Embolotherapy of Pulmonary Arteriovenous Malformations: Long-term Results in 112 Patients

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PURPOSE: To evaluate the long-term results of embolotherapy of pulmonary arteriovenous malformations (PAVMs) in a large group of patients.

MATERIALS AND METHODS: Between July 1988 and August 2001, 134 consecutive patients underwent embolotherapy of PAVMs with feeding arteries larger than 3 mm or that had previously caused bleeding or systemic complications. The mean follow-up was 62.2 months. The primary endpoints of the study were the efficacy of embolotherapy, decrease in right-to-left shunt, and increase in partial arterial oxygen pressure (PaO_2); the secondary endpoint was the prevalence of complications. Standard follow-up consisted of yearly history, chest radiography, and arterial blood gas measurement.

RESULTS: Follow-up was available in 112 patients. Initially, 296 PAVMs were embolized in these patients. Nineteen patients (17%) underwent a second procedure and four patients underwent a third procedure because of recanalization of originally occluded feeding arteries (25 PAVMs, 8%) or interval enlargement of untreated PAVMs (53 PAVMs). In total, 349 PAVMs were embolized in 157 sessions. The mean diameter of occluded vessels was 4.7 mm. The long-term outcomes of embolotherapy were successful in 83% of patients overall and in 96% of patients in whom all angiographically visible PAVMs were embolized. Recanalization occurred in 12 of 16 patients who underwent repeat treatment because of enlargement of nonembolized PAVMs. Postprocedural pleurisy occurred after 14 of 157 sessions (9%). Periprocedural complications occurred in 12 sessions (8%) and included migration of an embolic device, transient ischemic attack (TIA), angina pectoris, and early cerebral infarction after embolization. Three patients experienced TIA and two patients experienced a cerebral abscess during follow-up after embolotherapy.

CONCLUSIONS: Embolotherapy of PAVMs is efficacious and durable in the majority of patients. Patients should remain under regular review because recanalization of PAVMs or enlargement of untreated PAVMs can occur years after treatment.

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Abbreviations: HHT = hereditary hemorrhagic telangiectasia, PaO_2 = partial arterial oxygen pressure, PAVM = pulmonary arteriovenous malformation, TIA = transient ischemic attack

PULMONARY arteriovenous malformations (PAVMs) are direct connections between the pulmonary artery and vein through a thin-walled aneurysmal sac. They result in a right-to-left shunt, often leading to hypoxemia. This anatomic right-to-left shunt, which allows emboli and bacteria to bypass the pulmonary capillary bed, can cause serious neurologic complications such as stroke or cerebral abscess. In addition, hemoptysis or hemothorax can occur (1–3). Because of these serious complications, treatment of PAVMs is indicated, even in asymptomatic patients, when the diameter of the feeding artery of the PAVM is 3 mm or larger (4,5).

Transcatheter embolization of the feeding arteries of the PAVMs (embolotherapy) with silicone balloons or stainless-steel coils is generally accepted as the therapy of choice (1–3). The first report of successful embolotherapy of a PAVM dates from 1977 (6). Until 1977, surgery was the only method of treatment, and as late as 1993, Puskas and colleagues (7) contended that surgical resection or ligation of PAVMs provides effective treatment. The disadvantages of surgical treatment are the morbidity associated with a thoracotomy, the possible loss of normal pulmonary parenchyma surrounding the PAVM, and the longer hospital stay. The technical details and efficacy of embolotherapy have been described in several reports (4,8–13). Lee and colleagues (14) showed that even large PAVMs can be embolized effectively in the majority of patients.

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Patient and PAVM Characteristics (N = 112)

Characteristic	Value
Sex (M/F)	44/68
Age (years)	
Mean	45
Range	7–85
Hypoxemia	98%*
Hemoptysis	1%†
Hemothorax	3%
Systemic abscesses	8%
TIA/stroke	14%
Cerebral AVM	11%‡
Hepatic AVM	4%§
Right-to-left shunt before (first) treatment	18.5% (±8.6%)‖
Right-to-left shunt after (first) treatment	7.3% (±4.2%)‖

Note.—TIA = transient ischemic attack.
* (PaO_2 < (104 − [0.24 × age])/7.6 kPa(17)
† n = 1.
‡ Screening with intravenous digital subtraction angiography, or MR imaging.
§ Screening with ultrasound, or CT.
‖ n = 98.

More recently, Faughnan and colleagues (15) showed that embolotherapy of the larger PAVMs in patients with diffuse PAVMs may reduce the risk of neurologic complications. However, data on long-term results in large groups are limited. In this study, we evaluated the long-term results of embolotherapy in 112 patients.

MATERIALS AND METHODS

The study was performed after approval of the medical review board of our hospital.

Patients

Between July 1988 and August 2001, 134 consecutive patients were treated with embolization for PAVMs. One hundred twelve patients remained under regular review in our hospital and were included in the study, with follow-up until May 2002. The short-term outcomes of 31 of these patients have been reported previously (12). One hundred eight patients had definite hereditary hemorrhagic telangiectasia (HHT) according to the Curaçao criteria (16). Seven patients had undergone resection for PAVMs before embolotherapy and were treated for new or enlarging PAVMs. Signs and symptoms caused by the PAVMs are listed in the **Table**. Thirty-eight of the patients were asymptomatic and were found in a screening program involving family members of patients with HHT. However, 36 of these patients had mild hypoxemia. Before and after embolization, chest radiography and arterial blood gas measurements were performed. In adult patients with hypoxemia (partial arterial oxygen pressure), (PaO_2 < [104 − 0.24 × age in years] / 7.6 kPa) (17), the right-to-left shunt was measured with the 100% oxygen method, as described previously (18), before and after embolization. A right-to-left shunt of less than 5% was considered normal.

Technique

All patients first underwent complete diagnostic pulmonary angiography with separate right and left contrast material injections before embolotherapy. Two radiologists performed embolization during the study period, but most procedures were performed by one radiologist (T.T.C.O.). After selective catheterization, the feeding vessels of the PAVMs were embolized as close to the sac of the PAVM as possible with coils of appropriate size. Coils were placed until flow through the PAVM ceased. In cases of high-flow PAVMs, a catheter with an occlusion balloon was used to interrupt blood flow in the feeding artery to prevent migration of the coils. In four PAVMs, large coils were placed in the sac because the feeding arteries were too short to embolize. In one patient, a detachable balloon was used in combination with coils because of a very large feeding artery. All PAVMs with feeding arteries larger than 3 mm at the site of coil placement were embolized, and, in case of hemorrhage or neurologic and septic complications, smaller PAVMs were also embolized. The true diameter of the artery at the site of coil placement was determined according to the diameter of the selective catheter as a reference for magnification corrections. PAVMs with blood supply from two or more segmental arteries were defined as complex PAVMs.

During our 14-year experience with embolotherapy, the types of coils have evolved. First, only stainless-steel coils were used; subsequently, platinum coils became available in polyester fibered and nonfibered variants. The polyester fiber promotes immediate thrombosis. During the past 8 years, push coils (which are pushed through the catheter) and detachable coils have been used. The detachable coils are detached from the push wire when they are placed in the artery.

An "underwater technique" was used for exchange of wires to prevent air from going through the PAVM during the procedure. Patients remained in the hospital overnight after the procedure. The next day, arterial blood gas measurements and chest radiographs were obtained. Patients with multiple PAVMs in both lungs were sometimes treated in two or even three sessions, depending on the patient's tolerance and the amount of contrast material used.

Self-limiting pleurisy and migration of a coil within the pulmonary artery were considered minor complications. Other complications such as migration of an embolic device into the systemic circulation, cerebral ischemia, and angina pectoris were considered major complications.

Follow-up

The clinical follow-up consisted of history, chest radiography, and measurement of arterial blood gases at least every year after embolotherapy. When the PaO_2 decreased consistently and by more than 10% versus the value directly after embolization and/or a

chest radiograph suggested recanalization of embolized PAVMs or enlargement of nonembolized PAVMs, the right-to-left shunt was measured. An increasing shunt fraction (>3%) led to more precise studies such as intravenous digital subtraction angiography of the pulmonary arteries or computed tomography (CT) without contrast media. When recanalization or enlargement of nonembolized PAVMs was suspected, pulmonary angiography and embolotherapy were performed.

Data Analysis

The patient outcome was tracked to the most recent follow-up examination. The paired Student *t* test was used to analyze differences in pre- and posttreatment PaO_2 values and right-to-left shunt. Kaplan-Meier curves and the log-rank test were used to evaluate the possible differences in outcome between patients with solitary PAVMs and multiple PAVMs, patients with and without residual small PAVMs after treatment, and patients with and without complex PAVMs.

RESULTS

Overall Results

The study group consisted of 112 patients, 44 men and 68 women, with a mean age of 44.9 years (range, 7–85 years). The mean follow-up was 62.2 months (range, 9–145 months). Initially, 296 PAVMs were embolized in one or two sessions in 110 patients and in three sessions in two patients. Nineteen patients underwent a second treatment and four underwent a third. In total, 349 PAVMs were embolized in 157 sessions.

The mean value of right-to-left shunts decreased from 18.5% (SD, 8.6%) to 7.3% (SD, 4.2%) after the first embolotherapy. This difference was significant (*t* test, $P < .001$). Only three patients had a right-to-left shunt of less than 5% before the first embolotherapy. The mean PaO_2 increased significantly from 9.4 kPa ± 1.7 to 11.8 kPa ± 0.9 ($P < .001$).

PAVMs were solitary in 37 patients and multiple in 75 patients. They were mostly located in the lower lobes: 146 in the right and 124 in the left. Twenty-eight PAVMs (8%) were classified as complex and 321 were classified as simple. The mean diameter of the occluded feeding arteries at the site of embolization was 4.7 mm ± 1.7 (range, 1.8–12.4 mm). Twenty-seven arteries were 8 mm or larger in diameter.

During follow-up after embolotherapy, three patients experienced TIAs and two patients experienced cerebral abscess. One of these patients underwent three embolotherapy procedures because of diffuse PAVMs in both lungs before the cerebral abscess developed. Before the first embolotherapy procedure, the patient experienced knee and kidney abscesses. During the second and third procedures, enlargement of nonembolized PAVMs was seen, but there was no recanalization of previously treated PAVMs. After treatment of the brain abscess, no evidence of recanalization or enlargement of nonembolized PAVMs was found. The other patient with a cerebral abscess previously underwent resection and later embolotherapy of two PAVMs, and two small peripheral PAVMs were left untreated. After the cerebral abscess, angiography did not show recanalization or enlargement of the small nonembolized PAVMs. One of the patients who experienced a TIA during follow-up showed minimal recanalization of one of four previously treated PAVMs and slight enlargement of four untreated small PAVMs, which were occluded during the second procedure. A second patient with a TIA after the first embolization also showed slight enlargement of three untreated PAVMs, but no recanalization. The third patient with a TIA previously underwent embolotherapy of a large PAVM, with no visible PAVMs left untreated. The right-to-left shunt was 5.2%, which was unchanged from the measurement immediately after embolotherapy. Repeat angiography showed no signs of recanalization or residual PAVMs. The source of the TIA remained unknown but may have been microscopic PAVMs.

Recanalization

Repeat treatment was indicated in 19 patients (17%), seven men and 12 women, because of recanalization of 25 of 296 previously embolized PAVMs (8%) and enlargement of 53 untreated PAVMs (20 in men and 33 in women). Recanalization occurred in 15 patients (13%), enlargement occurred in 16 patients, and both were present in 12 patients (11%), two of whom were pregnant. New PAVMs did not develop during follow-up. Three of the four patients who were treated three times showed enlargement of untreated PAVMs and (minimal) recanalization of previously embolized PAVMs after the second and third procedures. The fourth patient showed enlargement of untreated PAVMs without recanalization of previously embolized PAVMs after the second and third procedures.

Only three of the 37 patients (8%) with a solitary PAVM had recanalization, whereas 12 of 75 patients (16%) with multiple PAVMs underwent another embolization because of recanalization. However, this difference was not significant ($P = .198$). The four patients without definite HHT had solitary PAVMs and did not show recanalization after embolotherapy. Recanalization occurred in 19 of 231 PAVMs (8%) in the lower lobes and in six of 65 PAVMs (9%) in the remaining lobes ($P = .482$). The rate of recanalization was higher in complex PAVMs (three of 28, 11%) than in simple PAVMs (22 of 268, 8%), but the difference was not significant ($P = .429$). Recanalization occurred in two of 27 PAVMs (7%) with a feeding artery 8 mm or larger and in 23 of 269 PAVMs (9%) with a feeding artery smaller than 8 mm in diameter ($P = .596$). The aneurysmal sac of the PAVM did not disappear on the chest radiographs of five patients; four of them were treated for recanalization. In two of these patients, the angiogram showed appearance of an accessory vessel to the PAVM. It was a third feeding artery to the PAVM in one case and a second feeding artery to the PAVM in the other case. Accessory growth of a feeding vessel has been described before (14), but it is also possible that the vessels were missed in the first procedure. In nine patients, the embolized PAVMs disappeared very slowly but were reduced to fibrous scars on the chest radiographs within 1 year.

Between 1988 and 1996, 43 patients underwent embolotherapy for PAVMs and nine of them (21%) developed recanalization, with a mean duration until the second embolization procedure of 41 months. Between 1997 and 2001,

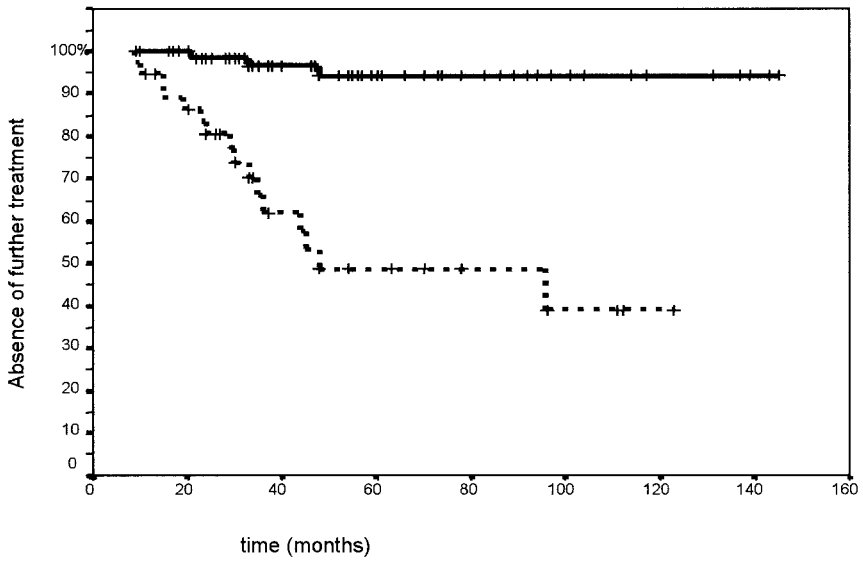


Figure 1. Kaplan-Meier curves of long-term results of embolotherapy in patients who underwent embolization of all angiographically visible PAVMs (solid line) and patients with PAVMs left untreated (dotted line).

79 patients underwent embolotherapy and six of them (8%) developed recanalization, with a mean duration until the second embolization procedure of 23 months. The difference was not significant (log-rank test, $P = .64$).

Enlargement

Visible PAVMs were left untreated in the first procedure in 38 patients (34%) because they were too small and there had been no septic or hemorrhagic complications. In 16 of these 38 patients (42%), embolotherapy was repeated because of increasing right-to-left shunt (and neurologic complications in two patients). All visible PAVMs were treated in 74 patients. Only three of them (4%) required repeat treatment (**Fig 1**). The difference between the rate of repeat treatment in patients with all visible PAVMs embolized and the rate of repeat treatment in patients with some PAVMs left untreated was significant ($P < .001$). Seven patients with untreated PAVMs had many PAVMs, and five of these patients showed enlargement of untreated PAVMs (**Fig 2**). The mean right-to-left shunt fractions before first treatment were 22.3% ± 8.3% in the 38 patients with residual PAVMs after treatment and 15.7% ± 8.0% in the patients with all PAVMs treated (*t* test, $P < .001$). The mean shunt fraction in the patients with all PAVMs treated was still 6.2% ± 3.5% after embolotherapy.

Complications

Minor complications occurred in 17 patients (15%), or in 17 of 157 procedures (11%). Self-limited pleurisy occurred in 14 patients (13%) after 14 procedures (9%), and migration of a coil within the pulmonary circulation occurred in three patients (3%). Self-limiting pleurisy occurred within the first 48 hours after embolotherapy, lasted 2–8 days, and was sometimes accompanied by fever. One patient developed an infiltrate visible on the chest radiograph. The pleurisy and infiltrate most likely resulted from localized pulmonary infarction caused by occlusion of normal branches of the pulmonary artery. Dislocation of coils within the pulmonary circulation occurred in three patients. In one patient with a large, centrally located PAVM in the right lung, a dislocated coil had to be retrieved from the left pulmonary artery. In the other two patients, coils migrated to the aneurysmal sac. In each of these two patients, the coil was left in the aneurysmal sac and no complications occurred after embolization of the feeding artery.

Major complications occurred in nine patients (8%), or nine of 157 procedures (6%). Migration of an embolic device into the systemic circulation occurred in two patients treated at the beginning of our experience. In one patient with large pulmonary and hepatic arteriovenous malformations, a coil was retrieved from the left ventricle and a deflated balloon migrated to one of the hepatic arteriovenous malformations. Subsequently, the patient was found to have developed pulmonary hypertension caused by occlusion of the PAVMs in the presence of a left-to-right shunt resulting from the hepatic arteriovenous malformations. This case has been reported (19). In a second patient, a coil was retrieved from the left ventricle, without further complications. Three patients experienced cerebral ischemia during the procedure: two patients experienced TIAs, and the symptoms resolved slowly during a period of weeks in the other patient. An early cerebral infarction 1 week after embolization of a complex PAVM occurred in a 10-year-old girl, probably because there was also a feeder from the bronchial artery (20). One patient developed bradycardia and angina pectoris during embolization. She was treated with oxygen administration and atropine. She recovered quickly, and the procedure was completed. Another patient developed thrombosis of the femoral vein used for catheterization; the treatment did not cause complications, and the patient was found to have deficiencies of proteins C and S.

Finally, in one patient, a coil could not be detached mechanically from the push wire after placement in the pulmonary artery. Because the coil and wire could not be retrieved, the PAVM was resected and the push wire was removed. In a second session, the remaining PAVMs were embolized without complications. There were no fatal complications.

DISCUSSION

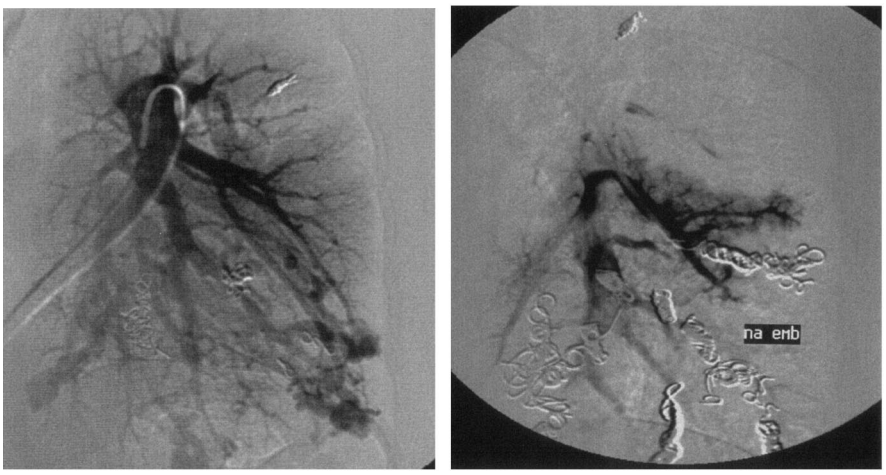
The goals of treatment of PAVMs are prevention of hemorrhage, improvement of hypoxemia, and, most importantly, prevention of the complications that are associated with the local absence of the pulmonary capillary filter. It is estimated that 24% of patients with PAVMs experience TIA or

stroke and 9% experience cerebral abscess on presentation of PAVMs (1). In 76 consecutive patients, White and colleagues (5) reported TIAs in 37%, strokes in 18%, and cerebral abscesses in 9% before embolotherapy. Eight percent of our patients experienced a systemic abscess before embolotherapy: paradoxic septic emboli resulted in cerebral abscesses in eight patients and in abscesses in the knee and kidney in one patient. The rate of documented previous stroke or TIA was relatively low at 14%. However, this may be an underestimation because we did not perform routine CT scanning or magnetic resonance imaging of the brain in our patients. The fact that 38 of our 112 patients with PAVMs had no obvious symptoms and were identified by family screening may also have attributed to the relatively low rate of previous ischemic events.

During follow-up after embolotherapy, three patients experienced TIAs and two experienced cerebral abscess. Although it is well known that PAVMs with large feeding vessels are associated with a high risk of neurologic complications, these cases show that smaller vessels also pose a risk. Vessels smaller than 1 mm in diameter can be large enough for (septic) emboli to enter the systemic circulation. The mean right-to-left shunt in 74 patients who had no angiographically visible PAVMs after treatment was still 6.2%, indicating the presence of microvascular PAVMs. In these patients and in the patients with residual PAVMs after treatment, the extent of the right-to-left shunts likely reflects the risk of systemic sequelae. We recommend antibiotic prophylaxis before dental and nonsterile surgical procedures to all patients with treated or untreated PAVMs.

The long-term outcomes of the first embolotherapy procedures were successful in 93 of 112 patients (83%). Recanalization of originally occluded feeding arteries occurred in 15 of 112 patients (13%), or 25 of 296 PAVMs (8%). The rate of recanalization in our patients corresponds to the results of others (9,13,14), but is higher than the rate of 3% reported by Pollak and colleagues (10) and the rate of 6% we found previously in 31 of the patients reported herein (12). The relatively long follow-up of our series (62 months) compared with these reports (3–19 months [10] and 2–17 months [12]) probably explains the somewhat higher rate of recanalization. The mean duration until the second embolotherapy procedure for recanalization was 34 months. It was longer than 3 years in seven of 15 patients, including an interval of 8 years in one patient. The rate of recanalization is not explained by the use of coils instead of balloons. Balloons are primarily used in large feeding arteries, and our results with coils are the same for arteries with diameters of 8 mm or more and those with diameters smaller than 8 mm. Moreover, the rate of recanalization in large arteries in our series corresponds to the experience of Lee and colleagues (14), who used both balloons and coils. Known causes of recanalization, such as increased pulmonary venous pressure, were not present in our population. Interim pregnancy occurred only in two patients who were treated for recanalization. The recanalization rate in patients treated before 1997 was 21%, versus 8% in patients treated from 1997 to 2001. However, these data do not represent the effect of increasing experience, because the difference in recanalization rate was not significant (log-rank test) and was probably caused by the fact that the follow-up of the first group was much longer.

In our series, the causes of recanalization did not appear to be related to the angioarchitecture or the site of the PAVM. However, the patients with single PAVMs in the setting of HHT tended to have less recanalization than patients with multiple PAVMs, and the outcomes in patients with all visible PAVMs embolized was much better than the outcomes in patients with residual PAVMs after the first treatment ($P < .001$). The patients with residual PAVMs had more severe pulmonary disease than the patients with complete embolization, as shown by the difference in shunt fractions before treatment. More severe pulmonary disease might be a reflection of more severe underlying HHT. The results of a recent study in mice strongly suggest that genetic factors other than the mutation of the endoglin gene alone influence the phenotype (21). Enlargement of remaining PAVMs may therefore be related to the severity of underlying disease. More severe HHT might also explain why recanalization occurred in 12 of the 16 patients with enlargement of remaining PAVMs. Our results indicate that regular follow-up after embolotherapy is necessary. In our experience, the combination of yearly history, chest radiography, and arterial blood gas measurement normally provided sufficient information for follow-up after embolotherapy. However, in recent years, we have also used unenhanced CT, which improves the evaluation of the effect of embolization because it is a sensitive method to document persistence of a PAVM after therapy. CT



a. b.

Figure 2. **(a)** Angiogram showing growth of previously untreated PAVMs 3 years after first embolotherapy. **(b)** Results after second embolotherapy procedure.

can also be useful as a noninvasive technique to detect the presence of small PAVMs and is recognized as a valuable tool in screening procedures for PAVMs, evaluation of the effect of embolization, and follow-up (22,23).

Complications other than pleurisy occurred in 12 of 112 patients (11%), or in 12 of 157 sessions of embolotherapy (8%). In five patients, the complications consisted of migration of an embolic device. When two migrations of embolic devices into the systemic circulation had occurred during the procedure, occlusion balloons were used in high-flow feeding arteries. Thereafter, only three minor migrations occurred, without consequences for the patients. The most serious complication was the early cerebral infarction after embolotherapy described earlier. Perfusion of a previously occluded PAVM by an enlarged bronchial artery is rare, but has also been described by Sagara and colleagues (24). However, we do not think routine bronchial arteriography is necessary after complete embolization of PAVMs. In our opinion, spiral CT, as described by Remy and colleagues (22), may be helpful to evaluate the cause of persistence of an embolized PAVM.

In summary, our long-term follow-up study in a large group of patients with PAVMs confirms that embolotherapy is relatively safe and efficacious. In addition, embolotherapy is durable in the majority of patients. Our study shows successful long-term outcomes in 83% of all patients and in 96% of patients in whom all angiographically visible PAVMs were treated. The procedure can be easily repeated when recanalization or enlargement of untreated PAVMs occurs. In our series, enlargement of untreated PAVMs is often associated with recanalization of one or more previously embolized PAVMs, which may be an expression of more severe HHT. Antibiotic prophylaxis before dental and surgical procedures should still be recommended after treatment of PAVMs to minimize the risk of systemic abscesses. It is important that patients remain under regular review after treatment of PAVMs because recanalization of originally occluded feeding arteries or enlargement of untreated PAVMs can occur years after embolotherapy.

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