Contrast Echocardiography Remains Positive After Treatment of Pulmonary Arteriovenous Malformations*

Warren L. Lee, MD; Anthony F. Graham, MD; Robyn A. Pugash, MD; Stuart J. Hutchison, MD; Patricia Grande, RN; Robert H. Hyland, MD, FCCP; and Marie E. Faughnan, MD

Study objectives: Pulmonary arteriovenous malformations (PAVMs) in patients with hereditary hemorrhagic telangiectasia (HHT) can cause hemorrhage, stroke, and cerebral abscess. Therapy consists of transcatheter embolotherapy (TCET) to occlude the PAVMs. Contrast transthoracic echocardiography (TTE) can be used to screen for PAVMs, but little is known about the performance of contrast TTE after TCET has been performed. Our objective was to determine the effect of the successful performance of TCET on the performance of contrast TTE, specifically, in what proportion of patients the findings of contrast TTE normalized or remained positive after the performance of TCET.

Design: Retrospective chart review.

Setting: HHT clinic at university teaching hospital.

Patients: Patients who have undergone TCET for the treatment of PAVMs.

Interventions: Patients were screened for PAVMs with a chest radiograph (CXR), oxygen shunt test (OST), and contrast TTE. Pulmonary angiography was recommended for patients with any positive findings on a screening test. PAVMs ≥3 mm were occluded by TCET. Contrast TTE, OST, and CXR were performed approximately 1 month later. The results of contrast TTE before and after patients underwent TCET were compared.

Measurements and results: Thirty-nine patients underwent contrast TTE prior to undergoing TCET, and 29 patients underwent contrast TTE both prior to and after undergoing TCET. In all patients, TTE findings were positive prior to TCET. All PAVMs with feeding vessels ≥3 mm were successfully occluded based on completion angiography. After TCET, 48% of patients had no detectable residual PAVMs, and the remainder had small (ie, <3 mm) residual PAVMs. Of the 29 patients, 90% had positive contrast TTE findings after undergoing TCET. In the subset of patients who had no residual PAVMs on the completion angiography, 80% had positive contrast TTE findings after undergoing TCET.

Conclusions: In most patients, contrast TTE findings remain positive after they undergo TCET, even in patients without residual PAVMs seen on angiography. This may reflect residual PAVMs that are too small to visualize using angiography. These findings have important implications for the follow-up and management of HHT patients.

Key words: arteriovenous malformations; contrast echocardiography; embolotherapy; hereditary hemorrhagic telangiectasia

Abbreviations: ASD = atrial septal defect; CXR = chest radiograph; HHT = hereditary hemorrhagic telangiectasia; OST = oxygen shunt test; P(A-a)O₂ = alveolar-arterial oxygen pressure difference; PAVM = pulmonary arteriovenous malformation; ROC = receiver operating characteristic; TCET = transcatheter embolotherapy; TTE = transthoracic echocardiography

*From the Divisions of Respirology (Drs. Lee, Hyland, and Faughnan) and Cardiology (Drs. Graham and Hutchison, and Ms. Grande), Department of Medicine, and the Department of Medical Imaging (Dr. Pugash), St. Michael's Hospital, University of Toronto, ON, Canada. This study was supported by the Squires Club (Dr. Faughnan), the Nelson Arthur Hyland Foundation, and St. Michael's Hospital Research Institute.

Manuscript received March 22, 2001; revision accepted June 27, 2002.

Correspondence to: Marie E. Faughnan, MD, St. Michael's Hospital, 30 Bond St, Suite 6045, Toronto, ON M5B 1W8 Canada; e-mail: faughnanm@smh.toronto.on.ca

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal-dominant disorder that is characterized by skin and mucosal telangiectasias, epistaxis, and the presence of arteriovenous malformations in various organs.1,2 Although the disease is thought to be rare, its prevalence varies greatly depending on geography. Although traditionally the prevalence is reported as being between 1 and 20 cases per

Downloaded From: http://publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21989/ on 06/17/2017
100,000 population, it has more recently been described in 1 per 2,351 persons in the French department of Ain and in 1 per 16,500 persons in Vermont.

Mutations in two different genes have been associated with HHT in different families. HHT-1 involves a mutation in the gene for endoglin, while a mutation in the activin receptor-like kinase gene is responsible for HHT-2. Both genes are expressed on endothelial cells and may be involved in the signaling of transforming growth factor β and vasculogenesis.

The clinical aspects of pulmonary arteriovenous malformations (PAVMs) have been reviewed. Fifteen to thirty-five percent of patients with HHT have PAVMs, which consist of a direct connection between a branch of the pulmonary artery and a branch of the pulmonary vein through a thin-walled aneurysm. Although PAVMs can be asymptomatic, they act as right-to-left shunts and can be associated with dyspnea, fatigue, and hypoxemia. In as many as 36% of cases, PAVMs lead to serious neurologic complications such as brain abscess or embolic stroke. Less frequently, patients with PAVMs may present with massive hemoptysis or spontaneous hemothorax. Since PAVMs can cause life-threatening complications and effective treatment exists, research in the area has focused on methods to improve early detection.

Many different screening tests for PAVMs have been studied including chest radiographs (CXR), oxygen shunt test (OST), CT scanning, and contrast transthoracic echocardiography (TTE). Some evidence suggests that among these tests, contrast TTE may be the most sensitive screening method for detecting PAVMs. Ultimately, the “gold standard” for diagnosing PAVMs is pulmonary angiography.

Natural history studies of PAVMs suggest that those with a feeding artery of at least 3 mm in diameter confer the highest risk of embolic stroke and should be occluded. The current treatment for these PAVMs is by transcatheter embolotherapy (TCET), in which the feeding artery is obliterated with a detachable balloon or with metal coils. TCET is quite successful, leading to the immediate occlusion of PAVMs in 90 to 100% of cases and to continued occlusion in >85% of cases at 1 year postprocedure. It is also recommended that all patients with PAVMs receive antibiotics prior to undergoing bacteremic procedures in order to reduce the risk of brain abscess.

Although contrast TTE has been studied as a screening test, there is little information regarding its use in follow-up after the performance of TCET. Currently, most centers have different follow-up protocols after a patient undergoes TCET, generally including CT scan and OST. However, a CT scan involves exposure to radiation, and OST is uncomfortable and somewhat invasive. Contrast TTE may be useful in the follow-up of patients after the occlusion of PAVMs, but there is little information in the literature regarding the results of contrast TTE after the performance of TCET. One small study reported that contrast TTE findings remained positive in 10 of 11 patients after they had undergone TCET for treatment of PAVMs, but it did not report or compare to other measures of TCET outcome or the presence of residual PAVMs after the performance of TCET. Clarifying the performance of contrast TTE after the performance of TCET is important since it is desirable to confirm the occlusion of PAVMs after the patient has undergone TCET.

In this context, this study was designed to determine the effect of a successful TCET procedure on contrast TTE results, specifically, in what proportion of patients contrast TTE results normalized or remained positive after undergoing TCET for the treatment of PAVMs.

Materials and Methods

Patients

All patients who had been seen at the Toronto HHT Clinic between February 1, 1998, and February 28, 2000, who had undergone TCET for the treatment of PAVMs were eligible (n = 43), although only those who had undergone contrast TTE prior to undergoing TCET were included (n = 39). The Toronto HHT Clinic, established in February 1997, is a specialized HHT clinic at St. Michael’s Hospital, a tertiary care, university-affiliated, teaching hospital.

Thirty-five of the patients (90%) met the diagnostic criteria for definite HHT, and of the remaining 4 patients, 3 had suspected HHT. All patients referred to the Toronto HHT Clinic were screened for PAVMs with standard posteroanterior and lateral CXRs, OST, and contrast TTE. Diagnostic pulmonary angiography was recommended to patients if the finding of any one of the screening tests was positive.

Investigations

For the performance of contrast TTE, patients were positioned in the left lateral decubitus position, and views were obtained from the parasternal, apical, and subcostal regions. In each patient, a 19-gauge, 2.5-cm IV catheter with a saline solution lock was placed in the forearm. A three-way stopcock was attached, and two 10-mL syringes were attached to the other two ports. One syringe was empty with air excluded, and the other was full of saline solution. The contrast (bubbles) was obtained by flushing the saline solution from one syringe to another. A forceful hand injection of 10 mL agitated saline solution was performed while images were obtained simultaneously in the apical four-chamber view.

A positive finding on the contrast TTE was defined as the
appearance of any bubbles in the left atrium following the injection of agitated saline solution. The appearance of bubbles in the left atrium was prespecified to be greater than three cardiac cycles after first appearance in the right atrium. This was done to exclude intracardiac shunting due to a patent foramen ovale, atrial septal defect (ASD), or ventricular septal defect. Echocardiograms were read by the same two cardiologists (AFG and SJH). We have recently demonstrated very high interobserver agreement ($\kappa = 0.926$) in the evaluation of contrast TTE findings in this population.

The methods for OST have been described previously. A sample of arterial blood gas with the patient breathing room air was obtained from the radial artery. The patient then breathed 100% $\text{O}_2$ for 20 min, after which another arterial blood gas analysis was performed. A positive OST result was defined as an alveolar-arterial oxygen pressure difference ($P(A-a)\text{O}_2$) of $>175$ mm Hg while breathing 100% $\text{O}_2$, based on a receiver operator characteristic (ROC) curve that was constructed at our institution (Fig 1).

Patients underwent conventional pulmonary angiography with a 7F catheter, which was introduced into each pulmonary artery under fluoroscopic guidance through the common femoral vein. A total dose of 40 to 60 mL iodinated contrast material was injected for each angiographic run, at a rate of 20 to 30 mL/s. Multiple projections and magnification views were employed as necessary. All angiograms were performed and interpreted by the same radiologist (RAP).

If diagnostic angiography revealed the presence of PAVMs, TCET was performed for PAVMs with feeding arteries with a diameter of $\geq 3$ mm. Underwater delivery of coils was used for TCET. The successful occlusion of PAVMs was confirmed immediately after the performance of TCET with nonselective injection of both the right and left pulmonary arteries (ie, completion angiography). Care was taken to rule out residual accessory feeding vessels to the PAVMs. PAVMs with feeding arteries with a diameter of $<3$ mm were not routinely embolized. In this study, a successful TCET was defined as the lack of residual perfusion through embolized PAVMs and no residual PAVMs with feeding arteries with a diameter of $\geq 3$ mm. The same radiologist performed all TCET procedures. In patients with too many PAVMs to occlude in one session, a second session was performed, generally within 1 month.

Subsequent TCET sessions in the same patient that were separated in time by $>1$ month were considered to be distinct procedures and were not included in the analysis. In other words, if a patient underwent a second TCET procedure at a later period in time, only the findings of the first TCET procedure were included in this study.

Routine follow-up investigations after the performance of the TCET consisted of contrast TTE, OST, and CXR at least 1 month after the procedure.
Analysis

Analysis was limited to patients who had undergone contrast TTE before undergoing TCET. A more detailed analysis also was done on the subset of patients who had undergone contrast TTE both before and after undergoing TCET. The proportions of patients with abnormal (positive) contrast TTE or OST findings were compared using a χ² test statistic with a continuity correction, with p > 0.05 being considered significant.

Results

Forty-three patients had PAVMs and underwent TCET procedures during the study period. Of these patients, 39 underwent contrast TTE prior to undergoing TCET and were included in the study. Twenty-nine of the 39 patients also underwent TTE after TCET within a mean of 4 months (SD, 5 months). The distribution of the patients is shown in Figure 2.

Patient Characteristics

The mean age of the 29 patients was 49 years (range, 19 to 77 years), and 62% were women. On average, 5 PAVMs were embolized per patient (range, 1 to 20 PAVMs).

TCET Results

Of the 29 patients who underwent TCET and subsequent contrast TTE, 14 (48%) had no residual PAVMs detected on completion angiography. The other 15 patients (52%) had residual PAVMs with feeding vessels that were < 3 mm in size. Of the 15 patients with small residual PAVMs after undergoing TCET, 1 had PAVMs diffusely throughout most of the pulmonary vasculature. No patient had residual PAVMs with a feeding artery > 3 mm in diameter.

Results of Contrast TTE Before TCET

In all 39 patients (100%) who underwent contrast TTE prior to undergoing TCET, contrast TTE findings were positive, suggesting the presence of intrapulmonary right-to-left shunting. Of the 39 patients, 37 (95%) underwent OST prior to undergoing TCET. Of these 37, only 22 were positive (59%). The difference between the proportions of positive findings from contrast TTE and OST prior to TCET is statistically significant (p < 0.00001).

Results of Contrast TTE After TCET

Of the 29 patients, 26 (90%) had persistently positive findings on contrast TTE after undergoing TCET (Fig 1). Of those 29 patients, 26 underwent OST after undergoing TCET, and the findings remained positive in only 7 patients (27%; p < 0.00001 [for the comparison of the proportion of positive contrast TTE findings to positive OST results]).

When the analysis was restricted to the 14 patients who had no detectable residual PAVMs on completion angiography, 11 (79%) had persistently positive
contrast TTE findings after undergoing TCET (Fig 3). Of the 14 patients, 13 had undergone OST after undergoing TCET, and the findings remained positive in only 2 patients (15%; \( p < 0.01 \) [for the comparison of positive contrast TTE findings to positive OST results]). When the patients with and without residual PAVMs seen on completion angiography were compared, the proportions of patients with positive contrast TTE findings after undergoing TCET (100% vs 79%, respectively) were not significantly different (\( p = 0.06 \)).

Varying the OST Cutoff Point

The above results for OST have been based on a predetermined cutoff for the \( P(A-a)O_2 \) of 175 mm Hg. Decreasing the \( P(A-a)O_2 \) used as the threshold (with an estimated shunt of 5.6%\(^{19} \)), the OST results remained positive in 21 of 26 patients (81%) after they had undergone TCET. Using the same cutoff in the 14 patients with no detectable residual PAVMs on completion angiography, OST results remained positive in 9 of 13 patients (69%).

Excluded Patients

The 10 patients who had undergone contrast TTE prior to, but not after, undergoing TCET were not included in the above comparisons. Patients who had undergone contrast TTE after undergoing TCET and those who did not are compared in Table 1. The only statistically significant difference noted was in the rate of residual detectable PAVMs.

Table 1—Comparison of Patients Who Underwent Contrast TTE after Undergoing TCET With Those Who Did Not

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Contrast TTE After TCET (n = 29)</th>
<th>No Contrast-TTE After TCET (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yr</td>
<td>49 (range, 19–77)</td>
<td>39 (range, 17–67)</td>
</tr>
<tr>
<td>Female gender, %</td>
<td>62</td>
<td>60</td>
</tr>
<tr>
<td>PAVMs embolized, mean (SD)</td>
<td>5.0 (3.0)</td>
<td>7.8 (7.4)</td>
</tr>
<tr>
<td>Patients with no detectable PAVMs after TCET, %</td>
<td>48</td>
<td>83*</td>
</tr>
</tbody>
</table>

\( ^* p = 0.05 \).
HHT is an uncommon disorder that traditionally has been regarded as having relatively minor sequelae. More recently, we have begun to appreciate that, far from being innocuous, HHT can cause life-threatening complications due to visceral PAVMs. In particular, untreated PAVMs frequently cause embolic stroke, brain abscess, and pulmonary hemorrhage. As a result, there is growing interest in the early diagnosis and therapy of PAVMs.

One issue, however, that has not received much attention is the follow-up of HHT patients after the treatment of PAVMs with TCET. In particular, although contrast TTE has been shown to be a very sensitive screening test for PAVMs, its role after patients undergo TCET remains poorly defined.

Our results demonstrate that contrast TTE findings remain positive after TCET for the treatment of PAVMs in > 90% of patients. Even when angiography performed immediately after TCET showed no detectable small residual PAVMs, contrast TTE findings remained positive in almost 80% of patients.

These findings have a number of important implications. First, they reaffirm the sensitivity of contrast TTE for intrapulmonary shunting. Second, our data suggest that most patients with PAVMs secondary to HHT have additional small PAVMs that are undetectable by standard angiography. Such individuals therefore should still receive antibiotic prophylaxis before undergoing dental and surgical procedures to reduce the risk of bacteremia and brain abscess. They also merit lifelong follow-up in order to detect the enlargement of small PAVMs to a size that should be treated.

This study has some limitations that warrant discussion. With the mean 4-month interval between the performance of TCET and the performance of follow-up contrast TTE, it is possible that the positive contrast TTE results represent either the reperfusion of occluded PAVMs or the growth of new PAVMs in the interim. The reperfusion of PAVMs can be due either to recanalization of the occluded feeding artery or to the perfusion of the PAVMs through an accessory vessel, either a new one or one that was previously unrecognized. We believe that all of these possibilities are unlikely to account for the high rate of positive contrast TTE findings after the performance of TCET. TCET is known to permanently occlude the vast majority of angiographically detectable PAVMs. In a cohort of 45 patients who were observed for a mean of 4.5 years, 85% of large PAVMs that were treated with TCET were permanently occluded on the first attempt. Our own experience has been similar and corroborates the effectiveness of TCET. Although it is possible that the reperfusion of PAVMs occurred in the 4-month interval before the patients underwent contrast TTE, this should occur in < 15% of PAVMs after the performance of TCET. We attempted to minimize reperfusion through the incomplete closure of complex PAVMs (with multiple feeding arteries) using nonselective completion angiography after the performance of TCET in all patients, with particular attention paid to identifying or excluding accessory vessels. The growth of PAVMs is thought to be fairly slow and would not likely be significant in 4 months’ time. Although the occlusion of the feeding artery with TCET occurs rapidly, the involution of the thrombosed aneurysmal sac may take many months. Long-term follow-up (eg, with CT scan) in these patients with documented involution of the embolized PAVMs will eventually provide definitive proof of successful TCET.

It is possible that the high percentage of positive contrast TTE findings after the performance of TCET reflects a high number of false-positive tests, rather than the presence of small PAVMs that are undetectable by conventional angiography. Since there are no large studies of contrast TTE in healthy individuals, this possibility is difficult to disprove. However, early studies examining the role of contrast TTE for the detection of intraluminal communications, using cardiac catheterization as the “gold standard,” found no false-positive results by contrast TTE in normal control subjects.

It is also possible that some of the patients had occult interatrial shunts, accounting for the high rate of positive contrast TTE findings after the performance of TCET. This is unlikely, given the a priori requirement that the appearance of bubbles in the left atrium be greater than three cardiac cycles after their first appearance in the right atrium in order to suggest an intrapulmonary shunt (rather than an intracardiac shunt), as previously described.

In addition, the prevalence of ASDs in the general population is quite low (ie, < 1%). To our knowledge, there is no evidence that patients with HHT have a higher than expected prevalence of ASDs, making it unlikely that the high rate of positive TTE findings after the performance of TCET reflects a high number of false-positive tests.
contrast TTE findings after the performance of TCET is due to occult ASDs.

In this study, we have compared the results of contrast TTE to those of OST after the performance of TCET. Using a P(A-a)O₂ of 175 mm Hg as a cutoff, we have found that OST results normalize after the performance of TCET in most patients, while contrast TTE findings remain positive after the performance of TCET in most patients. We used a cutoff point for OST (selected to optimize both sensitivity and specificity) based on an ROC curve that was constructed at our institution prior to the routine use of contrast TTE at our center. It is interesting to note that if the cutoff were changed to a P(A-a)O₂ of 88 mm Hg (ie, a shunt of approximately 5.6%),¹⁹ the number of positive OST results before and after the performance of TCET increases to a level similar to that of contrast TTE. Indeed, this remains consistent with the notion that small PAVMs persist, undetectable by angiography, even after the successful performance of TCET.

One issue that has not been addressed in this study is the grading of positive contrast TTE results. In our experience, most positive contrast TTE results improve (ie, fewer bubbles appearing in the left atrium) after the performance of TCET, although they remain abnormal. We have not reported on contrast TTE grading in this study as no grading system has been validated. Indeed, our results highlight the need for such a system, which would assist in evaluating the success of TCET and might be useful in predicting patient prognosis or the recurrence of PAVMs.

Another potential limitation of the study is that not all patients underwent all of the investigations described. In particular, only 74% of patients who underwent contrast TTE prior to undergoing TCET also underwent contrast TTE after undergoing TCET. It is possible that these patients were somehow different from those who did not undergo contrast TTE after undergoing TCET and that this bias is contributing to the high rate of positive contrast TTE results after TCET. We believe that this bias is unlikely to be important for two reasons. First, the two groups of patients are not that dissimilar. The only significant difference noted was in the proportion of patients found to have residual small PAVMs after undergoing TCET. Assuming the worst-case scenario, if all of the patients who did not undergo contrast TTE after undergoing TCET were assumed to have negative contrast TTE results after undergoing TCET, the percentage of patients with positive contrast TTE findings after undergoing TCET would still remain high (ie, approximately 66%).

Finally, the most important question raised by our findings is whether the very small PAVMs detected by contrast TTE after the performance of TCET are clinically relevant. Although it is thought that PAVMs with feeding arteries with a diameter of ≥ 3 mm pose the highest risk of sequelae, the natural history of smaller PAVMs is unclear. It is known, however, that PAVMs can grow with time and that, therefore, patients with small residual PAVMs are likely to be at increased risk of future complications. Furthermore, patients with small residual PAVMs may remain at risk for brain abscess and therefore should receive antibiotic prophylaxis before undergoing bacteremic procedures. Ultimately, the cohort of patients with positive contrast TTE findings after undergoing TCET will have to be observed for their prognosis to be determined.

In conclusion, this study has demonstrated that contrast TTE findings remain positive after the performance of TCET for the treatment of PAVMs in most patients with HHT. This suggests that most patients with HHT and PAVMs have additional small PAVMs that are not detected by conventional angiography. These findings have important implications for the follow-up and management of patients with HHT.

References

4 Plauchu H, Bideau A. Épidémiologie et constitution d’un registre de population à propos d’une concentration géographique d’une maladie héréditaire rare. Popul 1984; 4:5:765–786
6 McAllister KA, Grogg KM, Johnson DW, et al. Endoglin, a TGF-β binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. Nat Genet 1994; 8:345–351