Clinical Commentary

Noninvasive Tests for Acute Venous Thromboembolism

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It is now accepted that acute pulmonary embolism (PE) and deep vein thrombosis (DVT) are two clinical presentations of the same disease: venous thromboembolism (VTE). The clinical diagnosis of VTE is fraught with uncertainty and clinical management is enhanced significantly by laboratory tests. Noninvasive tests are attractive because of their low morbidity and mortality rates.

Noninvasive tests can be performed by technicians rather than physicians. Usually, they are less expensive, more available, and logistically simpler than their invasive counterparts. The most direct approach to testing their clinical validity is to determine the outcome when management decisions are based on results of the noninvasive test in prospective studies on consecutive patients. Before undertaking this step, the results of the noninvasive test are compared with a standard reference test.

REFERENCE TESTS

Current teaching is that traditional clinical skills were of little value for the diagnosis of DVT. This view arises from early clinical studies that found that no one symptom or sign could distinguish between a true or false DVT (1). It was the lack of demonstrable confidence in the clinical diagnosis of DVT that led contrast venography to become the standard reference test. However, combinations of symptoms were not explored until more recently. In a retrospective study of 354 patients who underwent contrast venography, five clinical correlates were associated with proximal vein thrombosis: swelling above the knee of the affected leg, swelling below the knee, recent immobility, cancer, and fever. Of 95 patients with proximal vein thrombosis, 5% (95% confidence limits [CL] 0–26%), 15% (95%CL 6–29%) and 42% (95%CL 31–64%) has none, one, or two of five clinical findings respectively (2). Therefore clinical evaluation should be discounted as entirely valueless.

The safety of withholding anticoagulants in patients with suspected DVT and negative venography has been well established in a prospective study (3). The diagnostic findings of an intraluminal defect or a nonfilling venous segment should be constant in all films. Certain caveats need to be heeded. For example, the contrast should be followed through to the inferior vena cava; otherwise it will be incomplete, because thrombosis in the iliac veins may be missed. Overly proximal injection into a vein on the foot may result in nonfilling of venous segments. The technique requires careful attention to detail (4).

Similarly, the clinical diagnosis of pulmonary embolism is believed to be inaccurate. However, the multicenter, prospective investigation of pulmonary embolism diagnosis (PIOPED) study did provide some glimmer of hope (5). The study was comprised of a random sample of 933 patients for whom a $\dot{V}/\dot{Q}$ scan or pulmonary angiogram was requested. The clinical impressions of physicians in the PIOPED study were able to predict PE with some degree of accuracy. The problem is that this information is of limited value because it has not been captured in a manner that transmits the knowledge to others, such as a neural network.

The reference test for PE is pulmonary angiography. The safety of withholding anticoagulants in patients with suspected PE and a negative pulmonary angiogram has been well established in prospective studies (5). Even when available, it is not invariably diagnostic for a variety of reasons, some of which are not related to technical difficulties with the test and may be avoidable. In the Hamilton study (6), only 70% of 139 consecutive patients had an angiogram performed that was of diagnostic value. In 19% of the patients, the angiogram was not done because patients were considered too critically ill to undergo the procedure, or had allergy to the dye. For 6% of the patients, either attending physicians considered the patient unfit, the patient refused, or the angiogram obtained was technically difficult. In 5% of patients, visualization was inadequate. However, the diagnostic yield appears to be better in the PIOPED study, although those data are not strictly comparable (5, 7). Nevertheless, even if a test has perfect sensitivity (true positive rate) and specificity (true negative rate), its value is diminished if it does not yield diagnostic results in a wide range of patients. Indeed, some authors have suggested that the conventional terms of sensitivity and specificity should be redefined to include diagnostic yield, in order to take account of indeterminate test results (8).

NONINVASIVE TESTS

The noninvasive tests that have gained prominence in the management of VTE are impedance plethysmography (IPG), compression ultrasonography, and ventilation-perfusion scan. Several other noninvasive tests have been developed, including digital subtraction pulmonary angiograms, radionuclear venography, and a variety of blood tests, but their clinical utility has yet to be demonstrated convincingly.

Although both IPG and compression ultrasonography are inaccurate for the detection of calf vein thrombosis, only proximal vein thromboses lead to clinical significant pulmonary embolism (9, 10). The only calf vein thromboses that are considered to require anticoagulant therapy are those that extend to the proximal veins. This approach has not attained uniform acceptance (11); indeed, a case has been made for long-term anticoagulant treatment of symptomatic calf vein thromboses (12). Nevertheless, it is on this rationale that successful strategies have been developed with these noninvasive tests that include serial testing to detect extension of calf vein thromboses with the goal of preventing symptomatic pulmonary embolism.

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Impedance Plethysmography

Impedance plethysmography gained a reputation as a powerful tool for clinical management of acute venous thromboembolism. In patients with suspected DVT, IPG has a 91% sensitivity (95%CL 86–95%) and 96% specificity (95%CL 93–98%) for detection of proximal vein thrombosis, provided it is performed according to protocol (13). The combination of IPG for proximal vein thrombosis and the leg scanning for calf vein thrombosis was as accurate as venography at detecting DVT (14).

The safety of withholding anticoagulants in patients with suspected DVT and negative serial IPG has been well established in two prospective outcome studies comprised of both inpatients and outpatients. It is important that serial studies are done over the ensuing 10 to 14 d (15, 16); up to 15% of proximal DVT were detected after the initial study. In the Canadian study there were no fatal PEs in the 311 patients for whom treatment was withheld, but there were 1.9% (95%CL 0.7–4.2%) of patients who developed a DVT during the 12-mo follow-up (15). In the Dutch study there were no fatal PEs in the 289 patients for whom treatment was withheld, but there were 0.3% (95%CL 0–1.9%) of patients who developed a DVT during the 6-mo follow-up (16). IPG could not be performed in only 2.8% of 992 patients (14). The Canadian study was conducted with both inpatients and outpatients. The Dutch study was performed with outpatients only; three of 471 patients lived too far from the study center to come in for serial testing. Although neither study entirely eliminated the incidence of VTE during follow-up, even with negative contrast venography there is a 1.3% (95%CL 0.1–4.4%) risk of DVT due to the procedure (3).

The advantages of IPG are twofold. First, the outcome data are available from prospective studies; therefore, the difficulty in deciding clinical significance of the test result is circumvented. Second, the results are expressed in binary form (positive/negative) with a discriminant function relating venous outflow to venous filling. Therefore, interpretation is simple and the result is decisive. Disadvantages of IPG are related to its performance. Patients are required to lie still while a thigh cuff is inflated and change in blood volume of the calf is measured from the impedance of the calf by electrodes strapped around it. The cuff is deflated and the proportional change of impedance over a 3-s period is used to measure venous outflow obstruction in a manner analogous to measurement of the FEV_1/FVC ratio. The patient's leg must be positioned correctly to avoid obstructing venous outflow and the patient must lie still for a period of more than 2 min. Therefore, the procedure can be difficult to perform in paraplegics with involuntary muscle spasms. Obviously, the test cannot be performed if the patient's leg is in a plaster cast. Previous venous disease, severe arterial disease, and raised venous pressure associated with congestive cardiac failure, and raised intrathoracic pressure may result in false positive results. Therefore, there are circumstances where a false positive result might occur and other investigations would be required.

Recently, the IPG has come under fire. Prandoni and colleagues reported four patients who died from PE after testing for DVT with a computerized from of IPG (17). It should be emphasized, however, that the equipment described in that report differed substantially from that used by the McMaster group of investigators (15). Furthermore, Prandoni and co-workers did not follow the McMaster protocol, using the first adequate test instead of the validated criteria developed by the McMaster group (18). The prolonged venous occlusions were for 90 s instead of 120 s. Not surprisingly, the discriminant line to separate those patients with and without DVT differed substantially from the McMaster version; this demonstrates the need to pay scrupulous attention to the details of McMaster IPG technique. Deviations from these protocols (19) should be viewed with great caution.

New doubt was cast on the previously recorded high sensitivity of IPG even with the McMaster protocol (20). A 66% (95%CL 52–78%) sensitivity was reported in 56 patients. This result is at least in part due to the proportion of nonocclusive thrombi in the proximal veins. These clots are known to escape by IPG and usually occur in asymptomatic rather than symptomatic patients. The spectrum of the disease may have changed over the years at the McMaster hospitals. No outcome data was available, which is critical for a complete interpretation. The IPG may be detecting thrombi that are liable to produce symptomatic thromboembolism that are of clinical importance. The propensity to embolize may be related to the amount of thrombosis obstructing venous flow. This study differs from several large, well designed, prospective studies. As the authors themselves stated, the results should be interpreted with caution. It seems prudent to follow the advice of the authors that centers using this test check its sensitivity.

The IPG never gained widespread clinical usage despite its scientific validity. In part, this slow beginning was related to the fact there were several poorly controlled studies in the radiologic literature, some perceived difficulties in its conduct, and some confusion with other inaccurate forms of leg plethysmography. Another contributing factor was an apparent lack of interest on the part of the original manufacturer in marketing the equipment. Differences in reimbursement for contrast venography, serial IPG, and compression ultrasonography may also have played a role. Another factor is that the IPG depends not on diagnosis but on a satisfactory outcome. It requires a utilitarian approach, as opposed to the logical approach taught in medical school of making a diagnosis before considering treatment options. Perhaps the most likely reasons for the rise in popularity of compression ultrasonography are the physician's familiarity with direct imaging, the possibility of making other diagnoses, and the attraction of high technology.

Compression Ultrasonography

In many institutions, IPG was rapidly superseded by duplex ultrasound even before its diagnostic accuracy had been tested. Duplex ultrasound is so named because it combines the older, less reliable Doppler venous flow detection with venous imaging. Its diagnostic utility is due to the imaging of a venous filling defect that persists with compression of the lesion rather than its Doppler or qualitative color display of flow. Compression ultrasonography has been reported to have an impressive sensitivity (100%, 95%CL 95–100%) and specificity (99%, 95%CL 97–100%) for proximal vein thrombosis (21) in consecutive outpatients with clinically suspected DVT. These results are similar to those obtained in a number of earlier, smaller studies (22).

Compression ultrasonography is at a distinct advantage in circumstances where IPG can result in false positives, as described above. Its disadvantages are that it does not detect isolated thrombus in the iliac veins or in the superficial femoral veins within the adductor canal. It is limited by the presence of plaster casts and deformities, as is the case with IPG. In addition, patients must assume the prone position if popliteal veins are to be examined adequately.

A retrospective outcome study reported only five episodes of thromboembolism in 1,022 symptomatic patients, for whom treatment for DVT was withheld (23). There were two fatal cases of PE occurring more than 3 mo after the initial event. Retrospective studies are subject to unintentional bias; more convincing evi-

dence has come from a recently published prospective trial that directly compared compression ultrasonography with IPG (24).

The study was conducted in both Canada and the Netherlands. 985 consecutive outpatients with suspected DVT were randomized between IPG and compression ultrasonography. The serial studies were performed on Days 1, 2, and 7. The incidence of venous thromboembolism over a 6-mo follow up of patients with a negative test and anticoagulants withheld was not statistically different: 2.5% (95%CL 1.2–4.6%) for IPG and 1.5% (95%CL 0.5–3.3%) compression ultrasonography. There were no fatal PEs in either group. Nevertheless, compression ultrasonography was superior to IPG in terms of its positive predictive value: 94% (95%CL 87–98%) for compression ultrasonography and 83% (95%CL 75–90%) for IPG. As a result, 11.2% (95%CL 2.7–20%) more patients were anticoagulated unnecessarily in the IPG group than in the compression ultrasonography group. This study provides evidence to support the use of compression ultrasonography, at least in outpatients with suspected DVT, and demonstrates that it has distinct advantages over IPG. The study also confirms the efficacy of IPG, which could be used still in areas where the more sophisticated equipment required for compression ultrasonography is unavailable.

Ventilation-perfusion Lung Scanning

Hull and his colleagues (6, 25) have done much to clarify the clinical utility of $\dot{V}/\dot{Q}$ scans. In a prospective study of 483 consecutive patients, the sensitivity of a high probability scan was 57% (95%CL 47–67%) and specificity of 90% (95%CL 87–93%) using Biello's criteria (26), and a sensitivity of 53% (95%CL 43–63%) and specificity of 92% (95%CL 89–95%) using McNeil's criteria (27). Therefore, a high probability scan is strong confirmatory evidence in a patient with suspected acute PE, but the diagnosis can be made in only about half of the patients. Withholding anticoagulants in patients with a negative perfusion scan resulted in a 0.6% (95%CL 0.1–1.7%) rate of nonfatal venous thromboembolism in 515 consecutive patients (28). These results were confirmed by the PIOPED study (4): a high probability scan had a sensitivity of 41% (95%CL 34–47%) and a specificity of 97% (95%CL 96–98%). Radioactive xenon gas was used for ventilation scans and ^{99m}Tc-labeled macroaggregated albumin was used for perfusion scans. Perfusion scans were completed satisfactorily in 96% of patients and ventilation scans in 95% of patients. Both studies indicated that intermediate and low probability scans are of little diagnostic value.

The outcome of low probability $\dot{V}/\dot{Q}$ scan has been reported as satisfactory; none of the 90 patients (95%CL 0–4%) had clinical evidence of a PE, but the study was retrospective (29). The PIOPED study shows the potential utility of the low probability or near normal scan combined with clinical impression. Clinical impression was based on history, physical examination, chest X-ray, arterial blood gas composition, and ECG. With high probability estimates of 80% or more, 68% were correct but the confidence limits were wide (95%CL 57–77%). With low probability estimates of < 20%, the PIOPED investigators were remarkably accurate: 91% correct with acceptable confidence limits (95%CL 86–95%). However, the criteria for clinical impression were not formalized and therefore cannot be generalized. Furthermore, the definition developed by the PIOPED study for these scans is complex. Five criteria were used to categorize a low probability scan and these were subject to interobserver variability. As a result this approach cannot be recommended until these issues have been resolved and tested in a prospective study.

These results indicate that only the high probability $\dot{V}/\dot{Q}$ scan is useful for confirming the diagnosis. A normal scan is useful for excluding the diagnosis. In many patients with suspected PE, the $\dot{V}/\dot{Q}$ scan is nondiagnostic. One useful approach to circumvent this problem has undergone a prospective trial: those patients with suspected PE and with indeterminate $\dot{V}/\dot{Q}$ scans, but without severe cardiopulmonary disease, were not treated unless the initial IPG or subsequent serial studies became positive (30). Patients were considered to have severe cardiopulmonary disease if they had pulmonary edema, right ventricular failure, hypotension (systemic blood pressure < 90 mm Hg), syncope, acute tachyarrhythmias, abnormal spirometry (FEV_1 < 1.0 L or VC < 1.5 L), or respiratory failure (P_aO_2 < 50 mm Hg and/or $Paco_2$ > 4 mm Hg on room air). With this approach, venous thromboembolism occurred in 3% (95%CL 1–5%) of 414 patients. This rate is similar to the 1% (95%CL 0–3%) rate occurring in the 315 patients with a normal $\dot{V}/\dot{Q}$ scan. This study has yet to be confirmed.

Various alternative strategies have been proposed to circumvent this problem without resorting to pulmonary angiography by adding clinical suspicion (31) or compression ultrasonography (32) into the algorithms. These algorithms are of interest and worthy of further study but they are based on retrospective data and lack prospective outcome data (31, 32). As a result, risks and benefits can only be surmised. The decision regarding pulmonary angiography is moot in many hospitals where it is not readily available. Under these circumstances, this option is impractical unless the patient can be transferred to a more appropriately equipped facility.

RECOMMENDATIONS

Availability of tests varies by hospital. Some tests are impractical for certain patients. Ideally, contrast venography, pulmonary angiography, $\dot{V}/\dot{Q}$ scans, IPG, and compression ultrasonography should be readily available and executed according to the standard method. This ideal is achieved rarely; therefore, some flexibility is needed. No existing algorithm encompasses all circumstances.

There are numerous articles that make recommendations about management of acute VTE. The algorithms that they describe can be divided into three broad groups, in order of preference. First are algorithms for which the outcome has been both tested and confirmed in prospective studies. The only concern with these approaches is that there has not been a change in the demographics of the patient population upon which they were validated. Second are algorithms that have been tested but are not yet confirmed by additional studies. The main concern with these studies is that they may not be efficacious in a different population of patients. Third are algorithms that have not been tested, but are based on tests for which the sensitivity and specificity of the test has been established prospectively in consecutive patients.

Group 1 algorithms are contrast venography (3) and serial IPG (15, 16, 24) for suspected DVT; pulmonary angiography (5, 7), a normal $\dot{V}/\dot{Q}$ scan (5, 6), and a highly probable $\dot{V}/\dot{Q}$ scan in patients with suspected PE but without severe underlying cardiopulmonary disease (5, 6). Group 2 algorithms are serial compression ultrasonography for suspected DVT (24), and serial IPG in patients with suspected PE and an indeterminate $\dot{V}/\dot{Q}$ scan (30). Examples of Group 3 algorithms are compression ultrasonography for patients with suspected DVT, and strategies incorporating clinical impression with low probability scans for patients with suspected PE (32).

The clinician prefers to use an algorithm of the highest grouping. However, it is important to verify that the test is being conducted in the precise manner described in the original articles. Frequently, the clinician is unable to use any algorithm in the first

three groups. Under these circumstances, the patient should be transferred to a hospital where such facilities as those described in the first three groups are available.

If transfer is impractical, then the best option is to determine what diagnostic tests are available and apply decision analysis to the individual problem at hand (33). An analysis of this kind would need to include the clinical impression of the probability of PE, the specificity sensitivity, diagnostic yield of test results, the benefit of treatment, the risks of the test, of treatment (anticoagulants and/or a Greenfield filter), and of failing to treat pulmonary embolism. Treatment is highly efficacious (6) and there is a 26% (95%CL 9–52%) mortality and similar recurrence rate if PE is left untreated (34). As a result the physician usually leans to the side of treatment. With the increasing amount of literature on the subject and the widespread availability of computers, at least the mathematical aspects of decision analysis are becoming much easier to perform.

Regardless of the approach used, three questions need to be answered about patients with suspected acute VTE before any clinical management decision is made. First, what is the evidence for acute DVT? Second, what is the evidence for acute PE? Third, the most difficult question: are there sufficient grounds for withholding treatment?

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