Diagnosis and management of upper extremity deep vein thrombosis

Baarslag, H.J.

Publication date
2003

Chapter 3

Prospective comparative study of duplex color ultrasonography and contrast venography in patients suspected of having upper extremity deep vein thrombosis

Henk Jan Baarslag[1], Edwin J.R. van Beek[1,2], Maria M.W. Koopman[3], Jim A. Reekers[1]

Departments of Radiology [1] and Vascular Medicine [3], Academic Medical Center, Amsterdam, The Netherlands, Academic Unit of Radiology [2], Royal Hallamshire Hospital, Sheffield, United Kingdom

Ann Intern Med 2002;136:865-872

Abstract

Background: The optimal diagnostic strategy of upper extremity deep vein thrombosis is less well established than for the lower extremity. Duplex color ultrasonography can be difficult due to the anatomy, and contrast venography is often indicated. Moreover, limited data in small patient series exist on its use in this setting.

Objective: To assess the diagnostic accuracy of duplex color ultrasonography for diagnosis of upper extremity deep vein thrombosis.
Design: Prospective comparative study of duplex color ultrasonography versus venography.

Patients: 126 consecutive in- and outpatients with suspicion of upper extremity deep vein thrombosis.

Measurements: Contrast venography was obtained following duplex ultrasonography and judged independently. A three-step protocol, involving compression ultrasonography, color ultrasonography and color-Doppler ultrasonography was used. Sensitivity, specificity and likelihood ratio's for ultrasonography as a whole was calculated. The independent value of the three parts of ultrasonography was assessed.

Results: Venography and ultrasonography was not feasible in 23/126 (18%) and 1/126 patients (1%), respectively. Ultrasonography was inconclusive in 3 patients. Venography demonstrated thrombosis in 44 patients (prevalence 44 %), which was related to intravenous catheters or malignancy in 36 (36%). Sensitivity and specificity of duplex ultrasonography was 82% (95% CI: 67-92%) and 82% (95% CI: 69-91%) respectively. Venous incompressibility correlated well with thrombosis, while only 50% of isolated flow abnormalities proved thrombosis related.

Conclusion: Duplex color ultrasonography could be the investigation of choice in the initial diagnosis of patients with suspected upper extremity thrombosis. However, in isolated flow abnormalities contrast venography should be performed.

Introduction

The exact incidence of deep vein thrombosis of the upper extremity is unknown. A prevalence of 2 per 1000 hospital admissions has been reported (1). Deep vein thrombosis of the upper extremity is increasingly recognised as a condition with high mortality and morbidity comparable to deep vein thrombosis of the leg (2,3). It is intimately associated with malignancy and/or the use of central venous access lines (3-11). Nevertheless, few prospective studies on the diagnosis and management of deep vein thrombosis of the upper extremity have been published in the literature.

Contrast venography is generally considered the reference method to diagnose deep vein thrombosis of the upper extremity (2,3). However, due to the inherent problems of contrast venography, such as availability, the use of ionising radiation, the necessity for iodinated contrast media and the technical difficulties in obtaining intravenous access have led to a search for more appropriate, non-invasive methods.

Ultrasonography is widely available and there is extensive experience with the technique for the diagnosis of deep vein thrombosis of the lower extremity (12-18). However, only a few prospective studies with limited numbers of patients have been done to establish the role of ultrasonography for the diagnosis of deep vein thrombosis of the upper extremity (3,19-22). Besides this lack of data, there are inherent problems due to the anatomy of the upper extremity. The overlying bony structures and the inability to visualize the central intrathoracic venous system renders the performance of compression ultrasonography of limited value. Therefore, duplex color ultrasonography has been proposed as having additional value for the diagnosis of deep vein thrombosis of the upper extremity (3,19-24).

The aim of this study was to assess the diagnostic accuracy of duplex color ultrasonography in patients suspected of having deep vein thrombosis of the upper extremity in comparison with contrast venography.

Materials and Methods

Patient Population

During the period of August 1996 to March 2001, 126 consecutive out- and inpatients with clinically suspected deep vein thrombosis of the upper extremity were referred for diagnostic work-up. Three of these patients were referred twice and two patients were referred a third time. Patients were excluded for the following reasons: pregnancy, age younger than 18 years, renal failure prohibiting contrast venography, known allergy to iodinated contrast agents,

inability to obtain informed consent. Informed consent for duplex color ultrasonography and venography was obtained at referral from all but two patients, and the study was approved by the Institutional Review Board.

Technique of contrast venography

Contrast venography of the symptomatic extremity was performed using digital subtraction angiography equipment (Polytron, Siemens, Erlangen, Germany). A standardized protocol consisted of a 30 ml contrast injection in the antecubital vein, or if this was not possible a more distal forearm vein of the affected arm. No tourniquet was applied. Patients were studied with the examined arm in extension and little abduction of the upper arm to prevent self compression of the axillary vein by soft tissues. Low osmolar nonionic contrast was used with a concentration of 300 mg Iodine/l (Omnipaque, Nycomed-Amersham, Oslo, Norway). All injections were performed by hand. Digital subtraction images at a rate of one frame per second were obtained of the brachial, axillary, subclavian and superior caval veins.

The diagnosis of deep vein thrombosis of the upper extremity in this study was defined as either the presence of an intraluminal thrombus or persistent non-filling of a venous segment in the presence of filling of collateral vessels, as demonstrated by contrast venography. All other findings were regarded as inadequate for interpretation.

Technique of duplex color ultrasonography

Duplex color ultrasonography of the affected extremity was performed with assessment of the basilic, cephalic, axillary and subclavian vein. The jugular vein was not included into the study, because it is only visible by ultrasound and not by venography, therefore comparison is not possible. After identification of the relevant vessels, a three-step procedure was performed. This involved compression ultrasonography of those venous segments that could be reached, assessment of intravascular thrombus using color ultrasonography and flow measurements during respiration to determine the outflow of the venous system using color-Doppler ultrasonography. Patients were asked to perform Valsalva's maneuver to assess changes in flow pattern. Flow patterns of the non-affected upper extemity veins were used in case of doubt. All tests were performed by senior residents and staff radiologists with experience in duplex color ultrasonography as appropriate. Three qualified ultrasound machines were used, which were updated but not changed during the study (Hewlett Packard/Sonos 2000/Andover Massachusetts/USA, Aloka/1700 and 2000/Tokyo/Japan), with probes ranging 4.5-7.5 Mhz.

Duplex color ultrasonography was considered to demonstrate deep vein thrombosis in the following circumstances: non-compressibility of a venous segment, a visible intra-luminal thrombus or abnormal flow pattern (either absent flow or absence of phasic flow pattern indicating outflow obstruction) (3). If none of these findings were present, duplex color ultrasonography was regarded as normal. All other findings or the lack of visualization or performance of flow measurements were regarded as inadequate for interpretation.

Study design

A prospective comparative study in consecutive patients with clinically suspected deep vein thrombosis of the upper extremity was performed. All patients underwent duplex color ultrasonography as the first test, which was reported independently and within 4 hours prior to the reference method, contrast digital venography. The routine of the department in our teaching hospital was used, thus leading to the normal variety of qualified residents and staff personnel performing the ultrasonography and venography studies at any time during the day or evening. At all times the initial result from the color duplex was blinded for the radiologist who performed the venography.

Duplex color ultrasonography findings were compared with contrast venography as the reference method. Furthermore, we assessed potential factors associated with the cause of deep vein thrombosis of the upper extremity, like the presence of malignancy, indwelling catheters and the presence of a hypercoagulable state.

Statistics

The parameters of diagnostic accuracy (sensitivity and specificity) and likelihood ratio's were calculated (25). Indeterminate findings with duplex color ultrasonography were excluded of these parameters, as comparison with contrast venography is not possible. Furthermore, 95% confidence intervals were determined for these parameters.

Patient groups in whom deep vein thrombosis of the upper extremity was confirmed, excluded or remained uncertain were compared using Chi squared test with $p<0.05$ as level of statistical significance.

Results

During the inclusion period, 126 patients were eligible for enrolment in this study. A total of 27 patients had to be excluded from the analysis for the following reasons. Contrast venography could not be performed in 16 patients due to medical or technical reasons (failure to obtain venous access 10, renal

failure 3, pregnancy 2, iodinated contrast allergy 1). Another 5 patients had to be excluded because of logistic reasons. Informed consent was refused by two patients. So, venography could not be performed in 23/126 patients (18%). In one patient duplex color ultrasonography was not performed due to logistic reasons. Finally, duplex color ultrasonography was indeterminate in three patients, resulting in a conclusive rate of 98%. A flow diagram of patients is provided in Figure 1.

Thus, a total of 99 patients were available for evaluation, having undergone both duplex color ultrasonography and contrast venography. There were 44 men and 55 females with a mean age of 54 years (range 18 - 92 years). Deep vein thrombosis was demonstrated by contrast venography in 44 patients for a prevalence of 44%. The distribution of thrombi with venography in the right or

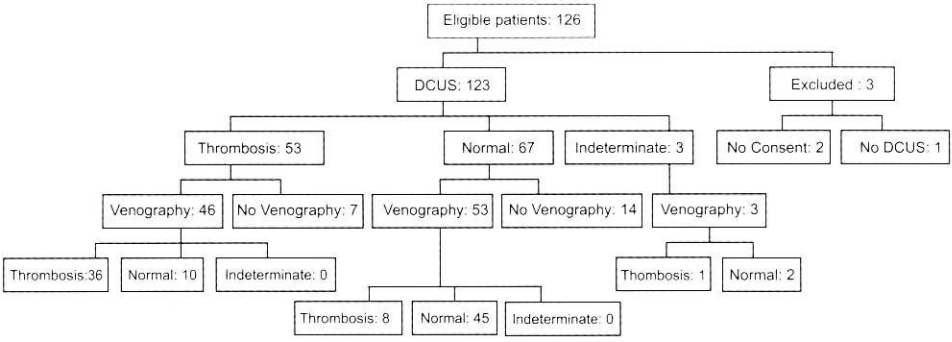

Figure 1: Flowdiagram of duplex color ultrasonography and venography in 126 patients suspected of having deep vein thrombosis of the upper extremity.

left upper extremity veins are show in Figure 2. The cause of thrombosis was considered to be primary in 8 patients, while an underlying cause could be shown in 36 patients (Table 1). Malignancy was present in 63% of patients with proven deep vein thrombosis of the upper extremity, while this was present in 19 of 55 patients (35%) in whom deep vein thrombosis was excluded ($p<0.01$).

Duplex color ultrasonography results were compared with the findings of contrast venography (Table 2). There were 8 false negative and 10 false positive studies, resulting in a sensitivity and specificity of 82% (95% CI: 70-93%) and 82% (95% CI: 72-92%), respectively. The likelihood ratio for a positive test was 4.5 (95% CI: 2.53-8.02) and for a negative test 0.22 (95% CI: 0.12-5.57).

Table 3 shows how the criteria for absence or presence of deep vein thrombosis of the upper extremity at duplex color ultrasonography were correlated with the findings at contrast venography. Isolated non-compressibility of a venous

segment was a relatively uncommon finding, but correlated with the presence of deep vein thrombosis of the upper extremity in all cases. The identification of an intraluminal thrombus was highly correlated, while flow abnormalities

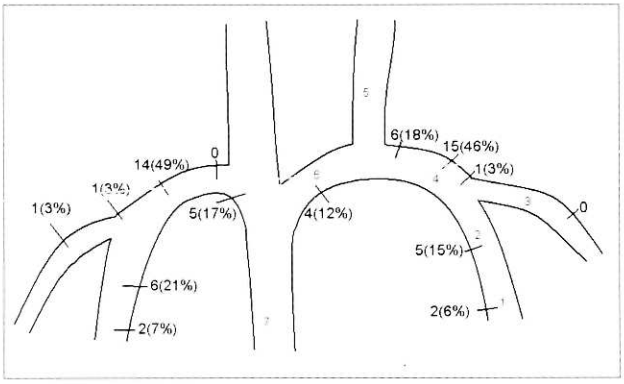

Figure 2: Distribution of 29 thrombi in the right and 33 thrombi in the left upper extremity veins with digital subtraction venography.

1 = basilic vein
2 = axillary vein
3 = cephalic vein
4 = subclavian vein
5 = jugular vein
6 = innominate vein
7 = superior caval vein

Tabel 1: Identified causes for 44 patients with proven deep vein thrombosis of the upper extremity

Identified causes			n (%)
Malignancy			28 (63%)
	CVC+	CVC-	
- Lymphoma/leukaemia	9	2	
- Pancreas cancer	5	1	
- Breast cancer	1	2	
- Chest malignancies (lung, pleura, oesophagus)	0	3	
- Others (GI tract, ovary, urothelial, myeloma)	3	2	
	18	10	
Central venous catheter without malignancy			6 (14%)
Hypercoagulable state			2 (5%)
- protein C deficiency with central venous catheter		1	
- factor II mutation		1	
Primary thrombosis of unknown cause			8 (18%)
			44 (100%)

n (%)= number and percentage of patients involved, CVC+ = with central venous catheter, CVC- = without central venous catheter

Table 2: Duplex color ultrasonography in comparison with contrast venography in 99 patients with suspected deep vein thrombosis of the upper extremity.

		Contrast venography		
		Thrombus present	Thrombus absent	Total (n)
DCUS	Thrombus present	36	10	46
	Thrombus absent	8	45	53
	Total	44	55	99
Sensitivity		82% (95% CI: 67-92%)		
Specificity		82% (95% CI: 69-91%)		
Likelihood ratio+		4.5% (95% CI: 2.53-8.02)		
Likelihood ratio-		0.22 (95% CI: 0.12-5.57)		

Note : Three indeterminate DCUS results were not accounted for in these parameters
DCUS = duplex color ultrasonography, n= number of patients involved

were least correlated with the presence of deep vein thrombosis.
Additional coincidential findings were disclosed in 8 duplex color ultrasonography investigations. These consisted of a solid mass (4 patients), cystic mass (2 patients), lymphadenopathy (1 patient) and abcess (1 patient). Contrast venography revealed additional information in 5 patients: external compression of the vein in four and a pneumothorax in one patient.

Table 3: Duplex color ultrasonography criteria for presence or absence of deep vein thrombosis of the upper extremity in relation with contrast venography.

		Contrast venography	
		Thrombus present (n)	Thrombus absent (n)
DCUS	Non-compressibility	5	0
	Intraluminal thrombus	24	3
	Flow abnormality	7	7
	Normal	8	45
	Total	44	55

DCUS = duplex color ultrasonography, n = number of patients involved

Discussion

Deep vein thrombosis of the upper extremity is a disorder, which is increasingly encountered in clinical practice due to a variety of reasons, such as long-term indwelling venous catheter use in a greater number of indications (2). Currently, the diagnosis often relies on clinical suspicion and contrast venography.

Venography is widely accepted as the reference method for establishing the presence or absence of deep vein thrombosis of the leg, although interpretation of venograms is subject to considerable observer variation (4-26%) (26,27).

Only a few prospective studies about the sensitivity and specificity of duplex color ultrasonography compared to venography in deep vein thrombosis are present, and as far as we know an observer variability study of digital subtraction venography of the upper extremity has never been done before. A short table listing previous studies and their major design limitations and findings is shown in table 4.

None of these studies disclosed much detail about observer variability of the reference tests. We performed a sub-analysis of the first consecutive 62 venograms. The interobserver agreement was 94% (kappa 0.88, 95% CI: 0.77-0.99) for a vascular radiologist and 76% (kappa 0.56, 95% CI: 0.33-0.79) for an experienced general radiologist compared with consensus, showing that (albeit imperfect) contrast venography can be used as a reference test for assessment of deep vein thrombosis of the upper extremity.

We think that errors in assessing thrombus of duplex ultrasonography and venography are likely independent. Although they both detect thrombus, both techniques are doing this differently, duplex color ultrasonography by a non-

Tabel 4: Performance characteristics of previous consecutive duplex color ultrasonography studies

Author	Yr.	Ref.	Sensitivity(%)	Specificity(%)	n=	Design DCUS objectives
Prandoni	1997	(3)	100	93	58	limited number of patients relatively small number of malignancies
Falk	1987	(19)	100	92	22	small number of patients normal volunteers included
Knudson	1990	(20)	78	92	91	reference standard: venography, CT and MRI
Baxter	1991	(21)	100	10	19	small number of patients
Köksoy	1995	(22)	94	88	44	all patients catheter-related thrombosis

Author = First author of publication, Yr = Year of publication, Ref = Reference according literature list, n = number of patients, DCUS = duplex color ultrasonography, CT = Computed Tomography, MRI = Magnetic Resonance Imaging

compressibility or flow abnormality of the vein, venography by showing a filling defect or absent vein. Because of overlying anatomical bony structures, like the clavicle and sternum, we can expect venography to do better in detecting thrombi more centrally. Jugular vein thrombosis, which is detectable by ultrasound and not by venography, is excluded in this study.

If the tests are considered as being independent, in general this means a slight underestimation of the sensitivity and specifity (28). So in our study we can expect the assessed sensitivity of 82% and specificity of 82% to be the lowest result in real practice.

In the present study, 13% of patients were unable to undergo contrast venography, largely due to medical conditions such as extreme arm swelling prohibiting venous access or contraindications for iodinated contrast injection. In another study 4 of 62 patients (6.5%) were unable to undergo venography (3). It is possible that this is due to more severe illness in our patients where intravenous access was not feasible. For example, in the present study 63% of patients with proven deep vein thrombosis of the upper extremity suffered from known malignant disease, whereas this was 30% in the group described elsewhere (3).

A possible methodological failure in our study could be the lack of randomization of ultrasonography and venography. However, all patients referred for diagnostic work-up for suspected deep vein thrombosis of the upper extremity were asked for their consent at referral and contrast venography was performed irrespective of the outcome of duplex ultrasonography. Furthermore, the diagnostic tests were performed independently, by different radiologists, and without knowledge of the test results. This in our opinion minimized the chance for bias. Three duplex color ultrasonography investigations were considered indeterminate (2%).

One patient was positive, two were negative for thrombus with venography. Although they would hardly influence the performance characteristics of this study, they were excluded.

Ultrasonography is widely available and circumvents several of the disadvantages of contrast venography. In the present study, duplex color ultrasonography could be performed in all but one patient. Compression ultrasonography and duplex color ultrasonography have been extensively validated for use in the diagnosis of lower limb deep vein thrombosis (12-18).

However, the upper extremity is anatomically much more complex than the lower extremity, due to the shape of the axilla and the overlying bony structures. Therefore, in contrast with lower limb ultrasonography (29), it has been postulated that duplex color ultrasonography has greater applicability for the diagnosis of deep vein thrombosis of the upper extremity, resulting in improvement of

diagnostic accuracy, when compared to compression ultrasonography (3,19, 20,21,22).

In the presented study, the sensitivity and specificity of duplex color ultrasonography was 82% and 82%, respectively. This compares slightly unfavorably with a previous publication in 58 patients, where figures of 100% (95%CI: 82-100%) and 93% (95%CI: 68-100%) were obtained (3). Other small prospective studies have found a sensitivity ranging between 78% and 100% and a specificity between 88% and 100% (19,20,21,22). Several explanations for this difference were sought. The prevalence of deep vein thrombosis of the upper extremity in our population was 44%, which is comparable to previously reported studies (3,19,20). The present study is the largest cohort described so far, and made use of a truly consecutive patient population. Some of the other prospective studies published to date may have suffered from selection bias, as only those patients with more severe symptoms and/or catheter-related and sometimes normal volunteers were assessed (19,20,21,22). Another possible explanation for the difference in diagnostic accuracy could be that the present study followed standard clinical practice, resulting in a variety of trained personnel to perform duplex color ultrasonography. It is well known that ultrasonography is operator dependent and it is possible that some of the less experienced ultrasonographers influenced the sensitivity and specificity results. Thus, other studies may have limited the ultrasonography to their best qualified personnel, leading to relatively better results. Nevertheless, we opted to perform this study using routine clinical practice, as this would result in a closer proximity of true clinical practice outcome.

The three criteria for the presence or absence of deep vein thrombosis were not assessed separately by each of the ultrasonographers, but show that non-compressibility, of the veins accessible for this technique, is highly correlated with the presence of deep vein thrombosis. This is similar to the use of compression ultrasonography in the lower leg veins, which has been validated extensively (29). The visualization of thrombus in a venous segment was also highly correlated with deep vein thrombosis. Finally, changes in flow were not correlated with the presence of deep vein thrombosis of the upper extremity. This latter finding contradicts two previous publications, which showed very high correlation of flow abnormalities with deep vein thrombosis of the upper extremity (3,22). In general, we would advocate that non-compressibility and/or presence of intraluminal thrombus on duplex color ultrasound would be sufficient for the diagnosis of deep vein thrombosis of the upper extremity,

whereas abnormal flow patterns should be regarded as suggestive only. This latter group should undergo subsequent contrast venography at present if flow abnormalities are found in isolation. Five of eight patients with false-negative duplex color ultrasonography findings were correlated with the presence of thrombus in the proximal subclavian vein on the left side, just below the clavicle. One patient with a false-negative duplex color ultrasonography finding had an isolated innominate vein thrombosis. Therefore, although a normal duplex color ultrasonography will be sufficient for the exclusion of deep vein thrombosis of the upper extremity in the majority of patients, one should still consider performing contrast venography if the clinical suspicion for deep vein thrombosis is high. This is also reflected in a likelihood ratio of a negative test of 0.22. Although this is relatively low, one can not conclude that a negative ultrasound investigation renders a venography unnecessary.

The presence of malignancy has been implicated as a risk factor for deep vein thrombosis. This has been shown for lower extremity thrombosis, where the risk increased from 1.5% in a first event to 7.5% in (recurrent) idiopathic deep vein thrombosis (30-32). In deep vein thrombosis of the upper extremity, a much higher proportion of patients suffered from malignancies. In the present study this was 63%, while this prevalence ranged from 24% to 62% in other studies (1,3,6-9). Explanations for this high incidence of malignancies in deep vein thrombosis of the upper extremity are that two-thirds of the patients with cancer also had a central intravenous access line in situ, which is an independent risk factor (7-11). Furthermore in those cases where malignancies arose as isolated risk factor, the types of cancer were mainly related to lymphnode metastases to the mediastinum or the axilla (breast, oesophageal and lung cancers).

In a substantial portion of our patient population, contrast venography could not be performed. This is a potential problem in patients with inconclusive duplex color ultrasonography findings. Some early studies have shown that contrast-enhanced Magnetic Resonance Venography could be used for the diagnosis of deep vein thrombosis of the upper extremity (33,34). However, this would not be ideal in these patients, as it would still require intravenous access. We anticipate that the development of non-contrast enhanced Magnetic Resonance Venography sequences could yield an alternative in the future.

Based on the present study and those in the literature, duplex color ultrasonography could be applied as the first line diagnostic test in patients with suspected deep vein thrombosis of the upper extremity. However, in patients with solely flow abnormalities or those with normal findings and a high clinical suspicion additional contrast venography should be performed.

We expect patients who cannot have a contrast venous study for a variety of reasons but have a history strongly suggestive of deep vein thrombosis of the upper extremity to have a Magnetice Resonance Venography without the use of contrast in the future, although further work-up on this issue has to be done.

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