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Articles

A Novel and Rapid Whole-Blood Assay for D-Dimer in Patients With Clinically Suspected Deep Vein Thrombosis

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Background The clinical utility of using a novel whole blood assay for D-dimer (SimpliRED), alone or in combination with impedance plethysmography (IPG), was investigated in a two-center, prospective cohort study of 214 consecutive patients with clinically suspected deep vein thrombosis (DVT).

Methods and Results All patients underwent the SimpliRED D-dimer assay, contrast venography, and IPG. According to the results of venography, 43 patients had proximal DVT (popliteal and/or more proximal veins), 10 had isolated calf DVT, and 161 had DVT ruled out. The D-dimer had a sensitivity of 93% for proximal DVT and of 70% for calf DVT, an overall specificity of 77%, and a negative predictive value of 98% for proximal DVT. The sensitivity and specificity of IPG for proximal DVT were 67% and 96%, respectively. When analyzed in combination with the IPG results, it was determined that (1) the combination of a negative D-dimer and a normal IPG had a negative predictive value of 97% for all DVT and of 99% for proximal DVT and occurred in 58% of patients (likelihood ratio, 0.1) and (2) the combination of a positive D-dimer and an abnormal IPG had a positive predictive value of 93% for any DVT and of 90% for proximal DVT and occurred in 14% of patients (likelihood ratio, 42.6). When the D-dimer and IPG results were discordant, it was not possible to exclude or diagnose DVT reliably; discordant results occurred in 28% of patients.

Conclusions The SimpliRED D-dimer assay, which can be performed and interpreted at the bedside within 5 minutes, has great potential in patients with clinically suspected DVT, especially for ruling out

DVT, and is complementary to IPG. The assay should be evaluated in large clinical management studies.

Key Words: veins • thrombosis • fibrinolysis

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Deep vein thrombosis (DVT) and pulmonary embolism (PE) are common causes of morbidity and mortality.[1] During the past three decades, several advances have been made in the diagnosis of DVT. These include the recognition of the need for accurate objective testing because of the inaccuracy of clinical diagnosis,[1] the establishment of contrast venography as the reference standard for the diagnosis of DVT,[2] and the validation of diagnostic strategies involving impedance plethysmography (IPG)[3 4 5] and compression ultrasonography (CUS).[6]

Despite these advances, there are several shortcomings with the currently recommended diagnostic tests and strategies. The first is the management of patients who present with suspected DVT at a time when diagnostic testing is unavailable, such as during the night and weekends. Given the perceived inaccuracy of clinical diagnosis, many patients presenting with suspected DVT at these times are admitted for heparin therapy until diagnostic testing can be performed. This frequently results in unnecessary exposure to anticoagulant therapy because in most cases DVT is ruled out. A second shortcoming of the currently available noninvasive tests is the occurrence of false-positive results. In a recent randomized trial comparing serial CUS with serial IPG, false-positives with CUS and IPG occurred in 6% and 17% of cases, respectively.[6] The third problem is that most patients who have normal CUS or IPG at presentation do not have DVT and therefore undergo serial testing unnecessarily.[3 4 5 6]

A potential solution to all three problems is the use of assays that detect D-dimer, a specific degradation product of cross-linked fibrin. Recently, elevated levels of D-dimer, measured using either latex agglutination assays, enzyme-linked immunosorbent assays (ELISAs), or, more recently, a whole blood agglutination assay (SimpliRED, Agen Diagnostics Limited), have been reported in studies of patients with DVT and PE.[7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23] The ELISAs have been reported to have a high sensitivity but a low specificity for DVT. Although the latex agglutination assays provide immediate results on individual patients, they lack the sensitivity for broad clinical application.[21]

The SimpliRED assay is a novel D-dimer assay that is faster and easier to perform than ELISA and latex agglutination assays because it can be done on whole blood.[24] This is possible because the assay uses a bispecific antibody with epitopes that are portions of D-dimer and red blood cells, respectively. Therefore, in the presence of elevated levels of D-dimer, the antibody causes agglutination of the patient's red blood cells.[24] This makes it suitable for bedside testing on either fingerstick or venipuncture samples. The test provides a result within 5 minutes and obviates the need to centrifuge blood or process plasma. The latter is required for both latex agglutination assays and ELISA.

The purpose of the present study was to determine the potential clinical utility of the SimpliRED assay both alone and in combination with IPG. To accomplish this, we performed a cohort study in consecutive patients with clinically suspected DVT. All patients underwent contrast venography, D-dimer testing using the SimpliRED assay, and IPG. We chose to evaluate IPG in conjunction with the SimpliRED assay for two reasons. First, IPG is limited by the necessity of performing serial testing if the initial test is negative. Second, we wanted to determine if the use of the SimpliRED assay in conjunction with IPG overcomes the problem of both the recently reported lower positive predictive value of IPG and its insensitivity for the detection of small, nonocclusive popliteal DVT.[25] The results of the present study demonstrate that the assay has high sensitivity and negative predictive value for DVT, is complementary to IPG, and merits evaluation in clinical management trials.

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Patients

Consecutive patients referred to the thromboembolism outpatient departments of Chedoke-McMaster hospitals and the Henderson General Hospital, Hamilton, Canada, with suspected DVT constituted the study population. The study was carried out between September 1992 and December 1993 at Chedoke-McMaster hospitals and between May 1993 and November 1993 at the Henderson General Hospital. More than 95% of the patients seen at these hospitals are ambulatory outpatients referred by practitioners from the local areas; the remainder are outpatients referred from other centers. Patients were excluded from the study for any one of the following reasons: previous DVT in the symptomatic leg, contraindication to contrast administration (eg, allergy, renal failure), anticoagulant therapy had been administered for >24 hours, and failure or inability to give informed consent. The study protocol was approved by the institutional review boards of the participating hospitals.

Clinical Evaluation

After informed consent was obtained, all patients were evaluated by a thromboembolism consultant. The presence or absence of comorbid conditions that can cause elevated D-dimer levels independently[15] was determined. The comorbid conditions that were identified a priori as potential causes of a false-positive D-dimer test were recent (within 10 days) surgery or trauma, recent (within 10 days) myocardial infarction or stroke, acute infection, disseminated intravascular coagulation, pregnancy or recent (within 10 days) delivery, active collagen vascular disease, or metastatic cancer.

Diagnostic Testing For DVT

Contrast venography was attempted in all patients using the technique of Rabinov and Paulin.[2] All venograms were interpreted by an independent panel of two expert observers. DVT was considered to be present if a persistent intraluminal filling defect was identified in two or more views. Proximal vein thrombosis was considered to be present if thrombosis involved the popliteal vein and/or more proximal segments, with or without calf vein thrombosis. Calf vein thrombosis was considered to be present if thrombosis was restricted to the calf veins. Patients who did not have technically adequate venography were excluded from analysis. Venography was considered inadequate if one or more of the following

occurred: (1) the proximal veins (including the common and external iliac veins, common and superficial femoral veins, and the popliteal vein) were not adequately visualized; (2) the posterior tibial or peroneal veins were not adequately visualized; nonvisualization of the anterior tibial veins was not considered inadequate; or (3) an intraluminal filling defect was seen in only one view.

IPG Testing

On the day of presentation, all patients underwent IPG, which was performed using the occlusive cuff technique as described previously.[26] The IPG was interpreted according to standard criteria and without knowledge of the venography or D-dimer results. The IPG 200 (Codman and Shurtleff Inc) and IPG 800 (Electrodiagnostic Instrument Inc) were used in the present study.

Laboratory Intervention

Blood was collected and processed by either a research nurse or physician at the time of referral, and the D-dimer was measured using the SimpliRED assay. The method for the performance of the assay has been described elsewhere.[24] Briefly, a drop of whole blood, obtained from either a venipuncture or fingerstick (according to the preference of the patient), is mixed with a drop of the test reagent in the test well for 2 minutes, and the presence or absence of agglutination is noted. The test reagent contains a bispecific antibody that is formed by the conjugation of a high-affinity monoclonal antibody against D-dimer (3B6/22) to a red cell–binding antibody (RAT-1C3/86). In the presence of elevated levels of D-dimer, the antibody induces red cell agglutination, ie, a positive test result. Although it is possible to grade the degree of positivity of the test, for the present study, the test was considered to be positive if any agglutination was observed and negative if no agglutination was observed. Tests that were considered to be "trace-positive" were interpreted as positive.

Data and Statistical Analyses

The adjudicated results of venography were used as the reference standard to determine whether patients had proximal DVT, calf DVT, or no DVT. The accuracy indexes (sensitivities, specificities, negative predictive values, and positive predictive values) of the D-dimer assay (both alone and in combination with IPG) for DVT were calculated. Where indicated, the 95% confidence intervals (CI) for the accuracy indexes were calculated according to the binomial distribution. Likelihood ratios and the corresponding 95% CIs for the four possible combinations of IPG and D-dimer were calculated by pooling patients with calf DVT and proximal DVT.[27] Bias in the study was avoided by interpreting venography, IPG, and D-dimer results independent of each other.

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During the course of the study, 272 patients with suspected DVT were referred to the participating centers. Of these, 28 were excluded from the study for the following reasons: previous DVT (21), contrast allergy (1), renal failure (1), and unwillingness to provide consent (5). Of the remaining 244 patients, 25 were excluded from the analysis because of inadequate or failed venography and 5 were excluded because of inadequate or failed IPG. Therefore, 214 patients (133 women) with a mean age of 56 years (range, 19 to

93 years) were enrolled into the study and used in the primary analysis; 43 (20%) had proximal DVT, 10 (5%) had calf DVT, and 161 (75%) had no DVT.

The results of the D-dimer combined with IPG and of D-dimer alone are summarized in Tables 1 and 2, respectively. When the results of the two tests are combined, two patterns emerge that have the potential to be useful clinically. First, in patients with a normal IPG and negative D-dimer (124 of 214 [58%]), only 4 had DVT (1 proximal and 3 calf), yielding a negative predictive value for proximal DVT of 99%, a negative predictive value for all DVT of 97%, and a likelihood ratio of 0.10. The negative predictive value of the D-dimer alone was almost as high as that for D-dimer combined with IPG. Second, in patients with an abnormal IPG and a positive D-dimer (30 of 214 [14%]), 28 had DVT (27 proximal and 1 calf DVT), yielding a positive predictive value for any DVT of 93%, a positive predictive value for proximal DVT of 90%, and a likelihood ratio of 42.6. The positive predictive value for proximal DVT is higher than the positive predictive value for either test alone (83% for IPG and 51% for D-dimer). When the two test results were discordant, DVT could be neither diagnosed nor excluded reliably. D-dimer and IPG were complementary, since D-dimer detected 13 of 14 proximal and 6 of 9 calf DVT missed by IPG, whereas IPG detected 2 of 3 proximal DVT were missed by D-dimer.

View this table: [in this window]

Table 1. Summary of Results of IPG, SimpliRED D-Dimer, and Venography in Patients With Suspected DVT

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Table 2. Summary of Results of SimpliRED and Venography In Patients With Suspected DVT

When analyzed alone (Table 2), the sensitivity (93%) and negative predictive value (98%) of the D-dimer for proximal DVT are high, the sensitivity for calf DVT (70%) is moderate, and the specificity (77%) is moderate. The sensitivity and negative predictive values of the D-dimer alone exceeded those of IPG alone. Although the specificity of the D-dimer increased marginally from 77% in all patients (to 85% [113 of 133]) by excluding patients with comorbid conditions, the positive predictive value was virtually unchanged by excluding these patients and remained too low (56%) to diagnose DVT reliably. In patients with comorbid conditions, the specificity of the D-dimer assay was 39% (11 of 28), whereas the sensitivity for proximal DVT was 91% (20 of 22) and the sensitivity for calf DVT was 100% (2 of 2). Consistent with recent studies from our institutions,[25] [28] the sensitivity of the IPG for proximal DVT was 67%, whereas the specificity was 96%.

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Results from the present study demonstrate that the SimpliRED D-dimer assay, a

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novel whole blood assay that can be performed and interpreted at the bedside within 5 minutes, has the potential to be a useful test in patients with suspected DVT. The assay has high sensitivity and negative predictive value for proximal DVT, moderate sensitivity for calf DVT, and moderate specificity for all DVT, and it is complementary to IPG. There are several practical implications of our findings. When used alone, a negative SimpliRED result occurred in more than half of the patients and reliably excluded proximal DVT. On the other hand, the positive predictive value of the D-dimer (56%) was not sufficiently high to reliably diagnose DVT, even in the subgroup of patients without comorbid conditions known to be associated with a positive D-dimer. Therefore, the finding of a positive SimpliRED D-dimer in a patient with suspected DVT necessitates further testing for DVT. When both IPG and D-dimer were positive, the predictive value was higher than for either test alone. Thus, when the D-dimer assay was used in combination with IPG, two clinically useful patterns emerged. These patterns, which occurred in more than 70% of the study population, are a normal IPG and a negative D-dimer assay, which reliably excludes DVT (and, in particular, proximal DVT), and an abnormal IPG and a positive D-dimer assay, which reliably diagnoses DVT. On the other hand, the other combinations of IPG and D-dimer results do not reliably exclude or diagnose DVT. Thus, the combination of a normal IPG and a positive D-dimer assay requires, at the least, serial testing with IPG, and the combination of an abnormal IPG and a negative D-dimer assay requires further diagnostic imaging with either ultrasonography or venography. The SimpliRED D-dimer assay showed a sensitivity of 70% for calf DVT, missing 3 of the patients with such thrombi. It is thought that calf DVT does not cause clinically important pulmonary embolism unless extension into the proximal veins occurs first, and that extension occurs in approximately 30% of cases.[4] It is reasonable to hypothesize that patients with extending calf DVT have thrombi that are more active biochemically, more likely to produce elevated plasma D-dimer levels, and, therefore, more likely to show an abnormal SimpliRED D-dimer result.

The finding that concordant results with the D-dimer and IPG can be used to make clinical decisions requires verification in large management studies before implementation into clinical practice because it is important to determine whether patients can be managed safely when decisions are made on the basis of a laboratory test. In addition, it should be determined whether similar results can be obtained when a variety of health care personnel perform the SimpliRED assay under "usual clinical conditions"; this is particularly important in a busy emergency department.

The results with the SimpliRED D-dimer assay cannot be extrapolated to other assay systems because there are important differences in the reagents used in the various D-dimer kits. Although the ELISA has very high sensitivity, the specificity is very low and the long turnaround time limits its clinical utility.[15] [17] [21] In a recent overview of D-dimer testing for the diagnosis of DVT and PE, it was reported that latex agglutination assays had a pooled sensitivity of only 83% for DVT.[21] Therefore, the SimpliRED D-dimer assay appears to have higher sensitivity than latex agglutination assays and higher specificity than ELISA. The results of the present study are also consistent with a recently completed study of the SimpliRED D-dimer assay in patients with suspected PE in which the sensitivity was 94% and the specificity was 66%.[29]

Based on the results of the present study, we believe that there are at least two potential applications for this assay. The first is for the evaluation of patients with suspected DVT who present when diagnostic testing is unavailable; the finding of a normal D-dimer may allow the patient to be discharged until further noninvasive testing can be performed. Second, the D-dimer assay could be used in conjunction with IPG in patients with a suspected initial episode of DVT to test two hypotheses: DVT can be ruled out and serial testing can be obviated safely in patients who have a normal D-dimer and IPG at presentation; and DVT can be diagnosed without further testing in patients who have an abnormal D-dimer and IPG at presentation.

To summarize, the present study was the first to demonstrate that a D-dimer assay that can be performed and interpreted rapidly at the bedside has potential clinical utility in patients with suspected DVT. Based on these promising results, clinical studies should be done to examine the safety of making management decisions using the results of the SimpliRED assay.

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Footnotes

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Table 1. Summary of Results of IPG, SimpliRED D-Dimer, and Venography in Patients With Suspected DVT

	Venography			Likelihood Ratio[1]
	Proximal DVT	Calf DVT	No DVT	
DD+ IPG+	27	1	2	42.6 (10.5 to 172.9)
DD- IPG+	2	0	4	1.5 (0.8 to 8.0)
DD+ IPG-	13	6	35	1.6 (1.0 to 2.5)
DD- IPG-	1	3	120	0.1 (0.0 to 0.3)

DVT indicates deep vein thrombosis; IPG, impedance plethysmography; DD, SimpliRED D-dimer result; +, positive; and -, negative.

[1] Likelihood ratio calculated by pooling proximal and calf DVT (eg, for DD+ IPG+, 28/53÷2/161); 95% confidence interval of observed likelihood ratio is reported in parentheses.

Table 2. Summary of Results of SimpliRED and Venography In Patients With Suspected DVT

All Patients	Venography		
	Proximal DVT	Calf DVT	No DVT
D-dimer			
+	40	7	37
-	3	3	124
Sensitivity overall=47/53=89%, 95% CI=77% to 96%.			
Sensitivity proximal DVT=40/43=93%, 95% CI=81% to 99%.			
Sensitivity calf DVT=7/10=70%, 95% CI=35% to 93%.			
Specificity overall=124/161=77%, 95% CI=63% to 80%.			
NPV overall=124/130=95%, 95% CI=89% to 98%.			
NPV proximal=127/130=98%, 95% CI=93% to 99%.			
PPV overall=47/84=56%, 95% CI=45% to 66%.			

DVT indicates deep vein thrombosis; D-dimer, SimpliRED D-dimer; +, positive; -, negative; CI, confidence interval; NPV, negative predictive value; and PPV, positive predictive value.