

Imaging of Pulmonary Embolism Too Much of a Good Thing?

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THE STUDY BY ANDERSON AND COLLEAGUES¹ IN THIS ISSUE OF *JAMA* convincingly demonstrates that computed tomographic pulmonary angiography (CTPA) is not inferior to ventilation-perfusion (\dot{V}/\dot{Q}) lung scanning for the exclusion of pulmonary embolism (PE). Confirmation on this point is comforting because CTPA has had a wide range of sensitivities reported for detection of PE² but nevertheless has largely supplanted \dot{V}/\dot{Q} scanning for several years for this purpose.³

This study is also notable for a number of additional reasons. First, the investigators' study design and management algorithms use D-dimer testing,⁴ structured pretest probability (of PE) assessment,⁵ and venous ultrasound of the lower extremities to identify deep venous thrombosis. In essence, the study represented a unique head-to-head comparison of \dot{V}/\dot{Q} scanning and CTPA conducted in a manner that duplicated real-world best-practice conditions. Moreover, because this was a multicenter randomized study with a large number of participants, these results can be confidently generalized. In addition, a large proportion of study participants having a technically adequate CTPA study (73%) were imaged using a multidetector CT scanner. This fact is important because multidetector-row CT is rapidly supplanting single-slice CTPA, in part as a technological response to concerns that single-slice scanners were relatively insensitive to and missed small clots in the distal (ie, subsegmental) pulmonary vasculature.⁶ Indeed, one of the principal arguments against the general use of earlier generation CTPA for the exclusion of PE was a perceived lack of sensitivity for detecting such clots.⁷ The study by Anderson and colleagues¹ indicates that this is no longer an issue, at least at the level of detection of \dot{V}/\dot{Q} scanning, long the first-line imaging technique for this purpose.

As often happens with research, this new study raises some additional and important questions. Chief among these is whether CTPA, if not inferior to \dot{V}/\dot{Q} , is it actually superior or even too good as a first-line imaging modality for patients suspected of having PE? Consider the implications of state-of-the-art CTPA scanning. On the positive side, in addition to sensitivity, CTPA has good interreader agree-

ment,⁸ is highly specific for pulmonary emboli,^{6,9} and eliminates some of the subjectivity and confusion associated with \dot{V}/\dot{Q} scan interpretation expressed in probabilities of PE. Computed tomographic pulmonary angiography can also identify alternative explanations for symptoms even as emboli are excluded¹⁰ and may provide additional important clinical information on the cardiac impact of emboli that can guide management decisions.¹¹

Less desirable attributes of CTPA are the requirement for dye with its attendant risk of allergic reactions and contrast nephropathy and the substantially greater radiation exposure of CTPA compared with \dot{V}/\dot{Q} scanning.¹² A more subtle issue is also raised by the data reported by Anderson et al. Specifically, CTPA may well lead to more diagnoses of PE than \dot{V}/\dot{Q} scanning. This is suggested by significantly more patients in the CTPA group than the \dot{V}/\dot{Q} scan group being diagnosed with PE (a statistically significant difference) and by the fact that several patients who crossed over to CTPA after having PE excluded by \dot{V}/\dot{Q} scanning were found to have PE. Why might this be a problem? Hypothetically, if CTPA identifies clots that are not likely to be of clinical significance and if patients with such clots are then treated for them, these patients are being unnecessarily exposed to the risks of anticoagulation and to the implications of carrying a history of PE. Moreover, society has to deal with the considerable costs associated with all of this.

Is it possible to have clinically insignificant PE? Presumably, the clots most likely to be insignificant would be small and would involve only a relatively small proportion of the distal pulmonary vasculature. Indeed, about 7% of the patients diagnosed with emboli using CTPA by Anderson and colleagues had isolated subsegmental pulmonary artery involvement. This is similar to the distribution reported in other studies.^{13,14} However, complicating matters is an analysis indicating that patients with such clots may have a very different clinical presentation than patients with larger clots; they are less likely to have new or worsening dyspnea, or to have proximal deep vein thrombosis detected by ultrasonography and are more likely to be assigned a low clinical (ie, pretest) probability

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of having PE.¹⁵ Such patients are also more likely to have negative D-dimer assays.¹⁶ This profile might well have caused such patients to have been overlooked or excluded from many studies of PE and possibly to be undercounted; the 7% estimate of subsegmental vessel emboli may well be an underestimate.

So just how risky are isolated subsegmental pulmonary emboli? Two recent reviews have assessed the limited available data addressing this issue.^{15,17} They suggest that a subset of patients with good cardiopulmonary reserve, no evident deep vein thrombosis, and limited predisposition to subsequent thromboembolism may not require anticoagulation for isolated subsegmental PE. However, overlooking potentially significant pulmonary emboli carries its own set of issues as exemplified by the 8 participants in the study by Anderson et al, some of whom may have had clots missed by CTPA or V/Q scanning but who subsequently developed evident venous thromboembolism including one fatal episode.

What are the clinical implications of these findings, and how should this information be considered in patient management decisions? First, clinicians should consider the likelihood of PE in a structured manner based on patients' presenting histories and physical examinations much the way Anderson and colleagues did, and based on those assessments, proceed, as necessary, to D-dimer testing. These 2 steps may substantially reduce the probability that PE, at least large clots, are present¹⁸ and obviate the need for additional study. Where significant concern remains, including some patients whose PE probability may not be very high but whose comorbidities put them at great risk were an embolism to occur, additional testing should be pursued. If readily available, lower extremity ultrasound studies to search for deep vein thrombosis to treat those patients found to have such clots is a reasonable next step. If deep vein thromboses are excluded or if ultrasound is not immediately available, then imaging of the chest is indicated. At the current state-of-the-art CTPA, using multidetector scanners, appears to be an excellent imaging choice unless there is a contraindication to dye administration or, perhaps, in pregnancy because of the higher dose of radiation with CTPA. For patients who cannot be studied by multidetector-row CTPA, V/Q scanning would still be available. Of note, there is no evidence from the study by Anderson et al¹ that single-detector scans are superior to V/Q scan.

In addition, more in-depth understanding is needed about distal subsegmental clots. For example, what is the natural history of such clots? Do subsets of patients with such clots share easily identified characteristics that put them at higher or lower risk of adverse outcomes? Is there still a role for conventional angiography? Answers will require additional clinical studies, likely involving multiple centers given the relatively small proportion of patients affected. Whether

or not to treat some of these patients will have to remain a decision made on a case-by-case basis for now.

Thirty years ago, Robin¹⁹ opined that "the emperor of embolism has no clothes" because overestimates of PE prevalence and underutilization of available diagnostics led to overdiagnosis. Today, diagnostics are better and likely to offer more accurate prevalence estimates, but clinicians may not know just what to do with all this information. Available technology and well-designed trials should, however, provide answers to important questions about PE. In that sense, perhaps, the emperor is now partially clothed.

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