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The Use of Leg Venous Ultrasonography for the Diagnosis of Pulmonary Embolism

David R. Anderson, MD, FRCP(C),* and David Barnes, MD, FRCP(C)†

The role of ultrasonography of the lower extremities for the evaluation of patients with suspected pulmonary embolism has become more clearly defined with time. Ultrasonography is a useful first-line test for pulmonary embolism in clinical circumstances in which radiographic imaging is contraindicated or not readily available (eg, pregnancy). Ultrasonography is likely not required for the evaluation of patients with suspected pulmonary embolism who have a negative computed tomography pulmonary angiography, particularly if there are no symptoms of deep vein thrombosis. Ultrasonography is helpful to exclude a diagnosis of deep vein thrombosis in patients who have nondiagnostic ventilation-perfusion scans. For patients with nondiagnostic ventilation-perfusion scans and negative ultrasonography who are considered clinically highly likely to have pulmonary embolism, it is recommended that computed tomography pulmonary angiography be performed.
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Pulmonary embolism is an important cause of morbidity and mortality.[1,2] The diagnosis of pulmonary embolism remains problematic because clinical symptoms and signs are mimicked by other disorders, pulmonary imaging procedures lack certainty, and patient comorbidities may limit the utility of certain tests.[1] The availability of a simple, accurate, noninvasive diagnostic test would be very beneficial to assist with the diagnosis of pulmonary embolism.

Compression ultrasonography is a well validated test for the diagnosis of deep vein thrombosis.[3-5] Given the close association between deep vein thrombosis and pulmonary embolism, there has been considerable interest in evaluating the utility of performing ultrasonography of the deep venous system of the lower extremities to assist with the diagnosis of pulmonary embolism.

In this article, the relationship between deep vein thrombosis and pulmonary embolism is reviewed, in addition to the rationale and evidence to support the use of diagnosing deep vein thrombosis with ultrasonography to ultimately assist with the management of patients with suspected pulmonary embolism. Finally, diagnostic algorithms for the investigation of patients with suspected pulmonary embolism focusing on the role of ultrasonography are presented.

*Departments of Medicine, Pathology and Community Health and Epidemiology, Dalhousie University and Capital Health, Halifax, Nova Scotia, Canada.

†Department of Radiology, Dalhousie University and Capital Health, Halifax, Nova Scotia, Canada.

Address reprint requests to David R. Anderson, MD, FRCP(C), Department of Medicine, Dalhousie University, 1278 Tower Road, Room 430, Bethune Building, VG Site, Halifax, NS B3H 2Y9, Canada. E-mail: david.anderson@dal.ca

Relationship Between Deep Vein Thrombosis and Pulmonary Embolism

Pulmonary embolism usually arises from deep vein thrombosis of the lower extremities. Usually, deep vein thrombosis originates in leg veins of the calf.[6] With time, the thrombosis will extend in a contiguous fashion to involve the more proximal venous system of the legs; the popliteal, superficial femoral, and common femoral veins. Less commonly, deep vein thrombosis originates in the iliac veins and, with time, will spread distally. Iliofemoral deep vein thrombosis tends to occur in certain settings such as pregnancy, after gynecological or urological surgical procedures, or in the presence of pelvic mass.

Deep vein thrombosis of the lower extremities is frequently associated with pulmonary embolism. This results from the thrombus dislodging from the deep veins of the lower extremities, traveling through the inferior vena cava, the right heart to finally lodge in the pulmonary arterial system. Patients with deep vein thrombosis involving the proximal leg veins are considered at greatest risk for developing pulmonary embolism (as opposed to those with isolated calf vein thrombosis).[7,8] The systematic performance of pulmonary imaging procedures demonstrates that at least 50% of patients with deep vein thrombosis of the proximal leg veins

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will have radiographic evidence of pulmonary embolism at the time of diagnosis.[7,9-11] Many of these pulmonary emboli are asymptomatic.

Pulmonary embolism may less commonly originate from other venous sources. Particularly, with the use of upper-extremity indwelling catheters, pulmonary embolism may arise from the veins in the upper extremities.[12,13] Pulmonary embolism also may arise from pelvic veins in the postpartum setting or in patients undergoing major gynecological, urological, or abdominal surgical procedures.[14] The de novo development of pulmonary embolism is thought to be uncommon.

Given the clear relationship between deep vein thrombosis and pulmonary embolism, it is not surprising that patients presenting with symptoms of pulmonary embolism often are found to have deep vein thrombosis. This observation was initially made with autopsy studies in which patients suffering fatal pulmonary emboli frequently had evidence of deep vein thrombosis on dissection of the leg veins.[15-17]

Subsequent studies in which the authors used venography detected the presence of deep vein thrombosis of the lower extremities in 70% to 90% of patients with pulmonary embolism with most thrombi found in the proximal leg veins.[18-20] Venography had been regarded as the gold standard test for the diagnosis of deep vein thrombosis, and it is the most reliable test for identifying thrombosis isolated to the calf veins. However, with the advent of ultrasonography, its use is largely of historical interest only.

With the use of bilateral compression ultrasonography of the proximal venous system, significantly fewer deep vein thrombi are detected in patients with pulmonary embolism than with venography. Only 25% to 50% of patients with pulmonary embolism will be found to have deep vein thrombosis when ultrasonography is used as a screening test.[21-24] Most of these thrombi will be asymptomatic. These lower sensitivity figures likely reflect the limitations of ultrasound as a screening test for deep vein thrombosis in asymptomatic patients.

Compression ultrasonography is a very accurate test for the diagnosis of proximal deep vein thrombosis of the lower extremities in symptomatic patients presenting with their first suspected episode. In this setting, compression ultrasound has been shown to have a sensitivity and specificity of approximately 97%.[3] Ultrasound is less sensitive and specific as a diagnostic test for DVT isolated to calf veins.[3] Many centers do not routinely image calf veins because of this lack of accuracy, the time commitment required for this test, and the fact that isolated calf clots have a relatively low risk of developing into pulmonary emboli in the absence of their extension into the more proximal venous system.[1]

Even for diagnosing proximal deep vein thrombosis, bilateral ultrasonography is a much less sensitive test when used as a screening procedure in high-risk patients with no symptoms of deep vein thrombosis than in symptomatic patients. Screening studies largely performed in the postoperative setting have found that the sensitivity of ultrasound for the diagnosis of proximal deep vein thrombosis is only approximately 60%.[25,26] The suspected reasons for this lack of sensitivity in asymptomatic patients are that thrombi are smaller, less likely to be occlusive, and their anatomic location is unpredictable.

A single-center study evaluated the use of venous ultrasound imaging of the entire leg venous system in patients with confirmed pulmonary embolism and reported an 83% sensitivity[27] with most of the detected thrombi involving the proximal venous system. The authors acknowledged that specialized training and additional procedure time were required for a complete calf vein assessment.[27] Most research studies in which authors evaluated ultrasonography of the lower extremities to assist with the evaluation of patients with suspected pulmonary embolism focused the evaluation on the proximal venous system between the popliteal and common femoral veins. The ultrasonographic screening procedure evaluated most commonly in studies of patients with suspected pulmonary embolism is bilateral compression ultrasonography of the proximal venous system of the legs. With this technique, a 5- or 7.5-MHz linear array probe is used to compress the veins at 1-cm intervals between the proximal portion of the common femoral vein to the trifurcation of the popliteal vein below the popliteal fossa.[28] The absence of vein compressibility is the most sensitive and specific feature of deep vein thrombosis. Doppler flow and color Doppler are used to assist with the identification of veins but do not appear to otherwise add to the diagnostic accuracy of the technique.[28]

Usefulness of Ultrasound Screening as an Initial Test for Pulmonary Embolism

Although bilateral compression ultrasound of the proximal leg vein has been demonstrated to have a relatively low sensitivity for the diagnosis of asymptomatic deep vein thrombosis in patients presenting with symptoms of pulmonary embolism, some clinicians have advocated it be the initial test in this patient population.[29-31] The rationale for this approach is that ultrasound can be rapidly performed, it is noninvasive and, if a diagnosis of venous thromboembolism can be made, a pulmonary imaging procedure can be avoided. In the event that ultrasonography is normal, pulmonary arterial imaging should then be performed (either computed tomographic pulmonary angiography [CTPA] or ventilation-perfusion [V/Q] lung scanning).

Although it would be considered controversial whether ultrasonography should be used as an initial diagnostic test for all patients with suspected pulmonary embolism, arguments can be made for the performance of ultrasound as the initial diagnostic test in clinical situations where pulmonary imaging is relatively contraindicated or problematic to perform. Such settings would include pregnant patients in whom radiation exposure is undesirable or in critically ill patients in whom transport to radiology departments is problematic.

Critics of the performances of bilateral ultrasonography as the initial test for pulmonary emboli have argued that the

relatively low sensitivity ultrasonography makes it more appropriate to begin the diagnostic algorithm of suspected pulmonary embolism evaluation with a pulmonary imaging procedure (either CTPA or V/Q scanning). In addition, pulmonary imaging will provide information about the extent and location of the thrombosis. Given the prevalence of pulmonary embolism may be only approximately 10% to 30% in the evaluation of cohorts of patients suspected of this condition, this further reduces the utility of screening all patients initially with bilateral ultrasonography.[30,32,33] The exception may be the patient with suspected pulmonary embolism with clinical signs of deep vein thrombosis in which case the likelihood of diagnosing deep vein thrombosis with ultrasonography is increased about 4-fold.[34]

The Role of Ultrasonography in Management Strategies to Exclude Patients With Suspected Pulmonary Embolism

During the past 3 decades, substantive research efforts have been undertaken to evaluate diagnostic testing strategies for patients with suspected deep vein thrombosis or pulmonary embolism in which ultrasonography has been the cornerstone investigation to minimize the need for more invasive testing. Multiple studies have reported that the outcome of patients presenting with symptoms of suspected deep vein thrombosis is excellent as long as ultrasonography at the proximal venous system (popliteal to common femoral vein) remains negative.[9,35,36] Although a portion of the patients undoubtedly have deep vein thrombosis isolated to the calf veins, few of these patients develop symptoms of pulmonary embolism. It is hypothesized that isolated calf vein thrombosis may be a clinically self-limited condition and patients only becomes at significant risk for pulmonary embolism if the thrombus propagates to the proximal venous system.

Recognizing the limitations of the sensitivity of noninvasive pulmonary imaging procedures, investigators have evaluated whether ultrasonography may be incorporated into the diagnostic strategy for suspected pulmonary embolism to avoid the need for pulmonary angiography. This approach initially was evaluated in patients undergoing V/Q scanning. Although high probability and normal V/Q scan reports are very useful findings to rule in and rule out pulmonary embolism, respectfully, most patients undergoing V/Q scanning have nondiagnostic results (low probability, intermediate probability, or indeterminate probability) in whom the incidence of pulmonary embolism may vary from 15% to 30%.[37,38] Historically, the management of patients with nondiagnostic lung scans was problematic. The incidence of pulmonary embolism was too low to recommend the empiric treatment of all patients. However, not treating any patient undergoing a nondiagnostic lung scan with anticoagulants would be fraught with risk. Previous diagnostic approaches had recommended that patients with nondiagnostic V/Q scans undergo the "gold standard" invasive imaging procedure pulmonary angiography. However, this approach is simply not feasible or desirable for most centers.

In a search for safe, noninvasive strategies for the investigation of suspected pulmonary embolism, it has been recommended that ultrasonography be performed as an alternative pulmonary angiography in patients with nondiagnostic V/Q scans to look for evidence of deep vein thrombosis.[25,39,40] If deep vein thrombosis is found, then the patient can be treated without the need to conclusively diagnose pulmonary embolism because the treatment of deep vein thrombosis and pulmonary embolism usually are comparable. If deep vein thrombosis is not found, it has been postulated that the prognosis for the patient may be favorable and that they do not require anticoagulation therapy, as long as they do not subsequently develop proximal deep vein thrombosis and become at further risk for pulmonary embolism. It was initially advocated that patients with nondiagnostic lung scans should have pulmonary embolism excluded by the performance of serial compression ultrasound of the proximal venous system (3 or 4 ultrasound investigations over a 1- to 2-week period) before ruling out this condition.[26,38] With more recent research advances such as the development of clinical probability scores and D-dimer, the need for serial ultrasonography can be avoided.[41-44]

For patients with nondiagnostic V/Q scans, the following diagnostic algorithm has been validated to exclude the diagnosis of pulmonary embolism (Fig. 1). In patients with non-

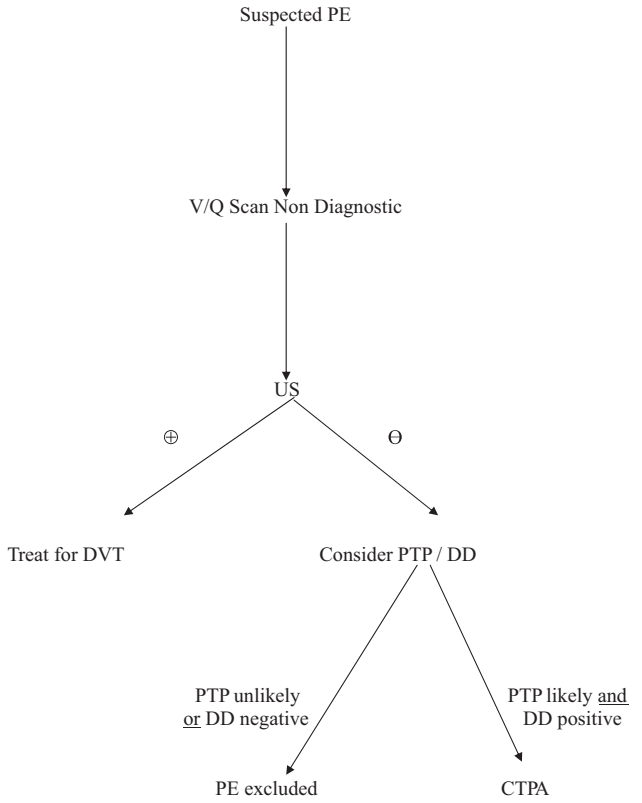

Figure 1 Diagnostic algorithm for investigation of suspected pulmonary embolism using V/Q scanning.

diagnostic V/Q scans in whom the probability of pulmonary embolism is scored as low or unlikely or the D-dimer result is negative, pulmonary embolism may be safely excluded on the basis of a single negative ultrasound test. The authors of several studies have demonstrated that, in using this approach, only about 1% of patients in whom a diagnosis of pulmonary embolism is considered excluded who are not managed with anticoagulant therapy will subsequently return with deep vein thrombosis or pulmonary embolism in follow-up.[32,43,45-48] This complication rate is similar to the development of pulmonary embolism in the follow-up of patients with normal pulmonary angiograms.[49]

The safety of this approach has not been evaluated in greater-risk patients with nondiagnostic V/Q scans (clinical probability of pulmonary embolism likely or high and the D-dimer is positive). It would generally be recommended that these patients go on to have an additional pulmonary imaging procedure before pulmonary embolism is excluded such as CTPA, repeat bilateral ultrasonography, or conventional pulmonary angiography.

The Role of Ultrasonography in Patients With Suspected Pulmonary Embolism Undergoing CTPA

During the past decade, many centers have adopted CTPA as the pulmonary imaging procedure of choice for patients with suspected pulmonary embolism. CTPA has an intuitive appeal for clinicians because it provides dichotomous results (either positive or negative), the thrombosis is directly visualized in the pulmonary arterial circulation, and alternative causes for symptoms may be observed.[50] Unlike V/Q lung scanning, a negative or normal CTPA does not exclude a diagnosis of pulmonary embolism. Reported sensitivity rates for CTPA for the diagnosis of pulmonary embolism have varied likely because of differing CT techniques and different gold standard evaluations.[51,52] The sensitivity of CTPA for the diagnosis of pulmonary embolism is improving with technological advances.[53] Multidetector CTPAs demonstrate greater sensitivity of pulmonary embolism than do previous generations of testing. It is the expectation that, with improvements in technology, this sensitivity will continue to increase with time. The Prospective Investigation of Pulmonary Embolism Detection II trial demonstrated that the overall sensitivity of multidetector CTPA for a diagnosis of pulmonary embolism was approximately 85%.[53] The sensitivity was greater for patients with massive pulmonary embolism involving the more proximal pulmonary arterial circulation.

Given the concerns about sensitivity, the authors of initial management strategies using a negative CTPA to rule out pulmonary embolism advocated performing bilateral ultrasound imaging of the proximal leg veins before excluding a diagnosis of pulmonary embolism. Several large cohort studies confirmed the safety of relying on a negative CTPA and a negative ultrasound to rule out pulmonary embolism with only about 1% to 2% of patients in whom a diagnosis of pulmonary embolism was excluded return to have confirmed pulmonary embolism in a follow-up.[54-57] The benefit of performing bilateral ultrasonography in these patients was considered justified because 10% to 20% of patients who eventually were diagnosed with pulmonary embolism had negative CTPA but were found to have deep vein thrombosis by ultrasonography.

The authors of 2 prospective cohort studies that were performed using multidetector CTPA have reported that negative scans were useful to exclude a diagnosis of pulmonary embolism without the need for performing ultrasonography of the lower extremities.[58,59] Patients with pulmonary embolism excluded on the basis of CTPA results had similarly low rates of complications as studies that relied on negative ultrasonography in addition to negative CTPA.

The role of ultrasonography for the diagnosis of pulmonary embolism has been more clearly defined by a recent clinical trial. Righini and colleagues[33] randomized patients with suspected pulmonary embolism to either a diagnostic strategy that used ultrasonography in combination with CTPA or a CTPA approach alone. Patients in whom pulmonary embolism was excluded in the initial diagnostic period were not started on anticoagulants and were then followed up for a 3-month period for the development of deep vein thrombosis or pulmonary embolism (failure rates).

Both arms of this study reported similar rates of pulmonary embolism (approximately 20%) in the initial evaluation period. The thromboembolic failure rates in follow-up in whom pulmonary embolism was considered excluded were identical (0.3%) in the 2 groups. Although the study investigators allowed for an alternative imaging procedures to be performed if the clinical suspicion was pulmonary embolism was high and the CTPA was normal or nondiagnostic, ultrasonography held no additive value. Approximately 9% in the ultrasound group of patients were confirmed to have deep vein thrombosis. The authors concluded that the routine performance of bilateral lower limb venous ultrasonography was not routinely required and that the diagnosis of pulmonary embolism could be reliably excluded with CTPA. They indicated ultrasonography was useful in patients with suspected venous thromboembolism if CTPA was contraindicated.[33]

CT Venography or Ultrasonography

With the use of CTPA for the investigation of patients with suspected pulmonary embolism, investigators have evaluated whether CT venography of the proximal venous system could be performed during the same procedure to diagnose deep vein thrombosis and potentially avoid the need to perform ultrasonography. Studies have demonstrated that it is technically feasible to perform CTPA and CT venography during the same procedure. Furthermore, combining the 2 modestly increased the diagnostic yield of venous thromboembolism.[60,61] CT venography offers the advantages of imaging the iliac system, which is not routinely evaluated by ultrasonography. Limited comparative studies of CT venography

versus ultrasonography for the diagnosis of deep vein thrombosis in patients with suspected pulmonary embolism have been favorable.[62,63] However, there are concerns about the routine performance of CT venography because of its high contrast load and additional radiation exposure. Given the availability of a noninvasive test like ultrasonography and the afore mentioned evidence that routine imaging for deep vein thrombosis does not improve the outcome of patients with negative CTPA, it does not appear the routine performance of CT venography is appropriate for the investigation of patients with suspected pulmonary embolism.[64]

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