authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in these studies involving human participants were in accordance with the ethical standards of the institutional and national research committee (Nippon Medical School, approval no. 28-07-615) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All patients who underwent PTSMA had been consecutively assigned to the institutional registry database at Nippon Medical School Hospital.

Informed consent Informed consent was obtained from all the individual participants included in the study.

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