EMBOLIZATION OF PULMONARY ARTERIOVENOUS MALFORMATIONS : OUTCOMES AND LONG-TERM FOLLOW UP IN 10 PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA

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Abstract

Background : Pulmonary arteriovenous malformations (PAVMs) complicated with hereditary hemorrhagic telangiectasia (HHT) are treated by embolotherapy with adaptation for afferent arteries ≥ 3 mm in diameter.

Purpose : To evaluate the efficacy of embolotherapy in oxygenation and event-free survival, even with persistent untreated small PAVMs.

Materials and methods : Ten consecutive patients with HHT and 35 PAVMs treated by embolotherapy were selected from a database between 1991 and 2009 for a retrospective investigation. We evaluated improvement in partial arterial oxygen pressure (PaO_2) and right-to-left shunt and followed up the prevalence of long-term complications after embolotherapy.

Results : Twenty-three PAVMs were cured by embolotherapy. Mean PaO_2 increased from 69.0 ± 19.2 to 84.9 ± 19.6 torr after embolization (P=0.005) and right-to-left shunt improved from 25.7 ± 9.5 to 13.8 ± 6.3 (P=0.005). Oxygenation was similarly improved in six patients with small PAVMs outside of treatment adaptation. Although new embolic episodes did not arise, one patient developed reperfusion and untreated PAVMs grew in two others during a mean follow-up period of 69 months.

Conclusions : Embolotherapy helped oxygenation and prevented paradoxical embolism even if small PAVMs remained untreated. However, frequent follow-up is necessary because untreated small PAVMs are at high risk for their growth.

Key words : Pulmonary arteriovenous malformations, Hereditary hemorrhagic telangiectasia, embolotherapy, Right-to-left shunt, Recurrence

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Abbreviations

$AaDO_2$: alveolar arterial oxygen difference
HHT : Hereditary hemorrhagic telangiectasia
PaO_2 : partial arterial oxygen pressure
PAVMs : Pulmonary arteriovenous malformations

TCE : Transcatheter embolotherapy

Introduction

The estimated prevalence of autosomal dominant hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Rendu-Weber syndrome, is at least 1/5,000, and this disease can frequently become complicated by clinically significant arteriovenous malformations in the brain, lung, gastrointestinal tract and liver[1]. Pulmonary arteriovenous malformations (PAVMs) that complicate 60% of patients with HHT[2] comprise direct connections between a branch of a pulmonary artery and a pulmonary vein through a thin-walled aneurysm. They act as direct right-to-left shunts, resulting in dyspnea, fatigue, cyanosis and polycythemia when the shunt is large. In addition, because the PAVMs bypasses the capillary bed, the lung loses its filter function, thus allowing emboli and bacteria to pass directly into the systemic circulation, resulting in stroke or cerebral abscess, even in patients with clinically silent PAVMs[3]. Accurate screening of patients with HHT and effective treatment of PAVMs are therefore essential to avoid potential complications and to reduce associated morbidity and mortality. Based on such findings, various authors have recommended treatment for all symptomatic PAVMs, PAVMs > 2 cm in diameter and afferent arteries ≥ 3 mm in diameter[3-5].

Transcatheter embolotherapy (TCE) using detachable balloons or stainless steel coils is the generally accepted treatment of choice for PAVMs instead of surgical resection or ligation[6]. The advantages of TCE such as relative safety, lower procedural morbidity, shorter hospital stay and a rapid return to work, favor this procedure[3]. Therefore, TCE is effective and the preferred treatment for PAVMs. Many reports have documented dramatic improvements in PAVMs involution, pulmonary gas exchange, prevention of neurologic sequelae and decreasing right-to-left shunts after treating PAVMs using TCE[3,7,8]. Patients with HHT often have multiple PAVMs in both lungs, and small PAVMs might not be indicated for TCE. Persistent untreated PAVMs in patients with HHT might lower the effectiveness of right-to-left shunts and lead to paradoxical embolisms.

The present study evaluates the effects of TCE in HHT patients, even if small PAVMs remained untreated. We assessed the oxygenation and event-free survival as short- and long-term effects of TCE, respectively.

Methods

Patients

We reviewed the medical records of 10 consecutive patients with HHT and PAVMs treated by TCE during the past 19 years (May 1991 to June 2009). We obtained complete histories, procedural reports and the results of physical examinations and laboratory tests. All patients were diagnosed with HHT based on the Curaçao criteria of spontaneous recurrent nosebleeds, mucocutaneous telangiectasia, visceral involvement, and having an affected first degree relative[9].

The following symptoms and various physiological parameters were serially measured before and one month after percutaneous transcatheter embolization as part of our routine practice : presence of dyspnea with or without exertion, standard pulmonary function tests, arterial oxygen saturation (SpO_2) breathing room air determined by pulse oximetry, partial oxygen pressure in arterial blood (PaO_2) of supine patients breathing room air, alveolar arterial oxygen difference ($AaDO_2$) calculated using blood gas analysis and right-to-left shunt fraction calculated using the 100% oxygen method[8].

Because chest CT is at least as sensitive and specific as pulmonary angiography for a diagnosis of PAVMs[10], an experienced radiologist assessed all patients by CT and/or selective digital-subtraction pulmonary angiography to determine sites and sizes of PAVMs.

Embolization technique

Where possible, all PAVMs > 2 cm in diameter and its afferent arteries ≥ 3 mm in diameter were embolized at Akita university Hospital by a single experienced interventional radiologist.

The afferent vessels of the PAVMs were embolized as close to the sac of the PAVMs as possible using appropriately-sized coils that were placed until flow through the PAVMs ceased. When afferent arteries were too short to embolize, large coils were placed in the sac and detachable balloons were used for a patient with early

PAVMs. Patients with several or difficult PAVMs in both lungs were often treated over the course of two or more admissions to limit contrast media load and to avoid the potential for bilateral pleurisy.

Follow up

Values for PaO_2 at rest, $AaDO_2$ and right-to-left shunt were evaluated one month after TCE in two groups separated based on having the untreated small PAVMs which outside treatment adaptation or not. Furthermore, patients were followed up at our clinic every 3-12 months after TCE. Routine clinical follow-up consisted of medical history, chest radiography and SpO_2 measurements. High-resolution computed tomography (HRCT) was performed when increased right-to-left shunt was suspected. Afferent arteries of non-embolized PAVMs ≥ 3 mm in diameter or recanalization diagnosed by HRCT and/or symptoms caused by right-to-left shunts were defined as exacerbation and pulmonary angiography and TCE were performed.

Data analysis

Data were analyzed using SPSS v 18.0 (IBM, Armonk, NY, USA) and are presented as means and standard deviation (SD) unless otherwise stated. Differences in PaO_2 values, $AaDO_2$ and right-to-left shunts before and after TCE were assessed using t-test. Possible differences in outcomes between patients with and without residual small PAVMs after TCE were evaluated using Kaplan-Meier curves and the log-rank test. Statistical significance was defined as $P < 0.05$.

Results

Assessments of patients before transcatheter embolotherapy

The study group comprised 10 patients (mean age, 44.4 y ; range, 19-76 y male, $n=6$). All patients were definitively diagnosed with HHT based on the Curaçao criteria (Table 1). The mean age at first assessment of HHT was 28.8 years. Although six patients had dyspnea upon effort as the chief symptom, four had essentially normal lung function, and two had restrictive patterns determined by spirometry. Neurological complications had occurred in three patients, and one patient had a liver abscess. None of the patients had a history of life-threatening hemorrhage, although one had experienced minor hemoptysis.

Before TCE, mean PaO_2 at rest was 69.0 ± 19.2 torr and the mean right-to-left shunt measured in the supine position was 25.7 ± 9.5%.

Thirty-five PAVMs were diagnosed in 10 HHT patients by HRCT and/or angiography. Nine patients had an average of 3.7 multiple PAVMs whereas one had a single PAVM. Table 2 shows the characteristics of the PAVMs. Twenty-two (63%) and 13 (37%) PAVMs were located in the lower and upper or middle lobes, respectively. The mean size of the aneurysmal sac was 24.1 ± 11.5 (range, 4-50) mm. Twenty-seven (77%) PAVMs had simple angioarchitecture defined as a single afferent segmental artery and a single draining vein[11] and eight (23%) had complex angioarchitecture with two or more afferent arteries or draining veins. Of the eight complex PAVMs, seven had two afferent arteries each and one had three afferent arteries. Twenty-three (66%) PAVMs were > 20 mm in diameter or had afferent arteries > 3 mm in diameter, and required treatment adaptation. The mean sizes of treated and untreated PAVMs were 26.8 ± 11.6 and 14.5 ± 5.8 mm, respectively.

Embolization

Successful occlusion was achieved within a single session for nine patients and two sessions were needed to achieve complete occlusion of bilateral multiple PAVMs in one. One (5%) and 22 (95%) PAVMs were occluded with a detachable silicone balloon and coils, respectively. The afferent vessels of the 22 (95%) PAVMs were embolized, and coils were placed in the sac in only one (5%) of the afferent arteries that were too short to embolize. No complications arose.

Oxygenation data

Values for PaO_2 at rest, $AaDO_2$ and right-to-left shunt before and one month after TCE were analyzed. Mean PaO_2 significantly increased (69.0 ±19.2 to 84.9 ±19.6 torr ; $P < 0.001$), and $AaDO_2$ as well as the right-left shunt significantly improved (37.7 ± 16.8 to 19.0±15.1

Table 1. Baseline characteristics of 10 patients with HHT and pulmonary arteriovenous malformations.

Patients	Age	Age at HHT onset*	Sex	Family history of HHT	Nosebleed	telangiectasia	Extrapulmonary visceral involvement	Dyspnea	Complications	PAVM location	No. of PAVM	No. of untreated PAVM	Device	PaO_2 (torr)	$PaCO_2$ (torr)	$AaDO_2$	Right-to-left shunt (%)	%VC (%)	FEV1/FVC (%)
1	22	5	M	+	+	+	Brain	+	Hemoptysis	RLL, LLL	3	1	Coil (in sac)	62	40	45.5	26.2	63	93.1
2	61	37	F	+	-	+	GI	+	Cereberal abscess	RUL,RML, RLL, LUL, LLL	7	5	Coil	39.9	33	64.9	27.5	84.7	90.9
3	46	41	F	+	+	+	Spleen	-	-	RML, LLL	2	1	Coil	91	34	12	18.7	123.1	80.3
4	19	12	F	+	+	+	-	+	Cereberal abscess	RLL, LLL	6	2	Coil	65.7	36.1	43.4	33.1	122	93.3
5	43	12	M	+	+	+	Liver	-	-	RUL, RLL, LUL	3	2	Detachable balloon	65.3	35	34.45	19.16	91.2	91.6
6	30	5	M	+	+	-	-	+	-	RUL, RLL, LUL, LLL	4	1	Coil	51.1	37.6	55.9	49.1	98.4	88.2
7	48	45	M	+	+	+	-	-	-	RML, LLL	2	0	Coil	105	40	7	19	118	80.9
8	44	5	M	+	+	+	GI	+	-	RUL, RML, RLL, LUL, LLL	5	0	Coil	75	32.7	33.7	22.5	113	80.3
9	55	55	M	+	+	+	-	-	Cereberal and liver abscesses	LLL	1	0	Coil	79	40.2	27.2	18.5	96.9	85.1
10	76	71	F	+	+	+	-	+	-	RML, RLL	2	0	Coil	56	34.4	44	23.15	67.1	77.86
mean±SD	44.4±17.5	28.8±24.0									3.5±1.9	1.2±1.5		69.0±19.2	36.3±2.9	37.7±16.8	25.7±9.5	97.7±20.5	86.1±5.6

HHT = hereditary hemorrhagic telangiectasia ; PAVM = pulmonary arteriovenous malformation ; PaO_2 = arterial oxygen content ; $PaCO_2$ = arterial carbon dioxide content ; $AaDO_2$ = alveolar-arterial oxygen difference before embolotherapy ; %VC = ratio of predicted vital capacity ; FEV1/FVC = forced expiratory volume/forced vital capacity ; RUL = right upper lobe ; RML = right middle lobe ; RLL = right lower lobe ; LUL = left upper lobe ; LLL = left lower lobe.
*Age at first assessment of HHT

Table 2. Characteristics of PAVMs ($N = 35$).

Characteristic	Value
Total PAVM (n=35)	
Simple/complex	27/8
Diameter of PAVM (mm)	24.1±11.5
Location	
RUL	4
RML	5
RLL	12
LUL	4
LLL	10
Treated PAVM (n=23)	
Diameter of treated PAVM (mm)	26.8±11.6
Diameter of treated AA (mm)	4.9±2.1
Untreated PAVM (n=12)	
Diameter of untreated PAVM (mm)	14.5±5.8

AA, afferent arterie ; PAVMs, pulmonary arteriovenous malformations ; RUL = right upper lobe ; RML = right middle lobe ; RLL = right lower lobe ; LUL = left upper lobe ; LLL = left lower lobe.

Table 3. Effect of embolization upon oxygenation

	Pre-embolization	Post-embolization	p value
PaO_2			
Total	69.0±19.2	84.9±19.6	0.001>
Group 1	78.5±20.1	89.2±17.5	0.009
Group 2	62.5±17.1	82.0±21.9	0.003
$AaDO_2$			
Total	37.7±16.8	19.0±15.1	0.001>
Group 1	27.9±15.6	13.5±12.7	0.013
Group 2	44.1±15.4	22.7±16.5	0.001
Right-to-left shunt			
Total	25.6±9.4	13.8±6.3	0.017
Group 1	20.7±2.3	10.4±7.2	0.032
Group 2	28.9±11.2	16.1±5.0	0.083

Complete occlusion of all angiographically visible PAVMs in Group 1 (n=4). Complete occlusion of all visible PAVMs in Group 2 (n=6) with treatment adaptation, but smaller lesions remained.

and 25.7 ± 9.5 to 13.8 ± 6.3 ; $P < 0.001$ and $P = 0.017$ for each) after embolization (Table 3). Dyspnea also disappeared or was improved in all patients. We separated the patients depending upon whether all angiographically visible PAVMs were completely occluded (Group 1 : n = 4, 40%) or completely occluded with a treatment adaptation and smaller lesions remained (Group 2 : n = 6, 60%). In both groups, PaO_2 and $AaDO_2$ significantly improved. Although there was not significant difference in Group 2, right-to-left shunt also improved.

Data for each of PaO_2 at rest, $AaDO_2$ and right-to-left shunt improved in both groups (Figure 1). Although embolotherapy was successful according to post-procedural angiographic findings, the right-to-left shunt did not recover to the normal range even in Group 1 (Table 3).

Clinical follow-up

The mean follow-up period was 69.2 ± 47.0 months (range, 18-160). During this period, SpO_2 decreased more than 3% in two of ten patients, and one was aware of aggravation of the shortness of breath. PAVMs reperfusion was evident on CT images of one patient at 98 months after TCE. Untreated PAVMs grew in two patients at 18 and 21 months after TCE. One patient died at 38 months after TCE due to pneumonia as a sequela of repeated brain abscesses, although an association with PAVMs or HHT was uncertain. All of these episodes occurred only in Group 2 (Figure 2).

Discussion

Pulmonary arteriovenous malformations are direct artery-to-vein connections that result in a direct right-to-left shunt. Although PAVMs are uncommon lesions, PAVMs can cause considerable morbidity and occasional mortality[12] and result in severe and frequent complications even at a young age. Three of our patients were complicated by cerebral abscesses and one had hemoptysis at average of 39 years of age. The high incidence of cerebrovascular events, including transient ischemic stroke, and cerebral abscess due to thrombus formed on, or passing through PAVMs is now recognized as the principal determinant of mortality and morbidity rates of 11% to 30% and 26% to 33%, respectively, found in large series[2,13,14]. Furthermore massive hemoptysis or hemothorax have been described as complications of HHT[15]. Therefore the goals of treatment are to improve dyspnea/

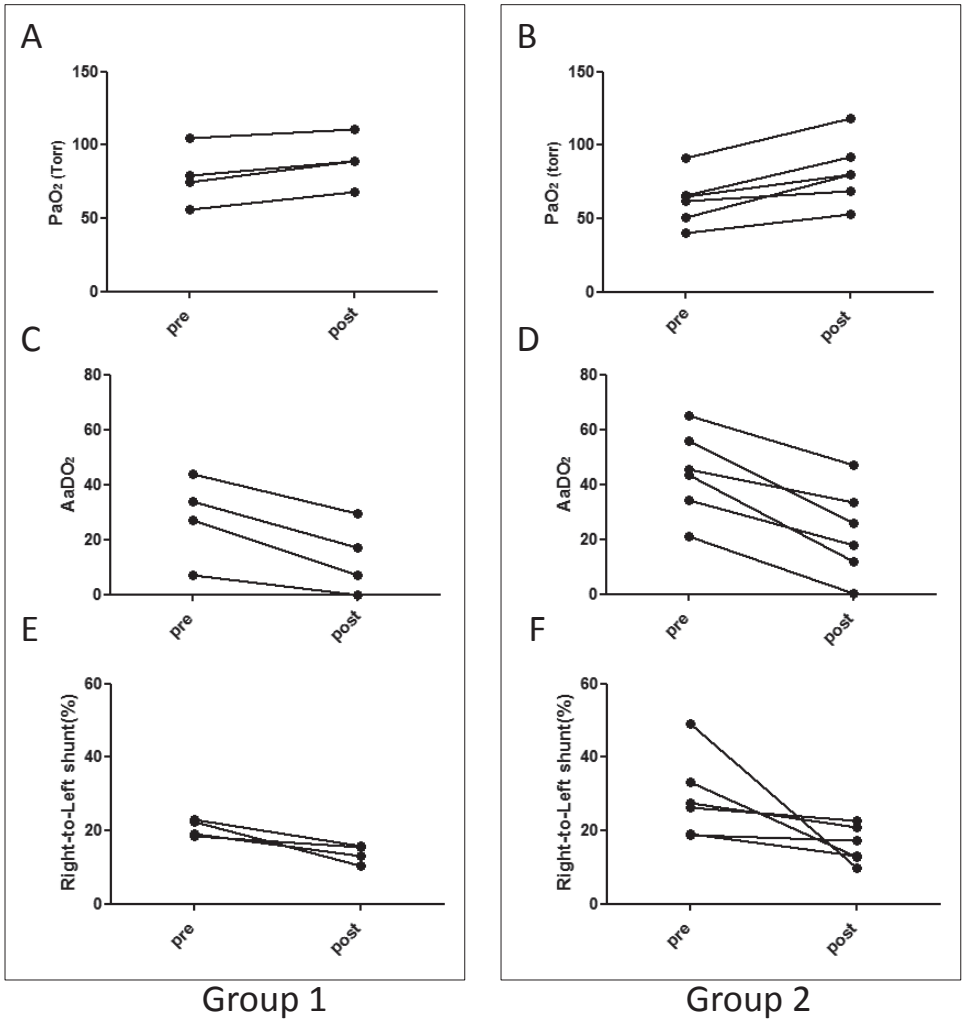

Fig. 1. Individual pre and post embolization details of patients.
Short-term outcomes of patients in Group 1 ($n=4$) who underwent embolization of all angiographically visible PAVMs (A, C, E) and those in Group 2 ($n=6$) with PAVMs that remained untreated (B, D, F).
A, B. Change in partial pressure of oxygen in arterial blood (PaO_2) pre- and post-embolotherapy. C, D. Change in alveolar arterial oxygen difference ($AaDO_2$). E, F. Change in right-to-left shunt.

hypoxemia, prevent lung hemorrhage and most importantly, to prevent neurological sequelae[3].

Although therapeutic options include angiographic embolization with metal coils or balloon occlusion and surgical excision, the recent success of transcatheter embolization has resulted in considerable debate over the optimal treatment for PAVMs. Traditional indications for treatment have included progressive PAVMs enlargement, paradoxical embolization and symptomatic hypoxemia[2]. Recently, PAVMs > 2 cm in diameter with afferent arteries ≥ 3 mm in diameter have been recognized as causing transient ischemic attacks, strokes and brain abscesses[3-14]. Based on these findings, White et al.[3,4] have recommended treatment of all PAVMs with afferent vessels ≥ 3 mm.

Some post-embolotherapy studies based on these cri-

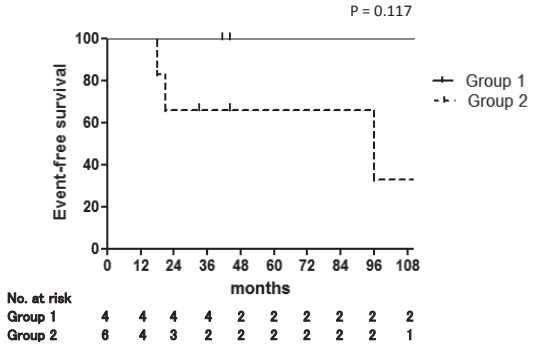

Fig. 2. Kaplan-Meier curves of event-free survival. Long-term outcomes of patients in Group 1 who underwent embolization of all angiographically visible PAVMs (solid line) and those in Gropu 2 with PAVMs that remained untreated (dotted line).

teria have shown improvements in dyspnea, oxygenation and shunt fraction in patients including HHT. Chilbers *et al.* described that coil embolization is effective for treating PAVMs and that mean shunt fraction and resting SaO_2 improved from 33% to 19% and from 86% to 92%, respectively[8]. Pennington et al. also reported that mean shunt fraction and resting PaO_2 improved from 24.9% to 13.3% and from 55.4 torr to 76.5 torr, respectively[16].

Mean shunt fraction, resting PaO_2 and $AaDO_2$ improved from 25.7% to 13.8%, 69.0 to 84.9 torr and 37.7 to 19.0, respectively, after embolization in all of our patients with HHT. Although the two groups could not be statistically compared in our study because few patients have this rare condition, improvements were similar in patients with complete occlusion of all visible PAVMs and in those in whom smaller lesions persisted.

Although oxygenation notably improved, shunt fraction did not recover to the normal range after TCE even in the group with complete occlusion of all visible PAVMs and normal lung function. This tendency is also evident in two published reports[8,16].

The residual shunt was believed to represent passage through PAVMs that were too small to embolize (afferent arteries < 3 mm)[8]. Our data suggested that residual shunts also passed through microvascular PAVMs that could not be identified by HRCT or pulmonary angiography. A subgroup of patients with HHT and diffuse tiny PAVMs has been reported[17]. These patients generally present with profound cyanosis and severe hypoxemia, and TCE does not significantly improve oxygenation even if TCE for large PAVMs is successful because many tiny diffuse PAVMs remain unaffected[17]. Our notion might be in line with these findings, although our patients did not have typical visible microvascular PAVMs.

Because mutations in a specific gene are clearly associated with an increased risk of PAVMs as are other manifestations of HHT, the prevalence of PAVMs apparently increases with age, reaching up to 33% over 50 years[16,18,19]. In addition, PAVMs tend to increase in size[20], especially if multiple, and they rarely regress spontaneously[14]. Therefore, long-term follow-up is needed regardless of whether patients with HHT have embolized PAVMs or no PAVMs. Follow-up allows the identification of embolized PAVMs that have become reperfused and those that have grown large enough to be considered for embolization. One recommendation states that patients should be assessed by multidetector thoracic CT with thin-section (1-2 mm) reconstruction within 6-12 months after embolization, and about every three years thereafter[1].

Although new embolic episodes did not arise in our study, PAVMs became reperfused at 98 months after TCE in one patient and untreated PAVMs grew in two others at around two years after TCE.

These episodes notably occurred in patients who had untreated, small PAVMs that persisted after TCE and thus might be at high-risk for reperfusion or PAVMs growth. Mager *et al.* also reported that PAVMs recurred around four years after TCE in patients (not limited to HHT) if left untreated. Two of our patients experienced recurrence within two years. Although the international guidelines for HHT recommend defining the CT follow-up period on a case by case basis, we consider that follow-up should be rather frequent at least during the early period after TCE.

This study has some limitations. Although we included all patients with HHT who had PAVMs treated at our hospital, we did not include untreated patients with PAVMs. We could not compare the natural history of PAVMs with those in our patients due to ethical considerations. Untreated PAVMs can cause life-threat-

ening complications and thus all patients with PAVMs had treated with adaptation at our hospital.

Although visible on CT images, we could not compare the diameters of treated and untreated afferent arteries as they were below the limits of our measurement capabilities.

The follow-up period of an average of 69 months might be short, because recanalization rates of 25% were reported even if initially successfully embolized in mean follow-up period of 120 months[21], although no patients with completely occluded PAVMs recurred in our study. Although HHT is rare, the number of patients with HHT treated by TCE might have been too small to generate statistically meaningful data in comparison between groups with or without untreated smaller PAVMs remained. Reexamination may be needed after cases increased in the future.

Conclusions

This study supports the safety and effectiveness of transcatheter embolotherapy for PAVMs in patients with HHT. Oxygenation was improved and paradoxical embolism was prevented in patients with and without tiny untreated residual PAVMs. However, patients with untreated small PAVMs were at high-risk for reperfusion or PAVMs growth and thus required frequent follow-up.

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Authors' statement of responsibility

All authors have read and approved the final version of this manuscript.

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