result than that reported in this series. The study also raises several questions. (1) Does epoprostenol therapy worsen the reperfusion pulmonary edema that occurs after successful PTE? The authors gradually weaned patients from epoprostenol therapy over a 1-week period postoperatively, yet permanent discontinuation once cardiopulmonary bypass is initiated may be considered as an alternative. We employ this approach at our center for patients with pulmonary hypertension who are receiving epoprostenol and undergo lung transplantation in an attempt to minimize postimplantation injury. (2) Are new, less invasive treatment modalities that are effective in patients with other forms of pulmonary hypertension comparably effective in the preoperative management of CTEPH? Bosentan (Actelion; Allschwil, Switzerland; and Genentech; South San Francisco, CA), the newly approved nonselective endothelin-receptor antagonist is orally active, and Iloprost is a prostacyclin analog that can be administered by nebulization. (3) Who are the best candidates for “epoprostenol bridge therapy,” and what is the optimal period of therapy before performing PTE? These questions can be addressed by clinical trials at large medical centers that have expertise in treating patients with this condition.

The development of the surgical techniques for PTE was a major advance in the treatment of patients with CTEPH. We recognize the challenge, and welcome the opportunity, to improve the medical management of this condition as well.

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References


The Role of Echocardiography in Screening for Pulmonary Arteriovenous Malformations

Pulmonary arteriovenous malformations (PAVMs) represent a direct communication between one or more pulmonary arteries and one or more pulmonary veins. Common anatomic forms include single sacs ranging from 1 to > 10 cm in diameter, macroscopic tangles, and microscopic telangiectases. The main complications of PAVMs are believed to relate to right-to-left shunting of blood through the PAVM and include stroke and brain abscess, which together occur in up to one half of patients if untreated. Other potentially serious complications include refractory hypoxemia, hemoptysis, and hemotherax. Fortunately, nearly all of these complications can be prevented by embolization of the feeding arteries (transcatheter embolotherapy [TCET]). PAVMs are associated with underlying hereditary hemorrhagic telangiectasia (HHT) in up to 90% of cases. Conversely, at least 30% of patients with HHT will also have PAVMs. In order to prevent the complications noted above, various screening strategies for PAVMs have been proposed in patients with known HHT or their undiagnosed relatives. The main screening tests are reviewed in the following paragraphs.

Contrast transthoracic echocardiography (TTE) is performed by IV injection of echocardiographic con-
contrast while visualizing the atria. In the case of PAVM, contrast appears in the left atrium 2 to 5 s after it is seen in the right atrium. Nanthakumar and colleagues\textsuperscript{5} screened 106 HHT patients with contrast TTE, oxygen shunt test, and chest radiography. All patients with one or more positive screening test results underwent standard pulmonary angiography. Contrast TTE findings were positive in 33 of 35 patients with PAVMs (94% sensitivity), and was the only positive test result in 11 patients with PAVMs; it is unknown what proportion of these PAVMs were amenable to TCET. In a study by Kjeldsen and colleagues,\textsuperscript{4} 48% of HHT patients with a positive contrast TTE result were found to have PAVMs that were amenable to TCET. Overall, contrast TTE has the advantages of exquisite sensitivity and good availability, but is fairly expensive and lacks specificity for treatable PAVMs.

Right-to-left shunt can be calculated by the oxygen shunt test (OST) by measuring a single arterial blood gas after a patient breathes 100% oxygen for 15 to 20 min. In a small screening study, Haitjema and colleagues\textsuperscript{2} found the OST to have a sensitivity of 85% for PAVM. Kjeldsen and colleagues\textsuperscript{4} evaluated various screening procedures in 25 patients with HHT who had a positive contrast TTE result; 15 patients had PAVMs by angiography. A $\text{PaO}_2 < 500 \text{ mm Hg}$ during an OST had a sensitivity of 100% and a specificity of 40%. Since they evaluated only patients with a positive contrast TTE result, the true sensitivity and specificity in a screening population are unknown. However, in a review of the literature, a shunt of $> 5\%$ by OST was seen in 97.5% of patients who had a PAVM large enough for TCET.\textsuperscript{1} The OST has the advantages of low expense and universal availability, but may overestimate shunt if technique is not adhered to.\textsuperscript{1} Some investigators have considered the OST to be invasive, but it is really only slightly more invasive than the other two screening tests that require an IV injection. Measurement of $\text{PaO}_2$ while breathing room air or use of pulse oximetry has inadequate sensitivity for screening.\textsuperscript{4}

Radionuclide perfusion lung scanning (PLS) can be used to estimate shunt after IV injection of radionuclide labeled macroaggregated albumin by measuring differential perfusion to the lungs vs either brain or kidneys. It shows excellent agreement with the percentage of shunt determined by OST.\textsuperscript{8} Thompson and colleagues\textsuperscript{3} evaluated 66 patients after TCET for PAVMs. Forty patients had small residual PAVMs with feeding arteries $< 3 \text{ mm}$, while 26 patients had no residual PAVMs. In patients with residual PAVMs, PLS demonstrated a mean shunt of 9.3%. A shunt $> 3.5\%$ was 87% sensitive and 61% specific for residual PAVM. This method would almost certainly be even more sensitive for detecting larger PAVMs prior to TCET. Radionuclide perfusion lung scanning and contrast TTE have the advantage of being fairly specific for anatomic shunt (in contrast to OST, which does not discriminate between anatomic and physiologic shunt). Because it is quantitative, PLS could theoretically show improved specificity over contrast TTE for treatable PAVM; however, PLS is not widely available and is also expensive.

In this issue of CHEST (see page 351), Lee and colleagues (see page 342) report on the use of contrast TTE in the follow-up of 39 patients after TCET. The authors screened all referrals to their HHT clinic for PAVMs with chest radiography, OST, and contrast TTE, and subsequently performed pulmonary angiography in all patients with one or more positive screening test result. Contrast TTE was 100% sensitive in detecting PAVMs vs the OST, which was only 59% sensitive. Twenty-nine patients underwent contrast TTE both before and after TCET. Although all PAVMs with feeding arteries $\geq 3 \text{ mm}$ were successfully occluded during TCET—an average of five PAVMs per patient—52% of patients had residual PAVMs with feeding arteries $< 3 \text{ mm}$. Following TCET, contrast TTE remained positive in 90% of patients while the OST result was positive in 27%. The results were not significantly different for those with and those without residual PAVM. The authors nicely reviewed and addressed potential limitations of their study, the most important being that only 29 of the 43 patients undergoing TCET had pre-TCET and post-TCET echocardiograms. They concluded that contrast TTE findings remain positive in most patients after TCET, suggesting the presence of at least microscopic PAVMs even in those without residual PAVMs on angiography.

This is a well-done study that makes an important contribution to the literature on screening of HHT patients and follow-up strategy for patients with known PAVMs. It confirms the high sensitivity of contrast TTE in detecting PAVM. It also confirms the widely-held suspicion that patients often demonstrate persistent shunt after successful TCET. The only criticism I have of their study relates to the cutoff used for the OST, which was based on optimal accuracy from a receiver operator characteristic curve. They chose an alveolar-arterial gradient of 175, which equates to a $\text{PaO}_2$ of approximately 488 mm Hg and a shunt of approximately 9.5%.\textsuperscript{1} Since numerous studies have shown that patients with treatable PAVMs may have a shunt at least as low as 5%, their cutoff was predestined to “stack the deck” against the OST. Although a grading system has not yet been proposed for estimating shunt during contrast TTE, it seems likely that lower
grades would be associated with less shunt and less clinical significance, as is the case for the OST. If they had used a $P_{aO_2}$ of 575 mm Hg (which equates to a shunt of approximately 5%) for their cutoff, they may have picked up more PAVMs during the screening process, which may have affected the sensitivity of contrast TTE.

There are several problems with interpretation of the current literature on screening for PAVM. First, all screening studies have lacked a control group without suspected HHT or PAVMs, and therefore true specificity cannot be determined. Second, no study has subjected all screened patients to standard pulmonary angiography; therefore, the true sensitivity for treatable PAVM cannot be determined.

Based on current data, I believe that contrast TTE is the best initial screening test due to its excellent sensitivity and availability. If the result is negative, the likelihood of significant PAVM is low. If suspicion for PAVM remains high despite a negative contrast TTE result, additional screening tests could be performed. If the contrast TTE result is positive, the patient is very likely to have at least microscopic PAVMs. Current contrast TTE techniques are not quantitative, however, and therefore do not predict the amenability of PAVMs to TCET. I can envision three general approaches to patients with a positive contrast TTE result. The most aggressive approach would subject all such patients to standard pulmonary angiography. A middle approach would subject all patients to contrast CT angiography followed by standard pulmonary angiography when the CT finding is positive for significant PAVMs. A conservative approach might involve additional testing to determine the likelihood that the PAVMs are amenable to TCET. This testing could include chest radiography, OST, PLS, CT angiography, or MRI; patients with a second positive test result would then undergo standard pulmonary angiography. Which of these approaches has the optimal accuracy, clinical benefit, and cost-effectiveness cannot be determined from current data. Alternatively, if cost is a concern, initial screening could be done with the OST, followed by either contrast TTE or PLS.

What about follow-up after TCET? Lee and colleagues recommended life-long follow-up and antibiotic prophylaxis in patients with a persistently positive contrast TTE findings after TCET. I would go one step further. Since at least 90% of patients with HHT and PAVMs will have a persistently positive contrast TTE findings, and since the natural history of those with a negative contrast TTE result is unknown, I would actually recommend long-term follow-up and antibiotic prophylaxis in all patients with HHT and PAVMs. The other goal of follow-up is to detect development of PAVMs that are amenable to TCET. I recommend the OST for this goal since it is fairly sensitive to treatable PAVMs, but not so sensitive that it picks up all PAVMs.

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Pembrey’s Dream

The Time Has Come for a Long-term Trial of Nocturnal Supplemental Nasal Oxygen to Treat Central Sleep Apnea in Congestive Heart Failure

In 1907, Pembrey showed that supplemental nasal oxygen improved Cheyne-Stokes respiration in patients with congestive heart failure (CHF). Almost 100 years have passed, and there has been no long-term trial to determine whether treatment of central sleep apnea (CSA) with oxygen improves the natural history of CHF! Yet, CHF is highly prevalent and carries a poor prognosis, and CSA could be a potential contributory cause. Meanwhile, there are