Does the type and size of Amplatzer vascular plug affect the occlusion time of pulmonary arteriovenous malformations?

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PURPOSE
Occlusion time (OT) is an important factor in the treatment of pulmonary arteriovenous malformations (PAVMs) since it can lead to serious complications. The purpose of our study is to calculate the OT of Amplatzer vascular plug (AVP, St Jude Medical), and correlate it to the type of the device used (AVP or AVP 2) and the percent of device oversizing. Technical success rates and complications were also recorded.

METHODS
We retrospectively studied a total of 19 patients with 47 PAVMs who received percutaneous transcatheter embolization therapy using either AVP or AVP 2. We recorded the location, type, feeding artery diameter, AVP device used, and OT of each PAVM. We correlated the percent of device oversizing and the type of AVP with the OT. We also studied the rate of persistence of PAVM for both devices.

RESULTS
Forty-six (98%) of the PAVMs were simple. Device diameters ranged from 4.0–16.0 mm with device oversizing ranging between 14% and 120%. There was a statistically significant difference in the OT of AVP and AVP 2 (3 min 54 s vs. 5 min 30 s, P = 0.030). There was a weak positive correlation between OT and device oversizing for AVP (r=0.246, P = 0.324) and AVP 2 (r=0.261, P = 0.240). No major complications were identified. Immediate technical success rate was 100%.

CONCLUSION
The use of AVP 2, and increase in device oversizing were not associated with reduction in the OT of PAVMs. There was no reported difference in safety between the two devices, and no major complications were noted.

Pulmonary arteriovenous malformations (PAVMs) are abnormal direct fistulous communications between a pulmonary artery and a pulmonary vein, which may be present alone or in association with other vascular anomalies as in hereditary hemorrhagic telangiectasia (1, 2). As a result of this abnormal communication, a right to left shunt can develop and may lead to serious neurologic complications due to paradoxical embolization (2, 3).

Introduced in 1977, transcatheter embolization is now the first line of management for PAVMs (4). Coils and amplatzer vascular plugs (AVP or AVP 2, St. Jude Medical) are the current endovascular approaches available. The occlusion time (OT) of an embolic device, which is defined as the time between the deployment of the device until complete occlusion of the artery, is of paramount importance, particularly in right-to-left shunt lesions such as PAVMs. The reason is that the thrombus formed on the surface of these embolic devices after deployment can migrate with the blood flow through the PAVM into the systemic circulation resulting in devastating complications related to paradoxical embolization (2, 5, 6).

The OT of AVP devices in the treatment of PAVMs has been previously studied and the results documented its safety with an acceptable OT of 2–3 min without higher risk of systemic paradoxical embolization (8). Compared with the AVP device, the AVP 2 has a finer, more densely woven nitinol frame and a multisegmented design, which allows for increased length-wise expansion (9). Theoretically, this design should decrease the OT and have greater efficacy (10).

The purpose of our study is to calculate the OT of AVP and AVP 2 used in treatment of PAVMs and correlate it to the type of the device used and the percent of device oversizing. Immediate technical success rates, persistence rates, and complications were also recorded for both devices.
Methods

Patients

Approval from our institutional review board was obtained. We retrospectively reviewed the medical records of 19 patients who had 47 PAVMs and underwent endovascular management using AVP and AVP 2 between September 2009 and September 2015. There were 13 females and six males. The average age of the patients was 45 years (range, 23–63 years). The clinical presentations and comorbid conditions are shown in the Table. Fourteen patients (74%) had self-reported dyspnea prior to the procedure. Six patients (32%) had a history of a cerebrovascular accident or transient ischemic attack due to paradoxical embolization. One patient presented with a left-sided hemothorax from a presumed ruptured PAVM sac. Another patient carried a diagnosis of Charcot Marie Tooth syndrome with advanced disease progression and severe neurologic involvement at the time of embolization. Although none of the patients underwent genetic testing, six patients (32%) had suspected hereditary hemorrhagic telangiectasia (HHT) based on Curacao criteria including clinical presentation and family history of first degree relatives with HHT. The clinical presentation of patients with suspected HHT included recurrent epistaxis and oropharyngeal, cerebral, and hepatic telangiectasia. Coagulation profiles for all the patients were within normal limits at the time of the procedure.

Technique

Before the procedures, all patients had a prior contrast-enhanced CT showing the number and location of PAVMs. The procedures employed mild to moderate conscious sedation using intravenous fentanyl citrate and midazolam hydrochloride. No heparin was administered during the procedure. After gaining access to the femoral vein, selective bilateral pulmonary angiograms were performed using an angled pigtail catheter (AP2, Cook Medical) in order to identify the location of the PAVM. Once identified, selective catheterization of the branch pulmonary artery was performed using angled catheter (Berenstein, Cook Medical) to identify the diameter and number of feeding arteries of the PAVM targeted for embolization. Using the classification system proposed by White et al. (3), the PAVMs were classified as simple with one feeding artery or complex with multiple feeding arteries.

The diameter of the feeding artery was then measured from the digitally subtracted images obtained during angiography. The AVP or AVP 2 were selected based on 30%–50% device oversizing compared with the feeding artery diameter. The AVP or AVP 2 was then introduced through the appropriate size guiding catheter (Envoy, Cordis) or sheath (Shuttle, Cook Medical) under water seal. The diameter of the AVP or AVP 2 device used was based on the size of the target artery. The AVP or AVP 2 was delivered and deployed as distal as possible in the feeding artery. The choice of whether to use AVP or AVP 2 was dependent on the availability of the devices and the length of the landing zone. AVP had a shorter landing zone than the new AVP 2 and was therefore more useful where there were proximal non-target branches that did not need to be occluded. Angiography was performed after device delivery to verify the correct positioning of the vascular plug. Once the device was deemed to be in a satisfactory position, it was deployed, and a single nonsubtracted image was obtained. Postembolization angiography was performed through the guiding catheter at 1 min intervals using hand injection of 5–10 mL of contrast, until total occlusion of the artery was visualized. In case of persistent patency on postembo-lization angiogram for more than 5 min, an additional device was used to achieve complete occlusion. In patients with bilateral PAVMs, embolization was performed on two separate sessions to avoid high radiation exposure and high volume of contrast administration.

Follow-up

Follow-up CT angiography of the chest was performed per our institution protocol every 3–6 months after the procedure to assess for PAVM reperfusion. The technique of CT angiography consisted of axial images of the chest before and after intravenous administration of nonionic contrast material (Omnipaque 350, GE Healthcare). The dose of the contrast material was 1 mL/kg which was administered through a peripherally inserted venous line using automated pump at a rate of 4 mL/s. Axial images were re-constructed at 2 mm thickness. Additional coronal reformatted images were also obtained. Imaging follow-up was continued until there was no significant change in the findings between two consecutive exams.

Definitions

The OT of PAVMs was calculated by subtracting the reference time recorded on the nonsubtracted image that was obtained immediately after placement of the vascular plug, from the reference time recorded on the angiogram that showed total occlusion of the PAVM. Immediate technical success was defined as embolization of the PAVM using only AVP or AVP 2 without the need for additional embolization material. Complications were classified as minor or major according to the Society of Interventional Radiology clinical practice guidelines (11).

Statistical analysis

The number, location, and type (simple or complex) of the PAVMs, as well as, the diameter and number of the feeding arteries and devices were recorded. The percent of device oversizing was calculated. The mean and standard deviation of the OT of AVP and AVP 2 were also calculated and were correlated with the percent of device oversizing, in an attempt to determine if the percent of device oversizing affected the occlusion time. The hypothesis was that an increase in device oversizing would decrease the OT. A Pearson correlation coefficient was used to measure the strength of a linear association between different variables. The P value was calculated using the r value obtained. The OT of AVP was compared with that of AVP 2 using an independent samples t-test, in an attempt to investigate if there is a difference in the OT between the two devices. The hypothesis was that the OT of AVP 2 device is shorter than AVP. A difference was considered significant when P value was less than 0.05.

Main points

• AVP 2 device does not offer improved occlusion properties compared with AVP when used in the treatment of PAVMs.
• The manufacturer recommendation of device oversizing for AVP and AVP 2 is sufficient in ensuring device stability and further increase in device oversizing does not result in improvement of the thrombogenic capability of the devices.
• The persistence rate of PAVMs was very low and was not statistically different between the two devices.
• There was no reported difference in safety between the two devices, with no major complications noted.
Results

The study group included 19 patients with 47 PAVMs. Forty-six (98%) of the PAVMs were simple with just one feeding artery, and one PAVM was complex with two feeding arteries. Fifteen patients (79%) had unilateral PAVMs and 12 patients (63%) had bilateral PAVMs. Eleven patients (58%) had a single PAVM, two patients (10%) had two PAVMs, and six patients (32%) had more than two PAVMs.

Forty-two PAVMs (89%) required only one device, and five PAVMs (11%) required two devices for embolization. Seventeen PAVMs (36%) were embozized using a single AVP, one PAVM (2%) was embozized using two AVPs, twenty-four PAVMs (51%) were embozized using a single AVP 2, four PAVMs (9%) were embozized using two AVP 2, and one PAVM (2%) was embozized using one AVP and one AVP 2. The immediate technical success was 100%, with complete occlusion achieved in all PAVMs using AVP and AVP 2 without any additional embolization material.

The mean diameter of the feeding arteries of PAVMs that were treated with AVP was 4.79±2.06 mm. In regards to the AVP devices used, the diameter of the devices ranged from 4.0–16.0 mm, and the average percent oversizing was 40%±9.53%. The feeding arteries that were embozized using AVP 2 had a mean diameter of 5.8±2.43 mm. AVP 2 devices had diameters ranging from 6.0–16.0 mm. The average percent oversizing used for AVP 2 devices was 53%±25.71%.

The overall average OT for all the devices was 4 min 50 s. The average OT for the AVP devices was 3 min 54 s (standard deviation [SD], 1 min 32 s). The average OT for the AVP 2 devices was 5 min 30 s (SD, 2 min 48 s). However, when the OT of AVP was compared with that of AVP 2, there was a statistically significant difference ($P = 0.030$).

The percent of AVP oversizing was weakly correlated with OT ($r=0.25, P = 0.324$). Similar results were seen with AVP ($r=0.26, P = 0.240$). However, these correlations were not statistically significant.

Regarding imaging follow-up, seven (37%) patients were lost to follow-up. Twelve patients with 35 PAVMs were available for imaging follow-up. Thirty-four (97%) PAVMs were treated successfully based on the criteria proposed by Remy-Jardin et al. (7), with no evidence of persistence. Recanalization was noted in one PAVM, which showed patency of the feeding artery distal to the AVP 2 device. Follow-up pulmonary angiography was obtained with the intent to treat, but showed no evidence of recanalization. It was retrospectively determined that the CT angiogram actually revealed an overlapping artery, causing this misinterpretation. No intervention was performed, and therefore this was considered a successful treatment.

### Table. Patient demographics, clinical presentation, comorbid conditions, and pertinent medical history

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Clinical presentation</th>
<th>Comorbid conditions and medical history</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>F</td>
<td>Wheezing, coughing</td>
<td>Asthma, TB post resection</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>F</td>
<td>Dyspnea, dizziness</td>
<td>Hypertension, arthritis, asthma</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>F</td>
<td>Dyspnea, chest pain, wheezing, coughing</td>
<td>Asthma, hypertension, GERD, hepatitis A, glaucoma, interstitial cystitis</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>M</td>
<td>Dyspnea</td>
<td>HHT, ophthalmic/cerebral/nasal/conjunctival AVMs, CVA, left renal abscess</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>F</td>
<td>Dyspnea</td>
<td>Asthma, cardiac arrhythmia, migraines</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>F</td>
<td>Dyspnea, hypoxemia</td>
<td>HHT, ulcerative colitis, aortic regurgitation, Meniere’s disease, CVA, liver AVM’s, nose bleeds</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>F</td>
<td>Left and right MCA strokes</td>
<td>Recurrent conjunctivitis</td>
</tr>
<tr>
<td>8</td>
<td>45</td>
<td>F</td>
<td>Dyspnea, hypoxemia</td>
<td>COPD, headaches, nose bleeds, lip telangiectasia ablation, gastritis, hypertension, recurrent pneumonia, elevated triglycerides</td>
</tr>
<tr>
<td>9</td>
<td>23</td>
<td>M</td>
<td>Pleuritic chest pain, left hemothorax, dyspnea</td>
<td>Epistaxis</td>
</tr>
<tr>
<td>10</td>
<td>28</td>
<td>F</td>
<td>Right MCA territory TIA/CVA</td>
<td>Anxiety, bipolar disorder, palpitations</td>
</tr>
<tr>
<td>11</td>
<td>39</td>
<td>M</td>
<td>Dyspnea, pleuritic chest pain</td>
<td>Hypertension</td>
</tr>
<tr>
<td>12</td>
<td>63</td>
<td>M</td>
<td>Hypoxemia, chest pain</td>
<td>Percutaneous coronary intervention, LVEF = 38%, coronary artery disease, seizures, brain abscess, CKD</td>
</tr>
<tr>
<td>13</td>
<td>44</td>
<td>F</td>
<td>Dyspnea</td>
<td>Emphysema, depression, anxiety, pseudoseizures, hypertension, gastric ulcers</td>
</tr>
<tr>
<td>14</td>
<td>46</td>
<td>F</td>
<td>Dyspnea</td>
<td>Charcot-Marie-Tooth with progressive gait imbalance, hearing loss, mastoiditis, migraines, diverticulitis with colon resection</td>
</tr>
<tr>
<td>15</td>
<td>45</td>
<td>F</td>
<td>Left MCA CVA</td>
<td>Patent foramen ovale, chronic sinusitis, hysterectomy, lumpectomy</td>
</tr>
<tr>
<td>16</td>
<td>60</td>
<td>F</td>
<td>Hypoxemia</td>
<td>First degree relative with HHT, epistaxis, fatigue, sleep apnea, migraines, hypertension, hysterectomy, cataract</td>
</tr>
<tr>
<td>17</td>
<td>57</td>
<td>F</td>
<td>Hypoxemia</td>
<td>Hypothyroidism, CVA, hemothorax with VATS, nose bleeds, previous gastrointestinal bleed due to AVMs</td>
</tr>
<tr>
<td>18</td>
<td>24</td>
<td>M</td>
<td>Hypoxemia, cyanosis</td>
<td>HHT, hypercholesterolemia</td>
</tr>
<tr>
<td>19</td>
<td>20</td>
<td>M</td>
<td>Incidental PAVM finding</td>
<td>No past medical history</td>
</tr>
</tbody>
</table>

F, female; M, male; TB, tuberculosis; GERD, gastroesophageal reflux disease; HHT, hereditary hemorrhagic telangiectasia; AVM, arteriovenous malformation; CVA, cerebrovascular accident; MCA, middle cerebral artery; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; LVEF, left ventricular ejection fraction; CKD, chronic kidney disease; VATS, video-assisted thoracic surgery.
Systemic-to-pulmonary reperfusion was encountered in one simple PAVM (3%) in a patient with dyspnea and an O₂ saturation of 91%. CT angiography was performed at four months postprocedure and revealed a 39% decrease in the aneurysm sac size without recanalization of the feeding artery, which raised suspicion of pulmonary-to-pulmonary or systemic-to-pulmonary reperfusion. Pulmonary angiogram revealed continued occlusion of the feeding artery with no feeders. A right subclavian angiogram was performed and confirmed the presence of a systemic supply to the aneurysmal sac from branches of the internal mammary and lateral thoracic arteries. PAVM persistence through a systemic supply in this case does not pose risk of paradoxical embolization and therefore, no further treatment was attempted for this patient.

There was no procedure related mortality and the 30-day mortality was zero. There were no complications during the procedures but minor complications were noted in six patients (32%) during the immediate postprocedure period. Three patients (16%) had transient elevations in their creatinine levels, which was attributed to contrast material administration during the procedure. These patients were treated with sodium bicarbonate drip according to our institution protocol, and their creatinine levels returned to the normal limits within 24 hours. One patient (5%) had pleuritic chest pain on the same side of the embolized PAVM, in spite of being on nonsteroidal antiinflammatory drugs, which resolved within 48 hours without further management. Another patient (5%) developed an erythematous papular rash on the chest and the back that was assumed to be an allergic reaction to contrast material, which resolved after treatment with antihistamine. There were no early or late postprocedural neurologic events.

Discussion

The purpose of our study was to calculate the OT of PAVMs when AVP and AVP 2 are used in their treatment, and to correlate the OT with the type of the device used. Due to the theoretical increased thrombogenic effect of AVP 2 compared with AVP, our hypothesis was that AVP 2 could have a shorter OT compared with AVP. The average OT for the AVP in our study was 3 min 54 s, which was in line with the published literature (8). The average OT for the AVP 2 was 5 min 30 s, which was unexpectedly longer than that of AVP.

Successful use of AVP and AVP 2 for embolotherapy of PAVMs has been reported in several studies (8, 12–17). Compared with the AVP device, the AVP 2 has multiple layers of finer, more densely woven nitinol mesh and a multisegmented design, which theoretically increases its thrombogenic effect and decreases the OT (9). The OT of AVP devices in the treatment of PAVMs has been previously studied and the results documented its safety with an acceptable OT of 2–3 min without a higher risk of systemic paradoxical embolization (8). However, to our knowledge, there are no studies published in the literature regarding the OT of AVP 2 used in the treatment of PAVMs.

The OT associated with different embolic devices determines the risk of embolic complications, due to small clots that can form over the surface of the device from the time of deployment to complete occlusion and migrate to the systemic circulation, causing increased risk of complications related to systemic embolization (18). While the difference in OT between the two devices was statistically significant, this difference does not appear to be clinically significant since the slightly prolonged OT of the AVP 2 was not associated with increased complications or worse outcomes. Furthermore, the difference in OT between the two devices could be the result of the redundancy associated with the calculation of the OT. This redundancy is inherent to both devices and is due to the fact that the OT was calculated from the reference time recorded on the follow-up angiograms that were done every 1 min with an assumption that this recorded time is the exact time at which the feeding artery was occluded. In fact, the exact OT could have occurred up to 60 s earlier.

A 30% to 50% device oversizing is recommended by the manufacturer. However, this is difficult to implement with feeding artery sizes. The sizes of these devices are available in increments of 2 mm making exact device oversizing of 30%-50% difficult to achieve, which resulted in a percent of device oversizing outside the recommended range in some patients. Theoretically, device oversizing not only adds stability to the device and prevents migration, but also increases blood flow impedance and the surface area of the thrombogenic mesh available for clot formation. Therefore, our hypothesis was that the OT is inversely proportional to the percent of device oversizing. The same theory was shared by a published review article on the device (10).

However, the results showed a weak positive correlation between OT and percent of device oversizing for both AVP and AVP 2, and the relationship was not entirely linear. Therefore, the manufacturer recommendation of device oversizing seems to be sufficient in ensuring device stability and the increase in device oversizing will not result in improvement of the thrombogenic capability of the device. Regarding the cost of the devices, the AVP 2 is sold in the US market at almost double the price of the AVP.

Five PAVMs (11%) required two devices to achieve embolization. The second device was placed when the feeding artery remained patent for more than five minutes due to increased risk of paradoxical embolization of small clots formed over the surface of the device that might flow through the PAVM. A published study suggested placement of coils proximal to AVP to avoid recanalization; however, in the authors' experience, using the deployment of another AVP or AVP 2 device proximally is faster, easier, and offers rapid occlusion of the shunt compared with placement of several coils (5).

There was no significant difference in the rate of persistence of PAVMs between both devices. There was only one case of systemic-to-pulmonary reperfusion encountered with use of the AVP2 device. Otherwise, no evidence of reperfusion was seen on imaging follow-up.

Regarding the safety of both devices, there were no procedure-related mortalities and 30-day mortality was zero. There were no major complications during the procedure as well; however, some minor complications were reported in the immediate postprocedure period including transient increase in creatinine level, pleuritic chest pain, and contrast dye induced allergic erythematous papular rash.

Certain limitations to the study included a relatively small sample size. Because of the retrospective nature of the study, there was an inherent selection bias and inconsistency in the technique of embolization. Most of the treated PAVMs in this study were simple in angioarchitecture, which does not represent the known incidence in the population. Another limitation was the redundancy associated with the calculation of the OT. The study represents a single center experience and the results cannot be generalized.

In conclusion, AVP 2 device does not offer improved occlusion properties compared with AVP when used in the treatment of
PAVMs. The manufacturer recommendation of device oversizing for AVP and AVP 2 is sufficient in ensuring device stability and further increase in device oversizing does not result in improvement of the thrombogenic capability of the devices. The persistence rate of PAVMs was very low and was not statistically different between the two devices.

Conflict of interest disclosure
Ahmed Kamel Abdel Aal is a consultant for St Jude Medical. The other authors have no conflicts of interest.

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