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# Long-Term Single-Center Retrospective Follow-Up After Embolization of Pulmonary Arteriovenous Malformations Treated Over a 20-year Period: Frequency of Re-canalization with Various Embolization Materials and Clinical Outcome

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## Abstract

*Purpose* The present study is a register-based observational study of an unselected consecutive patient cohort with pulmonary arteriovenous malformations (PAVMs) from a single national hereditary hemorrhagic telangiectasia and PAVM embolization center. The aim was to investigate the frequency of re-embolizations and the clinical outcome after embolization with the use of different embolization materials further, to define which PAVM morphology and size of feeding arteries that most often were re-embolized, and to estimate the clinical outcome of the patients including those that were re-embolized.

*Methods* The population was included from 1996 until 2016 and was made up of a total of 136 patients with 322 PAVMs. Median follow-up was 38.3 (0.3–241 months).

*Results* The re-embolization rate was 9.3%. None of the PAVMs treated with detachable silicone balloons were re-embolized, while 4.5% treated with vascular plugs and 11.7% treated with coils were re-embolized (p=0.07). In total, 16/74 complex PAVMs were re-embolized compared with 14/248 simple PAVMs. In big-sized feeding arteries ≥

6mm, 16/112 were re-embolized compared with 14/210 with smaller-sized feeding arteries. Out of the 30 re-embolized PAVMs, 23 resulted in a successful clinical outcome.

*Conclusions* Our results suggest that standard coils probably should not be the first choice for embolization of PAVMs, and vascular plug alone or in combination with coils might be a better primary option for embolization in these patients.

*Level of Evidence* Level 3A, non-randomized case controlled cohort/follow-up study.

**Keywords** Embolization, therapeutic · Pulmonary arteriovenous fistulas · Arteriovenous malformations · Reperfusion · Interventional radiology

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## Introduction

Embolization of pulmonary arteriovenous malformations (PAVM) is generally considered the treatment of first choice [1–6]. PAVM embolization is technically and clinically very successful and is now the standard of care for the treatment of these lesions [7, 8]. Recurrence can occur after embolization and attributed primarily to re-canalization, but also to pulmonary-to-pulmonary reperfusion, incomplete primary treatment and systemic-to-pulmonary reperfusion. PAVM reperfusion rates after embolization and re-embolization are estimated to be between 5 and 20% [1, 3, 6, 7, 9–19], most often due to re-canalization of embolized vessels. Small PAVMs have a

high persistence rate after coil embolotherapy, especially if the coils are deployed less than 1 cm away from the PAVM sac [20]. Provided that tight and optimal packing has been performed, there is no evidence that one embolization device is superior to others although amplatzer vascular plugs (AVP) recently have shown fewer re-canalizations than after standard coil embolization [21–24]. Further, AVP in conjunction with coils seems to have good long-term success [25], especially in first-generation AVP, but no randomized studies are available.

The aim of the present study was to investigate the clinical outcome and the frequency of re-embolization after embolization with different embolization materials with long-term follow-up of an unselected consecutive patient cohort from a single national hereditary hemorrhagic telangiectasia (HHT) and PAVM embolization center. The primary outcome measurement was to estimate the technical success without re-embolization after embolization of PAVMs. The secondary outcome measurements were to compare the outcome of different embolization devices with regard to rates of failure (re-embolization), to define which PAVM morphology (simple or complex) and size of feeding arteries that had the highest risk of re-embolization and finally to estimate the clinical outcome in the patients who were re-embolized.

## Materials and Methods

Odense University Hospital is the Danish reference center for HHT diagnostics and PAVM treatments. The present study is a single-center retrospective register-based observational study [26] including all consecutive patients with the intention to treat with embolization of PAVMs in the period from October 22, 1996, to December 31, 2016. The patients were enrolled and data registered prospectively in the study, and a cohort study identifying these patients was extracted from medical and radiological records and databases after termination of enrollment. There were no exclusion criteria. Mean age at first embolization was 46.5 years and median follow-up after first embolization was 38.3 months. 59% were females [27]. Numbers of PAVMs, feeding artery sizes, morphology of the PAVMs, treatment sessions, clinical data, contrast echocardiography (CE), and radiological examinations (chest X-ray, CT and pulmonary angiography) have been recorded. All patients who had a PAVM with feeding artery ≥ 3 mm or in some cases even smaller were treated and thus were included in this analysis I in the period 1996–2001, and it was performed with use of DSB (Interventional Therapeutics Corp., Fremont, CA, USA) [28] and standard coils (conventional, fibered, pushable/nondetachable, non-soft), with standard coils alone in the period 2002–2005, and vascular plugs (AVP) [29] (AGA Medical Corporation, Golden Valley, Minn., USA) and standard coils in the period 2006–2016. Special coils like detachable coils, microcoils, and hydrocoils [30] were also used in selected cases in the last years. The embolization materials were used according to availability on the market in the respective periods. The embolization materials were placed as close as possible to the PAVM sac (< 1 cm). Embolization of the sac itself was not intended but in two cases necessary because of direct arteriovenous communication with very short/nonexisting feeding arteries. The embolization procedure was considered technically successful when the embolization devices were delivered as intended with following flow-stop to the PAVM and without treatment-associated complications.

## Study Population

The population includes 136 patients with 339 PAVMs of which 114 patients (84%) had HHT [27].

*Clinical Evaluation* The clinical examination included evaluation of telangiectasia lesions, family history, and medical history regarding epistaxis, gastrointestinal bleeding, and neurological symptoms. The diagnosis of HHT was based on the clinical Curacao criteria and/or by the presence of a pathogenic variant in one of the known HHT genes [27, 31, 32].

*Contrast Echocardiography* was described with appearance of microbubbles after 6–8 heart cycles into the left atrium and graded with grade 1 being few bubbles < 10, grade 2 moderate amounts of bubbles, grade 3 large amounts of bubbles but less than on the right side, and grade 4 similar opacification of right and left ventricle [33].

*Interventional Procedure* All embolizations were performed by two experienced educational board of interventional radiology (EBIR)-certified interventional radiologists (PEA and SD) [27]. The aim was to obtain careful, tight, and optimal embolization in all cases with the optimal use of current embolization materials at any time, according to the choice of the radiologist. The endpoint of the embolizations was flow-arrest to the PAVM evaluated on the completion pulmonary angiogram.

The embolization materials were oversized about 20–25% according to the size of the feeding artery (measured based on the pulmonary DSA angiography) with following packing with smaller-sized materials. There was no absolute contraindication to embolization. Relative contraindications were high pulmonary arterial pressure, significant hepatic arteriovenous shunt and cardiac failure, pregnancy, renal insufficiency, and earlier contrast allergic reactions. The patients stayed overnight and were discharged the morning after the embolization.

The study was approved by the Danish Data Protection Agency (File no. 15/10194) according to the Danish Act on

Processing of Personal Data (Act No. 429 of 31 May 2000), and Danish Health and Medicines Authority (File no. 3-3013-974/1).

## Outcomes

### Follow-up

The follow-up plan was established individually for each patient at multidisciplinary team (MDT) conferences. All patients had a clinical examination together with CE and/or CT performed during follow-up. Follow-up was terminated: (1) when CE shunt was 0–1 and based on negative clinical findings (history, state of health, functional dyspnea/physical capacity, oxygenation) and CT evaluation, (2) if the patient refused, repetitively neglected planned visits or (3) died. Continuous follow-up: (1) if the patients were not fully grown, (2) became pregnant, (3) for control of growth of small PAVM [34], (4) for other reasons than pulmonary (e.g., nose bleedings or other arteriovenous malformations than PAVM), (5) if the CE shunt was $\geq$ 2, 6) based on positive clinical findings (history, state of health, functional dyspnea/physical capacity, oxygenation).

Follow-up included CT of the chest (Fig. 1), and further embolization was performed or planned, if indicated (Figs. 2, 3) [27]. Low-dose CT has been used during the last years, especially in young patients, in pregnant women, or in multiple controls. CT without contrast has been used during the last years following general recommendations. Controls for growth of small PAVMs were performed with CT with 2–5 years intervals, shorter intervals in non-fully grown patients.

All radiological images and medical and imaging reports have been saved for the present follow-up investigation and after cessation of patient enrollment on December 31, 2016, and all patients' files were perused. Clinically successful outcome was defined as having a CE shunt grade 0–1, CT without PAVM sac, obviation of surgical intervention for PAVM and no embolization-related complications at follow-up.

## Statistical Analysis

Quantitative data are expressed as mean ± standard deviation (SD) or mean and range, whereas qualitative data are shown as frequencies and percentages. Comparisons of



Fig. 1 41-year-old male with HHT type 2 primarily with embolization of big PAVM in right lower lobe with use of 7 standard coils with following flow-stop at pulmonary angio. CT control with contrast 9 years later demonstrated recanalization with flow through the coils; A coronal reconstruction (arrow demonstrating the coils), B (arrow demonstrating the coils), and C sagittal reconstructions (note the venous pouches closely related to the shunting area (thin arrows))
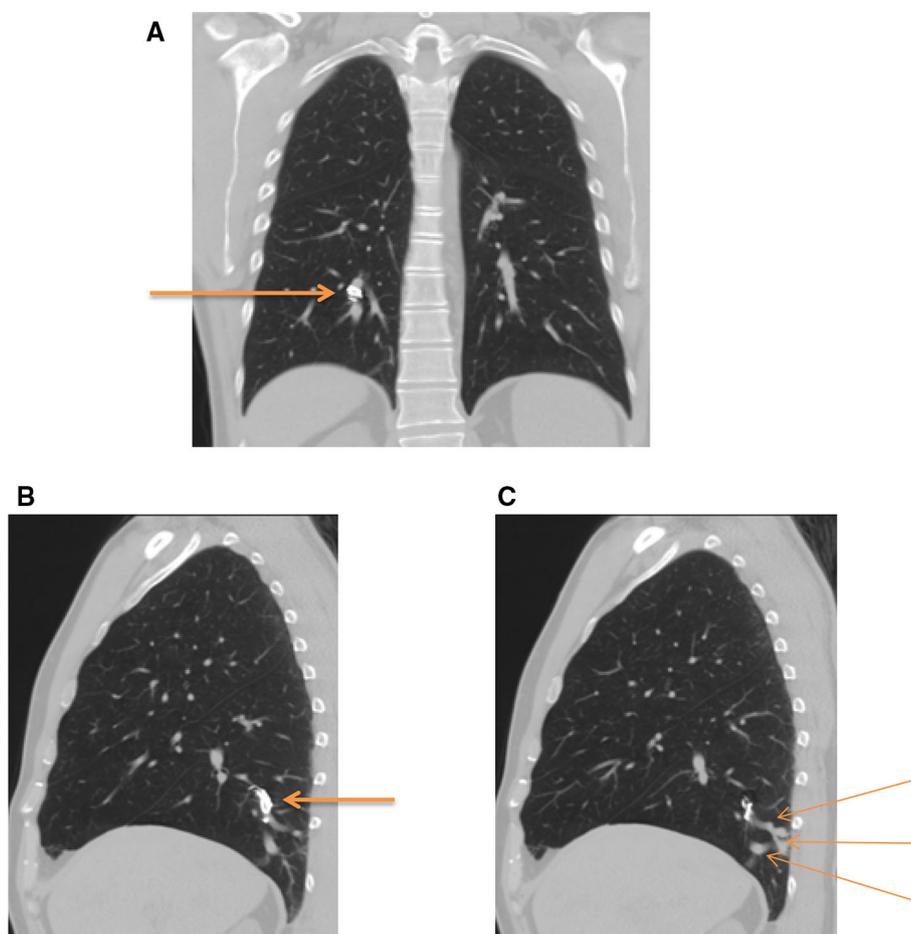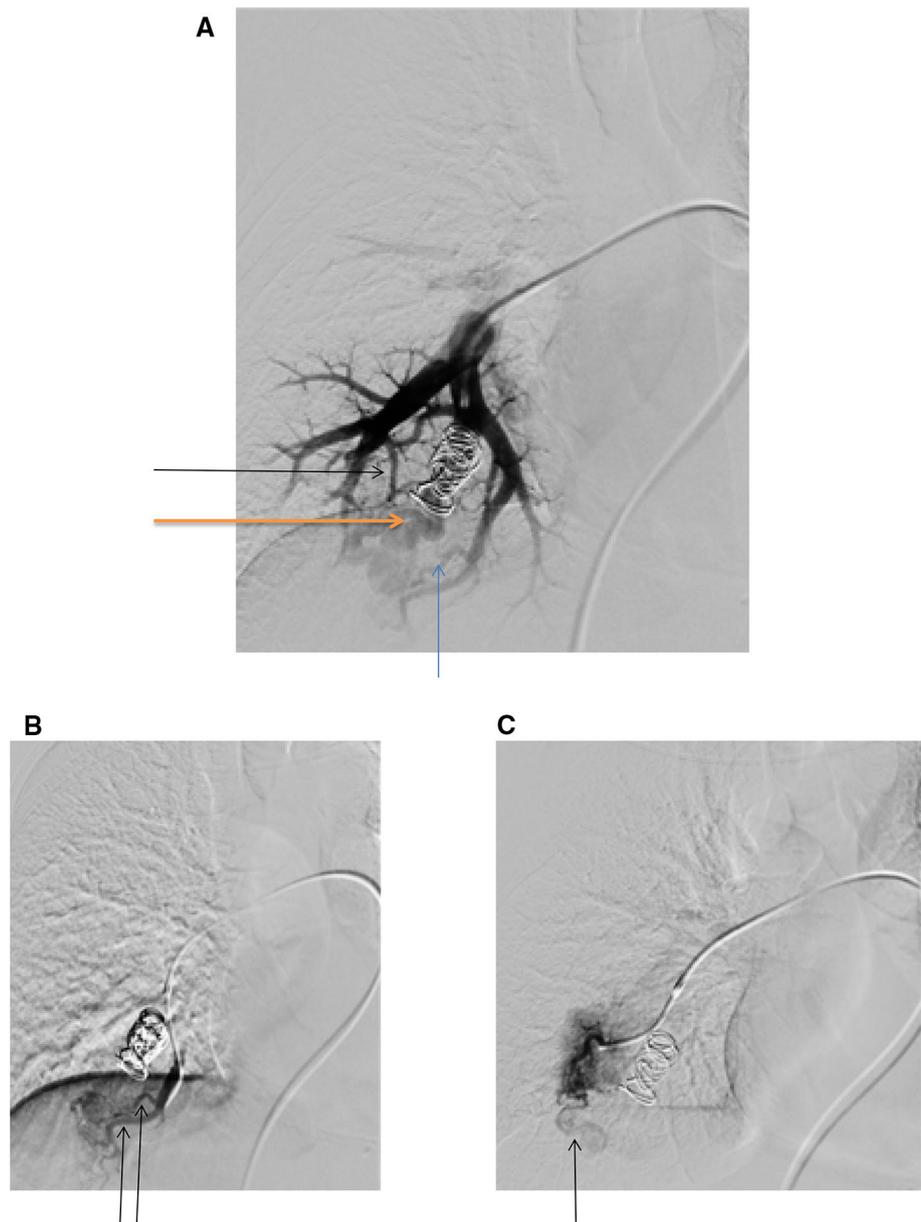
Fig. 2 **A** Same patient. Pulmonary angiography demonstrates flow distal to the earlier deployed coils through the coils (thick arrow) and further through two additional small medial (thin blue arrow) and lateral (thin black arrow) feeders to the complex PAVM. **B** Same patient. Medial feeders (two arrows) and **C** lateral feeder (arrow)



frequencies were performed using Fisher's exact test and two-sample test of proportions. All statistical tests were two-tailed, and the significance level was 5%. Stata/MP 15 (StataCorp LP, College Station, Texas 77845, USA) was used for data analysis.

## Results

Median follow-up after the first embolization and after the last embolization was 38.3 (mean 58.0 months ± 63.6, range 0.3–241) and 13 (mean 35.5 months ± 47, range 0.5–217), respectively.

Eight patients (with 13 PAVMs) stayed away, or follow-up was stopped according to the patients' wish and thus were lost to follow-up. In four patients (4 PAVMs), data were missing for follow-up. Thirty PAVMs underwent re-embolization because of residual or recurrent perfusion (19 once, 8 twice, 2 three times, and 1 four times)—in total 45 times (mean 1.48, range 1–4, SD 0.77) because of insufficient treatment with following re-embolization of the PAVM. Thus, in total, 322 PAVMs were eligible for inclusion and constituted the final cohort of patients with technically primary successful embolization. Full closure of PAVM and clinically successful outcome were considered, if CE shunt was 0–1. If the patient had more untreated PAVMs, CE would be positive in spite of the technically
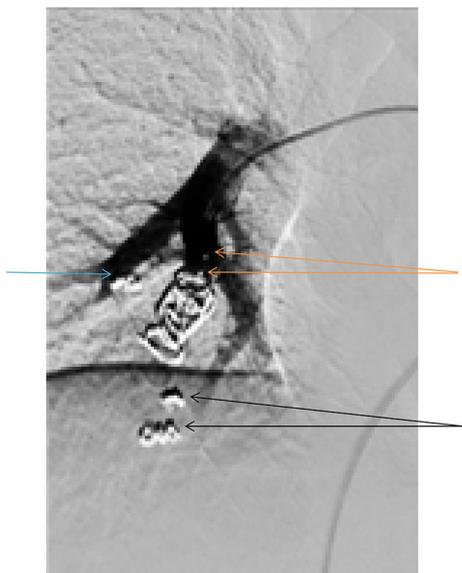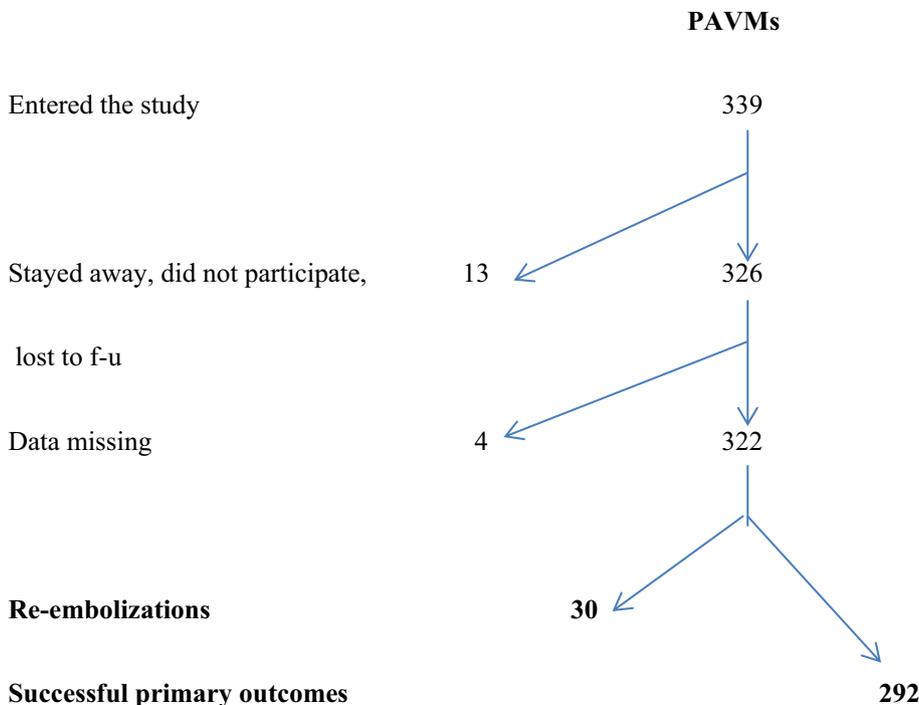
**Fig. 3** Same patient. Re-embolization with deployment of one additional AVP type 2 in the earlier coil embolized big feeding artery (two yellow arrows). Further coils in lateral feeder (blue arrow) and coils in two branches of the medial feeders (two black arrows). Embolization of the small feeders with the use of in total 5 coils. Total flow-stop to the PAVM hereafter

successful procedure, and in these cases, successful closure of the treated PAVM was considered if the PAVM sac had disappeared on CT leaving a scar or if there was no flow through the PAVM at follow-up pulmonary angiography. The 30 PAVMs that had re-embolization have been investigated further (Fig. 4).

Thirty of 322 PAVMs underwent re-embolization during the study period giving a re-embolization rate of 9.3%. None of the PAVMs treated with embolization with the use of detachable balloons alone were re-embolized, whereas 4.5% of the PAVMs treated with vascular plugs alone were re-embolized, and 11.7% treated with coils alone were re-embolized ($p = 0.074$; Table 1). Most re-embolizations were detected in complex PAVMs with more than one feeding artery compared with simple PAVMs with only one feeding artery, no matter the size of the feeding arteries and the embolization materials used (21.6% vs. 5.7%, $p < 0.001$). Further, re-embolization was more common in bigger sized feeding arteries, no matter the PAVM morphology and the embolization materials used ($p = 0.002$; Table 2). Standard coils have been used in the whole study period. In the period 1996–2001 when also DSB were used, 1 of 39 (2.6%) embolization sessions were re-embolization, in the period 2002–2005 where only standard coils were used, 14 of 40 (35.0%) sessions were re-embolization, and in the period 2006–2016 after introduction of AVP (and in the last part of the investigation period also special coils), 26 of 150 (17.3%) embolization sessions were re-embolization ($p = 0.001$). None of the patients that were re-embolized had had cerebral complications, and all were re-embolized following clinical (including CE) and CT controls. There were no patients with continuous hemoptysis after re-embolization.

Most of the re-embolized PAVMs (76.7%) had a successful clinical outcome, while the remaining were in continuous control (Table 3). No increased procedural risk

**Fig. 4** Flow diagram showing re-embolizations and successful primary outcomes



**PAVMs**

Entered the study               339

Stayed away, did not participate,    13       326

lost to f-u

Data missing                  4       322

**Re-embolizations**                **30**

**Successful primary outcomes**          **292**

**Table 1** Re-embolization related to occlusion materials and PAVM morphology

|  | Technically successful embolizations | Re-embolization × 1 | Re-embolization > 1 | Total number of re-embolizations (%) |
|---|---|---|---|---|
| Balloons—simple PAVMs | 9 | 0 | 0 | 0/9 (0%) |
| Balloons—complex PAVMs | 4 | 0 | 0 | 0/4 (0%) |
| Balloons total | 13 | 0 | 0 | 0/13 (**0**%) |
| Plugs—simple PAVMs | 67 | 0 | 0 | 0/67 (0%) |
| Plugs—complex PAVMs | 18 | 4 | 0 | 4/22 (18.2%) |
| Plugs total | 85 | 4 | 0 | 4/89 (**4.5%**) |
| Coils—simple PAVMs | 154 | 13 | 1 | 14/168 (8.3%) |
| Coils—complex PAVMs | 34 | 3 | 8 | 11/45 (24.4%) |
| Coils total | 188 | 16 | 9 | 25/213 (**11.7%**) |
| Plugs and coils—simple PAVMs | 4 | 0 | 0 | 0/4 (0%) |
| Plugs and coils—complex PAVMs | 2 | 0 | 1 | 1/3 (33.3%) |
| Plugs and coils total | 6 | 0 | 1 | 1/7 (14.3%) |
| Simple total | 234 | 13 | 1 | 14/248 (**5.7%**) |
| Complex total | 58 | 7 | 9 | 16/74 (**21.6%**) |
| Total | 292 | 20 | 10 | 30/322 (9.3%) |

**Table 2** Re-embolization related to size of PAVM feeders

|  | Technically successful embolizations | Re-embolization x 1 | Re-embolization > 1 | Total number of re-embolizations (%) |
|---|---|---|---|---|
| Feeders 2–3 mm | 83 | 1 | 0 | 1/84 (1.2%) |
| Feeders 4–5 mm | 113 | 9 | 4 | 13/126 (10.3%) |
| Feeders 6–9 mm | 80 | 8 | 3 | 11/91 (12.1%) |
| Feeders > 9 mm | 16 | 2 | 3 | 5/21 (23.8%) |
| Total | **292** | 20 | 10 | **30/322 (9.3%)** |

**Table 3** Re-embolization outcomes

|  | CE 0–1 (%) | CE > 1 (%) | Total |
|---|---|---|---|
| Complex—plugs | 4 (100%) | 0 (0%) | 4 (13.3%) |
| Simple—coils | 10 (71.4%) | 4 (28.6%) | 14 (46.7%) |
| Complex—coils | 9 (81.8%) | 2 (18.2%) | 11 (36.7%) |
| Complex—plugs and coils | 0 (0%) | 1 (100%) | 1 (3.3%) |
| Total simple | 10 (71.4%) | 4 (28.6%) | 14 (46.7%) |
| Total complex | 13 (81.3%) | 3 (18.7%) | 16 (53.3%) |
| Feeders < 5 mm | 11 (78.6%) | 3 (21.4%) | 14 (46.7%) |
| Feeders 6–9 mm | 8 (72.7%) | 3 (27.3%) | 11 (36.7%) |
| Feeders > 9 mm | 4 (80.0%) | 1 (20.0%) | 5 (16.7%) |
| Total | **23** (76.7%) | **7** (23.3%) | **30 (100%)** |

has been encountered during re-embolization compared with primary embolizations. There was no statistically significant difference in the re-embolization endpoints between clinically successful and unsuccessful outcome, i.e., between complex–plugs, simple–coils, complex–coils, and complex–plugs and coils, between simple and complex PAVMs or between the sizes of the feeders, although there is a tendency of better clinical outcome if the feeders are smaller. The number of patients in the groups are, however, rather small.

## Discussion

Stated re-embolization rate of 10% or more justifies the need for more investigations regarding the optimal embolization methods and use of materials. Most of the demographic and epidemiological data published so far are based on rather small cohorts, short follow-up, and incomplete data because PAVM is a rare disease with an incidence of about 2–3/1,00,000 [27, 35]. There are no randomized human studies comparing the outcomes after use of different embolization materials.

In the present study, 136 patients with 339 PAVMs have been detected by scouring patients from a 20-year period. The data are very precise and complete with few dropouts. The follow-up was long because the patients also were followed in the HHT center for other reasons than PAVM. All procedures were performed by the same two and very experienced interventional radiologists. The outcomes after use of DSB, coils, and AVP have been compared from a historical point of view. From these results, DSB came out to be a very good embolization material with few re-canalizations. Further, AVP seems to be superior to coils alone.

Re-canalization after embolization of PAVM has been described for decennia. Coils have, over time, been the most used device for PAVM embolization but have also been shown to be associated with rather frequent re-canalizations. The reasons have been explained to be insufficient coil packing, no embolization of supplementary supplying arteries in complex PAVM, embolization too far from the PAVM, or additional systemic supply to PAVM. DSB has been withdrawn from the market for about 10 years after having been in use for PAVM embolization for about 10 years. These balloons gave an optimal and lasting embolization [28].

AVP is probably nowadays the best available embolization material [21–25]. They are designed for optimal cross-sectional occlusion and are detachable with rapid, precise, and controlled deployment. Re-canalization after deployment of AVPs has been reported to be of 0–7% [24, 36–38] which seems lower than after coil embolization alone and vascular plugs are now also available in micro sizes [39, 40] but have not been on the market during the present study period.

Newer special coil types like detachable coils and hydrocoils may also be useful in preventing re-canalization [30]. These coil types were used in the last part of the treatment period in the present study and may also have influenced positively on the outcomes in that period.

We have demonstrated that re-canalization is correlated with size of feeding arteries to the PAVM and complexity of PAVM (complex more than simple).

The clinical outcome even after re-embolization was good with 77% ending up with a successful clinical outcome, but it is optimal for the patients and from an economic point of view to reduce the number of re-interventions as much as possible. This aim can be achieved by detecting and occluding all feeders to the PAVMs and by careful and tight cross-sectional packing of the supplying vessels. Further, choice of the best embolization material in each case is important. There is increasing evidence that AVP might be a better device for embolization of PAVMs than standard coils alone.

## Limitations

The patients were enrolled prospectively in the study with continuous systematic collection of data during the entire study period, but the study did not have a prospectively randomized design, and the data were analyzed retrospectively.

## Conclusion

In accordance with the literature, our data support that the standard coils probably should not be the first choice for embolization of PAVMs, especially not in big-sized feeding arteries and in complex PAVMs. If anatomically accessible, there is increasing evidence that AVP alone or in combination with coils seems to be the best primary option for embolization. The clinical outcome after embolization and re-embolization is good.

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