up, as noted by the authors of the report under discussion. Whether these trials will be possible remains open to question. Such trials would be required should be considered by various cooperative groups in an effort to answer the appropriate questions raised by the descriptive studies currently available.

Richard J. Thurer, MD, FCCP
Miami, FL

Dr. Thurer is Professor of Surgery, Division of Cardiothoracic Surgery, University of Miami School of Medicine. Correspondence to: Richard J. Thurer, MD, FCCP, Division of Cardiothoracic Surgery, University of Miami (RI14), PO Box 018960, Miami, FL 22101-6960; e-mail: rthurer@mednet.med.miami.edu

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Re-emergence of an “Orphan” Test for Pulmonary Embolism

Often clinically suspected, pulmonary embolism (PE) is a potentially fatal disease. Because highly effective but hazardous therapy exists, accurate diagnosis is extremely important. Indeed, much of the research and publications on PE, such as the Prospective Investigation of Pulmonary Embolism Diagnosis study, pertain mainly to methods of diagnosis.

Prior to the development of imaging techniques, the diagnosis of PE was based on a triad of dyspnea, hemoptysis, and chest pain, later shown to be nonspecific and unreliable, for the clinical spectrum can range from no symptoms at all to sudden death. The chest radiograph has been equally nonspecific and unreliable in diagnosis of PE.

In 1959, turning to the burgeoning field of clinical pulmonary physiology, Eugene Robin et al suggested, “a physiologic approach to the diagnosis of pulmonary embolism” based on the Bohr equation. The simple concept utilized was that embolized parts of the lung are ventilated but not perfused so that alveolar CO2 tension in these areas is low. Mixing of gas from perfused and unperfused units leads to an alveolar (measured as end-tidal) PCO2 abnormally lower than arterial PCO2. In practice, an arterial-alveolar CO2 gradient of > 5 mm Hg was considered abnormal. In 10 patients with clinically suspected PE studied by Robin et al, a gradient of that magnitude was found in 7 patients (and in 5 of 10 patients in a subsequent publication from the same institution). The authors stated that this test is useful to diagnose large emboli only. They also indicated that the test is nonspecific and could be abnormal in the presence of rapid, shallow breathing of any cause, or a variety of other lung diseases.

In 1962, Colp and Williams reported an arterial-alveolar (A-a) gradient of > 5 mm Hg in only three of seven patients with clinical diagnosis of PE. These patients were studied more than a week after onset of symptoms, and it was pointed out that with time both clot lysis and collateral circulation would minimize the gradient. In support of this, one of the patients was restudied after another PE had occurred, and his A-a gradient was abnormal. Also, decreased ventilation due to atelectasis, bronchoconstriction, pleurisy, or infarction would diminish the gradient.

Hatle and Rokseth studied patients whose diagnosis was confirmed by angiogram or at postmortem. They also noted lack of an abnormal A-a gradient with small emboli or with passage of time since embolization; however, all but one of their patients with large PE had gradients > 5 mm Hg. These authors note that false-positive results in patients with COPD, pneumonias, congestive heart failure, or nonembolic shock could be corrected by having the patient expire fully and using end-expired rather than end-tidal CO2 measurement in the calculation. (A significant difference between end-tidal and end-expired CO2 is due to uneven ventilation and should not occur in normal subjects or those with PE).

Due to all of these problems with the alveolar dead space test proposed by the late Dr. Robin, in 1977 he eschewed it. He wrote an editorial titled, “The Emperor May Have No Clothes,” in which he discussed overdiagnosis of PE, overreliance on the then-popular ventilation-perfusion scan (which is merely an imaging method of detecting alveolar dead space), and the need for frequent pulmonary angiography. In this editorial, he did not even mention capnographic measurement of alveolar dead space or CO2 gradient! Therefore, this test, which he fathered, now became an “orphan” test.

More recently, in 1986, Burki resurrected the orphan but calculated physiologic dead space based on expired CO2 instead of alveolar. They reported a dead space ratio of > 40% in all of 16 patients with abnormal angiograms. Twenty-nine patients with normal perfusion lung scan results had either normal dead space ratio or abnormal spirometry findings (thought to represent some lung disease other than...
Pe). In fact, many patients with PE will be unable to perform spirometry or will have abnormal spirometry results, perhaps due to splinting, pleurisy, etc.

In the 1990s, the orphan test has been adopted in a new way. Proposed by Kline et al. (1997), the alveolar dead space calculation, based on arterial and end-tidal CO2, is used only to exclude PE. In order to improve sensitivity, a rather low limit of 15% is set for an abnormal result, and the test is combined with the D-dimer determination, which also has a low specificity but good sensitivity. By combining the two tests, both of which are performed in the emergency department or hospital bedside, it is hoped that PE can be ruled out with enough confidence in many patients so as to obviate the need for the more expensive, time-consuming radiologic tests that are often difficult to arrange. Theoretically, this certainly sounds like a very good idea. However, further testing is necessary to ensure that small emboli are not missed by this technique, as patients with small emboli still must be treated to prevent recurrence, with its attendant morbidity and possible sudden mortality.

Also, as the authors point out, the capnographic studies require a fairly cooperative patient who can achieve a steady state, careful calibration of the equipment, and staff experienced with this test available on all shifts. In practice, each institution would have to validate this testing initially with full workup of all patients, both positive and apparently negative. Finally, another problem may prevent re-adoption of this orphan: unlike the well-established radiologic procedures, capnographic studies might present billing difficulties for some institutions.

Charlotte Colp, MD, FCCP
Albert Einstein College of Medicine
New York, NY
Myron Stein, MD, FCCP
UCLA School of Medicine
Los Angeles, CA

Dr. Colp is Clinical Associate Professor of Medicine, Albert Einstein College of Medicine; and Dr. Stein is Clinical Professor of Medicine, UCLA School of Medicine.

Correspondence to: Charlotte Colp, MD, 133 East 73 St, New York, NY 10021

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Should Echocardiography of the Right Ventricle Help Determine Who Receives Thrombolysis for Pulmonary Embolism?

Readers who think they know the answer to this question should read the carefully analyzed patient series of Hamel and colleagues published in this issue of CHEST (see page 120), and then think again.

In recent years, champions of thrombolytic therapy for patients with pulmonary embolism have identified a patient subset without gross hemodynamic compromise (shock) but having subclinical, echocardiographically identifiable, right ventricular (RV) dysfunction.1–3 Several articles1,2 have concluded that thrombolytic therapy saves lives in this group. Another thoughtful analysis4 concluded that evidence for benefit of thrombolytic therapy in the absence of shock is lacking. Can we draw a conclusion about what might be the truth? It is useful to break the question into two questions: (1) should identifying RV dysfunction (recently termed “submassive” pulmonary embolism) in the absence of shock (“massive pulmonary embolism”) make a difference in patient management, and (2) is thrombolytic therapy that difference, ie, is it a necessary-unless-contraindicated management strategy for these patients?

It would be reasonable to deduce that a poorly functioning right ventricle at the time acute pulmonary embolism is discovered portends a worse prognosis, whether the functional impairment is completely new, partially new, or chronic and predating the embolism. Pulmonary hypertension with RV dysfunction identifies a sicker patient whether the disease of concern is congestive heart failure,5 respiratory insufficiency waiting for lung transplant,6 or