Contrast echocardiography for detection of pulmonary arteriovenous malformations

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Background Pulmonary arteriovenous malformations (PAVMs) lead to stroke, brain abscess, and hemorrhage in hereditary hemorrhagic telangiectasia (HHT). The current screening approach for PAVMs in HHT patients with chest radiograph (CXR) and oxygen shunt study has not been validated and is thought to be insensitive. We hypothesized that agitated saline contrast echocardiography (ECHO) would be a useful screening test for PAVMs.

Methods and results A total of 106 sequential HHT patients underwent screening for PAVMs with ECHO in a prospective study. If the test was positive, or if the CXR or shunt study suggested PAVMs, pulmonary angiography was performed. A positive ECHO was defined as appearance of bubbles in the left atrium after injection of agitated saline solution. A positive shunt study was defined as a partial pressure of oxygen in arterial blood <500 mm Hg while breathing 100% oxygen. The mean age was 41 years (range 15-80 years); 66% were female. Forty-four patients had positive ECHO. Forty-one of the 44 patients underwent angiography. Three patients declined further testing. Thirty-three of the 41 patients who underwent angiography were diagnosed with PAVMs. Of the 62 patients with a negative ECHO, 18 underwent angiography because of either a shunt study or CXR that was suggestive of PAVMs. Of these 18 patients, 2 had PAVMs. In the total population of 106 patients, 35 (33%) had PAVMs. ECHO was the only positive screening test in 11 of 35 (31%) patients. The diagnosis of PAVMs in these 11 patients would have otherwise been missed.

Conclusions ECHO is a useful screening tool for PAVMs in HHT. (Am Heart J 2001;141:243-6.)
and were prospectively screened for PAVMs. The ECHO protocol was approved by the ethics committee at St Michael’s Hospital. One hundred six consecutive HHT patients referred to the Toronto HHT Clinic between February 1998 and June 1999 were screened for PAVMs with ECHO. All patients had clinical evaluation, CXR, and arterial blood gas on room air and 100% oxygen (shunt study). If the ECHO was positive, the patient underwent pulmonary angiography. In the group of patients with negative ECHO, pulmonary angiography was performed if the CXR suggested PAVMs or if the arterial blood gases suggested right to left shunting. The CXR was interpreted by radiologists experienced in identifying PAVMs. Patients who had been previously treated for PAVMs underwent the same screening tests to detect residual patent PAVMs.

**ECHO**

Standard echocardiography was performed on all patients. Particular attention was paid to identifying an intracardiac cause of shunting. In each patient a 19-gauge, 1-inch intravenous line with a saline lock was placed in the forearm. A forceful hand injection of 10 mL of agitated saline solution was performed while images were obtained simultaneously in the apical four-chamber view.

A positive ECHO was defined as appearance of bubbles in the left atrium after 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 resulting from a patent foramen ovale (PFO) or atrial septal defects (ASD). Two cardiologists, blinded to the clinical history, arterial blood gas, CXR, and pulmonary angiography results, reviewed ECHO films independently.

**Shunt study**

Initially a room air arterial blood gas was obtained from the radial artery. The patient then breathed 100% oxygen for 20 minutes, after which another arterial blood gas was obtained. A positive shunt study was defined as an arterial blood gas with a partial pressure of oxygen in arterial blood <500 mm Hg on 100% oxygen. This cutoff value was based on a receiver-operating characteristic curve interpreted to optimize sensitivity on the basis of local results.

**Pulmonary angiography**

Patients underwent conventional pulmonary angiography with a 7F catheter that was introduced into each pulmonary artery under fluoroscopic guidance through the common femoral vein. A total dose of 40 to 60 mL of iodinated contrast material was injected for each arteriographic run, at a rate of 20 to 30 mL per injection. Multiple injections and magnification views were used as necessary.

**Results**

The majority of patients screened were female (66%). The mean age was 41 years (range 15-80 years). Ten of the 106 patients who were screened had previously been diagnosed with PAVMs and treated with transcatheter embolotherapy.

Forty-four of the 106 patients screened had a positive ECHO. Forty-one of the 44 patients underwent pulmonary angiography; 3 declined further investigation. Thirty-three were diagnosed with PAVMs on angiography. Eight patients with positive ECHO had no PAVMs on angiography. Of these 8 patients, 2 had an ASD. None of the 8 patients had been previously treated for PAVMs. In the total population of 106 patients 35 (33%) had PAVMs. ECHO was the only positive screening test in 11 of 35 (31%) patients with PAVMs.

In the 62 patients with a negative ECHO, 18 patients underwent pulmonary angiography because of either a shunt study or a CXR that was suggestive of PAVMs, and 1 refused angiography. Of these 18 patients, 2 had PAVMs by pulmonary angiography (Figure 1).

In the total screening population of 106 patients there were 10 patients (9%) who had a PFO or an ASD. Of these 10 patients, 7 had a positive ECHO, of whom 5 patients had PAVMs by pulmonary angiography.

The interobserver variability (κ = 0.926) for identifying microcavitation in the left atrium was excellent between the two cardiologists. No complications occurred during the ECHO.

**Discussion**

Independent of symptom status, HHT patients with PAVMs are at risk of serious complications, including hemorrhage, stroke, and brain abscess. It is recommended that these patients undergo transcatheter embolotherapy. Although various screening tests are available for PAVMs, the literature does not specify the optimal screening protocol. This study demonstrates that ECHO is useful in detecting patients with PAVMs. A significant proportion of additional cases are detected and few cases are missed on the basis of comparison with CXR and shunt test. ECHO is simple, safe, noninvasive, and widely available. These qualities, in addition to the low false-negative rate compared with conventional screening methods, make ECHO an excellent screening test for PAVM.

There are no screening studies evaluating CXR or shunt test compared with a reference standard in consecutive patients. Haitjema et al used a stepped protocol in a population of patients referred for screening. Patients were prescreened with arterial blood gas and if this was abnormal had an arterial blood gas on 100% oxygen. Only those patients with an abnormal shunt test underwent pulmonary angiography. Those patients with a normal shunt test were not evaluated by any other modality.

The 33% prevalence of PAVMs in our population is greater than in previous studies. This may be because ECHO is more sensitive than other screening tests, although we cannot rule out referral bias. Barzilai et al studied 19 nonconsecutive patients with suspected PAVMs who were referred for management. Eleven of
the 14 with positive ECHO proceeded to pulmonary angiography and all 11 patients had PAVMs. In this study the patients with negative contrast echo were not included for analysis. A more recent study reported the performance of screening tests such as CXR and arterial blood gas in a group of HHT patients with positive findings on ECHO. Of the 25 nonconsecutive HHT patients with positive ECHO, 15 had PAVMs. In 10 patients, no PAVMs were demonstrated on pulmonary angiography. In this study the authors assumed the sensitivity of ECHO to be 100% because the patients with negative ECHO were not evaluated or reported. Although the performance of ECHO was never evaluated, the authors concluded that initial screening with ECHO followed by shunt test seemed to be the best screening procedure for patients with PAVM.

Our study included patients who did not have a positive ECHO. All patients had a CXR and arterial blood gas analysis on room air and 100% oxygen, regardless of the status of the ECHO. We feel that this was necessary to evaluate the sensitivity of ECHO and that it is superior to the method used in previous studies. We identified 2 patients in the screening population who had a negative ECHO but were diagnosed with PAVMs. This illustrates that, although the sensitivity of ECHO is high, it is not 100%. In the total population screened, 8 patients did not demonstrate PAVMs at angiography despite ECHO positivity. It is possible that very small PAVMs are present but are not detectable by diagnostic pulmonary angiography. We will follow these patients closely for the growth of detectable PAVMs. Although 2 of the 8 patients with false-positive ECHOs had an ASD, in both cases, surprisingly, contrast appeared late in the left atrium. Because the prevalence of ASD in our population is 9% and is in keeping with the incidence of ASD in the general population, it is unlikely that the remainder of the patients with false-positive ECHO actually have an ASD.

Clinical implications
Given the morbidity of PAVMs and the availability of effective therapy, it is important to screen patients with HHT. This study demonstrates that ECHO is a useful screening test for PAVMs. The availability, simplicity, and noninvasiveness of ECHO make it a feasible screening test. It is more sensitive than conventional screening methods and therefore should be included in the screening regimen.

Limitation
The most important limitation is the nonuniform use of a reference standard. In the ECHO-negative group, only the patients with a positive CXR or an abnormal shunt test underwent pulmonary angiography. We believe it is unwarranted to subject healthy individuals who are asymptomatic to an invasive procedure such as pulmonary angiography when all screening tests are negative. As a result of the above limitation, we did not report sensitivity and specificity values for the ECHO. We hope to follow these patients, especially those with negative ECHO, for development of PAVMs or their complications over time. This would provide us with a longitudinal reference standard in the test-negative
groups, enabling us to report sensitivity and specificity at a later time.

References