Two-Dimensional Contrast Echocardiography in the Detection and Follow-Up of Congenital Pulmonary Arteriovenous Malformations

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Pulmonary arteriovenous (A-V) malformation is frequently a manifestation of Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia). We identified 14 patients (9 men and 5 women) with A-V malformation by contrast echocardiography; 10 patients with atrial right-to-left shunt served as control subjects. Agitated saline solution (10 ml) was injected through a peripheral vein during echocardiographic imaging. The delay in the appearance of microcavitations in the left atrium was measured (in number of frames) after right atrial appearance. The degree of left ventricular opacification was graded 1 to 4+ (where 4+ = intense left ventricular endocardial outline, and 1+ = minimal opacification). Results indicated patients with A-V malformation had a significant delay (p < 0.001) in left atrial appearance of microcavitations compared with those with atrial right-to-left shunt (66 ± 27 vs 21 ± 7 frames, mean ± 1 standard deviation). In the group with A-V malformation, abnormal blood gases were present in only 6 of 14 patients and chest x-ray was positive in 7. Pulmonary angiography was performed in 11 of 14 patients with positive contrast echocardiography, and all 11 had A-V malformation identified. In patients with 3 to 4+ left ventricular opacification (n = 8), large (>5 mm feeding vessel) or multiple malformations were present, whereas patients with small or isolated malformation had 1 to 2+ left ventricular opacification. Balloon occlusion of malformations was performed in all 11 of these patients; repeat contrast echocardiography revealed significant diminution of right-to-left shunt in 9, and 2 required repeat embolotherapy for an additional previously undetected A-V malformation. Thus, contrast 2-dimensional echocardiography is extremely sensitive for the identification of pulmonary A-V malformation.

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The diagnosis of congenital pulmonary arteriovenous (A-V) malformation associated with hereditary hemorrhagic telangiectasia may be unsuspected, particularly when clinical signs of dyspnea, epistaxis or hypoxemia at rest are not present.1–3 Typically, confirmation of the diagnosis of pulmonary A-V malformation necessitates pulmonary angiography.4–6 Early reports described the use of contrast M-mode echocardiography to detect pulmonary A-V malformation.7–10 After peripheral intravenous injections of agitated saline solution, microcavitations are seen in the left atrium and ventricle after a predictable delay. Two-dimensional echocardiography has major advantages over M-mode techniques and provides direct visualization of the site of appearance of the contrast agent. We studied the accuracy of contrast 2-dimensional echocardiography for the detection of pulmonary A-V malformation and compared the results with those obtained in patients with intraatrial right-to-left shunt. We also examined use of this technique for follow-up of patients with pulmonary A-V malformation after embolotherapy.

METHODS

The study group consisted of 29 patients (17 men and 12 women). Nineteen patients had phenotypic Osler-Weber-Rendu syndrome. Four patients were index cases (i.e., they were known to have Osler-Weber-Rendu syndrome and were suspected to have pulmonary A-V malformation on the basis of radiography or clinical presentation). Fifteen patients were first-degree relatives of the index cases. They were diagnosed consecutively as they presented for screening. Ten patients with atrial right-to-left shunt due to patent foramen ovale (n = 8) or secundum atrial septal defect (n = 2) who had been previously studied were used as control subjects. Patients with patent foramen ovale exhibited
marked bowing of the intraatrial septum, and those with atrial septal defects had easily identified defects from the subcostal views. All patients underwent standard 2-dimensional echocardiography, including parasternal, apical and subcostal views. In each patient, a peripheral intravenous line (19 gauge butterfly) was established in an antecubital vein, and 2 to 10 ml syringes were connected by a 3-way stopcock. One syringe contained 10 ml of saline solution; a small amount of air (0.2 ml) was introduced into the other syringe. After agitating the saline solution for 10 seconds, a forceful hand injection was performed with simultaneous 2-dimensional imaging in an apical 4-chamber view.

Contrast 2-dimensional echocardiograms were analyzed for the time delay (in frames) between appearance of microcavitations in the left atrium and initial appearance in the right atrium. Relative opacification of the left ventricle was qualitatively assessed on a scale of 1 to 4+. Evidence of minimal left ventricular microcavitations was graded 1+, moderate microcavitations 2+, extensive microcavitations without outlining the endocardium 3+ and extensive microcavitations with clear endocardial definition 4+. Heart rate was measured as the RR interval in milliseconds.

In each of the patients with pulmonary A-V malformation detected by contrast 2-dimensional echocardiography, the following clinical information was obtained from the patient record: presence and location of a bruit; evidence of telangiectasia; history of epistaxis or dyspnea; and history of neurologic events including cerebral abscess and vascular accident, transient ischemic attack and parasthesias in the extremities. Partial pressure of oxygen in the arterial blood at rest was measured, and the standard chest x-ray was reviewed for radiologic evidence of A-V malformation.

In all but 3 patients, diagnostic pulmonary angiography was performed to confirm presence, number and size of malformations. Pulmonary angiography was performed as a clinical diagnostic procedure in patients suspected to have pulmonary A-V malformation. This suspicion was based on symptomatology, radiography, positive echocardiogram, or abnormal room air or 100% arterial blood gases, as well as certain clinical syndromes suggesting that occult pulmonary A-V malformation might be present (i.e., stroke or brain abscess). Informed consent was obtained. Pulmonary angiography was performed with standard 6 and 7Fr pigtail catheters that were introduced into the right femoral vein using the Seldinger technique. The catheter was advanced into the left and right main pulmonary arteries with selective catheterization of pulmonary arterial branches with suspected A-V malformations. Standard cut film angiography was performed; digital subtraction angiography was also performed to supplement these angiograms, as necessary. In all patients with A-V malformation, size of the feeding vessel

**FIGURE 1.** A, apical 4-chamber view before contrast injection. B, same view after right atrial (RA) and ventricular (RV) opacification, with microcavitations evident in left atrium (LA) and ventricle (LV) after delay of 38 frames. C, same view approximately 5 seconds later demonstrating 4+ opacification of left ventricle.
supplying the malformation was measured in millimeters. Malformations with feeding vessels >3 mm were embolized using appropriately sized balloons or coils. Follow-up contrast echocardiography was obtained either at the site of angiography or within 24 hours after embolotherapy in all but 1 patient.

All values are reported as mean ± 1 standard deviation. Statistical analysis was performed using Student’s t test for unpaired data. Differences between the 2 groups were determined to be significant when p values were <0.05.

RESULTS

There were 14 (9 men and 5 women; mean age 37 years, range 23 to 58) of 19 patients with suspected pulmonary A-V malformation who had positive contrast echocardiograms (Figure 1). No complications were observed during or immediately after intravenous injections of the saline solution contrast in any patient. No significant differences in heart rate (R-R interval 804 ± 145 vs 730 ± 156 ms) or relative opacification of the left ventricle (2.9 ± 1.3 vs 2.8 ± 1.2) were noted between patients with A-V malformations and those with atrial right-to-left shunt. There was a significant difference (p <0.001) in number of echocardiographic frames to left atrial appearance of microcavitations after appearance in the right atrium (66 ± 27 frames in patients with A-V malformations vs 21 ± 7 frames in those with right-to-left shunt). In all patients with A-V malformations, left atrial microcavitations appeared at ≥35 frames, whereas in those with right-to-left atrial shunt they appeared within 30 frames of right atrial appearance.

Table I lists the clinical and laboratory findings in the 14 patients with pulmonary A-V malformations. Only 1 patient had auscultatory evidence of an A-V malformation, with a bruit evident in the lower left base. All but 1 patient had telangiectasia and epistaxis. A previous neurologic event was documented in 6 of 14 patients (cerebral abscess in 3, transient ischemic attack in 1, cerebral vascular accident in 1 and an episode of peripheral numbness in 1). Dyspnea was noted in 6 patients (4 only on exertion). The chest roentgenogram was suggestive in 2 patients and diagnostic in 5 with A-V malformations, and as a consequence of chronic liver disease.1-3 However, approximately 50% of pulmonary A-V malformations occur in individuals with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome).3

Pulmonary angiography was performed in 11 of 14 patients with positive contrast echocardiography, and all had angiographic evidence of A-V malformations. Angiography was not performed in 3 patients (1 refused and 2 had very small right-to-left shunt). A total of 23 malformations were detected in 11 patients; 7 had multiple and 4 had isolated malformations. The majority of A-V malformations (61%) were located in the lower lobes. Patients with 3 to 4+ contrast opacification of the left ventricle (n = 8) had large, isolated or multiple A-V malformations, whereas those with 1 to 2+ opacification (n = 3) had an isolated or small malformation with a feeding vessel <6 mm. Repeat contrast echocardiography immediately after embolotherapy or within 24 hours disclosed a residual right-to-left shunt in all patients; in 2 this shunting was so significant that repeat angiography was performed revealing an additional malformation not apparent during the initial study. These were small, but necessitated embolotherapy. The 1 patient who did not have follow-up contrast echocardiography had a residual large (12 mm feeding vessel) malformation that could not be embolized.

DISCUSSION

Intrapulmonary shunting has been described in patients with presumed congenital pulmonary A-V malformations, and as a consequence of chronic liver disease.1-3 However, approximately 50% of pulmonary A-V malformations occur in individuals with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome).3

Contrast M-Mode echocardiography has been used to diagnosis pulmonary A-V malformation in children and adults.7-10 However, because 2-dimensional echocardiography provides spatial orientation of the cardiac chambers, we investigated its application in separating patients with intraatrial from those with intrapulmonary shunts. Contrast 2-dimensional echocardiography provided accurate detection of pulmonary A-V malformation. The appearance of microcavitations in the left

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**TABLE I Clinical (radiologic and echocardiographic) Findings in Patients with Pulmonary Atrioventricular Malformations Due to Hereditary Hemorrhagic Telangiectasia**

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Sex</th>
<th>RR (ms)</th>
<th>Delay</th>
<th>Opac</th>
<th>PO2</th>
<th>CXR</th>
<th>Angio (feed vessel in mm)</th>
</tr>
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<tbody>
<tr>
<td>49F</td>
<td>+</td>
<td>620</td>
<td>40</td>
<td>2</td>
<td>77</td>
<td>NL</td>
<td>LLL (3)</td>
</tr>
<tr>
<td>27M</td>
<td>+</td>
<td>710</td>
<td>43</td>
<td>4</td>
<td>75*</td>
<td>LLL</td>
<td>—</td>
</tr>
<tr>
<td>30F</td>
<td>0</td>
<td>630</td>
<td>37</td>
<td>1</td>
<td>88</td>
<td>NL</td>
<td>—</td>
</tr>
<tr>
<td>31M</td>
<td>+</td>
<td>730</td>
<td>70</td>
<td>2</td>
<td>91</td>
<td>NL</td>
<td>RUL (3,5); RLL (3)</td>
</tr>
<tr>
<td>29M</td>
<td>+</td>
<td>710</td>
<td>50</td>
<td>4</td>
<td>73*</td>
<td>RML</td>
<td>RLL (3); RML (6,4)</td>
</tr>
<tr>
<td>44F</td>
<td>+</td>
<td>880</td>
<td>38</td>
<td>4</td>
<td>90</td>
<td>LLL</td>
<td>LLL (8)</td>
</tr>
<tr>
<td>29M</td>
<td>+</td>
<td>980</td>
<td>65</td>
<td>3</td>
<td>83</td>
<td>NL</td>
<td>LLL (8)</td>
</tr>
<tr>
<td>47M</td>
<td>+</td>
<td>930</td>
<td>83</td>
<td>4</td>
<td>58*</td>
<td>LLL</td>
<td>LLL (8,6); RLL (7,6,2)</td>
</tr>
<tr>
<td>33F</td>
<td>+</td>
<td>800</td>
<td>77</td>
<td>4</td>
<td>69*</td>
<td>RML</td>
<td>RML (8); LLL (2,5)</td>
</tr>
<tr>
<td>32M</td>
<td>+</td>
<td>910</td>
<td>109</td>
<td>1</td>
<td>88</td>
<td>NL</td>
<td>RLL (3)</td>
</tr>
<tr>
<td>56M</td>
<td>+</td>
<td>580</td>
<td>62</td>
<td>4</td>
<td>51*</td>
<td>RML</td>
<td>RML (12)</td>
</tr>
<tr>
<td>33F</td>
<td>+</td>
<td>840</td>
<td>57</td>
<td>3</td>
<td>81</td>
<td>NL</td>
<td>LLL (6), RML (7)</td>
</tr>
<tr>
<td>58M</td>
<td>+</td>
<td>1060</td>
<td>127</td>
<td>1</td>
<td>74</td>
<td>NL</td>
<td>—</td>
</tr>
<tr>
<td>29M</td>
<td>+</td>
<td>880</td>
<td>75</td>
<td>4</td>
<td>55*</td>
<td>RLL</td>
<td>RLL (6); R hilum (9); L hilum (2)</td>
</tr>
</tbody>
</table>

*Abnormal for patient age:

Angio = pulmonary angiogram; CXR = chest x-ray; L = left; LA = left atrium; LLL = left lower lobes; LV = left ventricle; NL = normal; Opac = opacification; PO2 = partial pressure of oxygen in arterial blood; R = right; RA = right atrium; RLL = right lower lobes; RML = right middle lobes; RUL = right upper lobe; Telang. = telangiectasia; 7 = possible; p = present; 0 = absent; — = not obtained.
atrium after initial appearance in the right heart was significantly delayed in patients with A-V malformation compared with that in those with right-to-left shunt at the atrial level.

The clinical sequelae of pulmonary A-V malformation vary, but the majority of patients experience symptoms. White et al. have reported epistaxis and dyspnea in 79 and 71%, respectively, of 76 patients with A-V malformations. Neurologic symptoms including transient ischemic attacks, stroke and cerebral abscesses were evident in 37, 18 and 9%, respectively of these patients. In our series, isolated or multiple clinical manifestations (epistaxis, neurologic events, dyspnea and abnormal chest x-ray) were evident in all but 1 patient, but chest x-rays were abnormal in only half the group. There were 2 patients without dyspnea, neurologic symptoms or abnormal chest x-rays, and 3 additional patients with only mild exertional dyspnea, but normal blood gases and chest x-rays. Thus, our group of patients illustrates the value of 2-dimensional contrast echocardiography for enhancing diagnostic confidence.

Pulmonary angiography remains the definitive method to locate pulmonary A-V malformation, and selective embolotherapy has proved to be an effective alternative to surgical resection. The goal of embolotherapy is to reduce neurologic complications of A-V malformations and to improve hypoxemia. In our series all but 3 patients underwent angiography, and embolotherapy was performed in 17 of 23 detected A-V malformations resulting in improved arterial oxygenation in all cases. Contrast echocardiography was also used to monitor the effectiveness of embolotherapy. All patients continued to have 2-dimensional evidence of a trivial right-to-left shunt after successful balloon embolization suggesting the presence of A-V malformations too small for angiographic visualization. Importantly, contrast echocardiography was extremely helpful in 2 patients with persistent, significant shunts. Repeat angiography revealed previously occult A-V malformations needing further embolotherapy.

Study limitations: Contrast 2-dimensional echocardiography allows separation of intracardiac from intra-pulmonary right-to-left shunt, but definitive conclusions regarding sensitivity in the diagnosis of A-V malformation cannot be made from this investigation, because pulmonary angiograms were not obtained in patients with hereditary hemorrhagic telangiectasia and negative contrast echocardiographic studies. However, it was significantly more sensitive than chest radiography. Although a trend toward greater opacification of the left heart (3 to 4+) was observed in patients with multiple or large, isolated A-V malformations (feeding vessel >5 mm), 2-dimensional echocardiography cannot determine whether multiple A-V malformations are present, nor can it localize the site of the A-V malformation. We carefully reviewed studies to attempt to correlate location of the pulmonary veins with the appearance of microcavitations in the left atrium, but were unable to localize inflow to determine right versus left lung or upper versus lower lobes. Recent investigations have suggested that gradient echo magnetic resonance imaging may be another alternative for the detection of pulmonary A-V malformations. However, the expense of magnetic resonance imaging still makes contrast echocardiography a valuable, readily available noninvasive tool.

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REFERENCES