Contrast sonovenography – Is this the answer to complex deep vein thrombosis imaging?

AGW Smith, P Parker, O Byass and K Chiu

Abstract

Background: Deep vein thrombosis (DVT) is a potentially fatal condition causing significant morbidity and mortality in the patient population. Ultrasound (USS) is the mainstay for detecting DVT. This can sometimes be difficult in hostile limbs due to factors such as large body habitus and oedema. This pilot study investigated contrast-enhanced ultrasound (CEUS) as a viable method to improve visualisation of the venous system of the lower limb.

Methods: Patients at high risk for DVT were selected after an initial negative USS. A follow-up scan was performed 1 week later utilising standard B-mode imaging with a curvilinear 3–5 MHz transducer array. After the fundamental scan, intravenous Sonovue™ contrast was administered and visualisation of the proximal limb veins and visualisation gains in distance were mapped onto a proforma.

Results: Twelve patients were selected. Visualisation was not improved in the common femoral vein (CFV) but increases in full visualisation were demonstrated in the femoral vein (FV) and popliteal vein (Pop V) from ($n=8$) 67% and ($n=10$) 83–100% in both veins, respectively. Significant gains in visualisation distance were observed in the posterior tibial vein (PTV) ($p=0.0005$) and peroneal vein (Per V) ($p=0.02$) with increased full visualisation of the Per V from ($n=3$) 25% to ($n=7$) 58%.

Conclusion: CEUS is a viable and clinically safe method for increasing visualisation of the deep venous system. It has the potential to improve visualisation of the lower limb venous system, reducing follow-up costs and diagnostic uncertainty for patients and the clinician.

Keywords

Contrast enhanced ultrasound (CEUS), microbubble contrast agents, Doppler ultrasound, deep vein thrombosis

Date received: 15 October 2015; accepted: 30 November 2015

Introduction

Deep vein thrombosis (DVT) is a potentially fatal condition with complications such as pulmonary embolism (PE) and debilitating post-thrombotic syndrome.¹ It is a common condition, affecting around 1–2% of the population.^{2,3} Venous stasis, endothelial injury and hypercoagulability has long been associated with the pathogenesis of venothromboembolism as described in Virchow's triad.⁴ Utilising this description, DVT may be seen to be 'provoked', due to a transient or discrete event, or 'unprovoked', without any identifiable root cause or secondary to malignancy. Examples of transient risk factors include pregnancy, immobilisation post-surgery and trauma.⁵

Although conventional venography remains the 'gold standard' for diagnosing DVT, it is invasive and exposes patients to ionising radiation.⁶ Currently, Duplex ultrasound is the investigation of choice as it is widely available and does not involve ionising radiation. The overall specificity of ultrasound is around 94%.⁷ The sensitivity, however, for thrombus detection in the lower limb varies hugely depending on the location; for proximal lower extremity, the sensitivity is

Department of Academic Radiology, Hull Royal Infirmary, Hull, UK

Corresponding author:

AGW Smith, Hull Royal Infirmary, Anlaby Road, Hull, HU3 2JZ.
Email: aubrey.smith@doctors.org.uk

around 95%, dropping to 64% in the distal lower extremity.⁷ Furthermore, the image resolution and penetration depth of ultrasound can be suboptimal in many patient groups, such as in the obese population or those suffering peripheral oedema secondary to dependent factors or heart failure. This will limit the ability to identify deep underlying structures such as vessels in these patients.^{8,9} With the proportion of overweight patients (inclusive of those who are obese) increasing from 57.6% to 67.1% and 48.6% to 57.2% in the male and female populations, respectively between 1993 and 2013,¹⁰ diagnosing this incapacitating and potentially fatal condition in these patients is going to be an increasing challenge.

Clinically high-risk patients are determined by a combination of standardised clinical algorithm (two-level Wells score)¹¹ and serum D-dimer.¹² This may lead to serial duplex ultrasound scanning as per NICE guidance with the patient having a repeat scan in 6–8 days if the D-dimer is positive in the presence of a negative proximal ultrasound scan.^{1,13} These patients are put on anticoagulation therapy, most commonly a therapeutic dose of subcutaneous low molecular weight heparin during this period. As a result, they are at risk of complications from the anticoagulation therapy, such as haemorrhage and heparin-induced thrombocytopenia.^{14,15} On a practical level, these patients need to attend hospital clinics repeatedly if treated in the community or be admitted as inpatients for the administration of heparin. All of these not only cause discomfort and inconvenience to the patient, but also incur costs to the health service and the patient. Nonetheless, the uncertainty of a diagnosis can cause stress and anxiety to the patient.

With this background, ways to improve the sensitivity and specificity of distal lower extremity DVT detection is both beneficial to the patient and the healthcare system. In recent years, contrast-enhanced ultrasound has become an increasingly accepted adjunct for diagnostic imaging. It is well tolerated, non-nephrotoxic and is substantially cheaper than investigations such as CT and MRI.¹⁶ Contrast-enhanced ultrasound (CEUS) allows the assessment of real-time enhancement patterns without the need to pre-define scan-time points or to perform bolus tracking. Contrast acts as an echo-enhancing agent, which facilitates visualisation of deep-seated veins that return poor echo-signals.¹⁷ The aim of this study was to see whether it is feasible to use CEUS in identifying deep leg veins.

Materials and methods

Fifteen patients (mean age 66; range 49–84) deemed high risk for thromboembolic disease, as determined by clinical decision algorithm (Wells score) and/or raised serum D-dimer, were identified for this study.

All patients had a previously negative ultrasound. An approved informed institutional standardised consent on the utilisation of data for study purposes was obtained from each patient according to the World Medical Association Declaration of Helsinki (59th WMA Assembly, Seoul, 2008). Local Ethics and Research and Development approval was also obtained.

Ultrasound of the lower limb of these patients was performed with the patient in supine position with the affected leg externally rotated and marginally flexed. The patients were examined using B-mode compression sonography along the transverse plane. Colour/power Doppler analysis additionally was used down to the distal calf. Visualisation of the veins was recorded and a measurement was made from the crease of the knee in the popliteal fossa to the extent that the calf veins could be visualised. Results were mapped onto a pro-forma.

After initial assessment with B-mode ultrasound and/or colour Doppler, a single bolus of 5 ml of sulfur hexafluoride contrast agent (SonoVue, Bracco International B.V.) was given intravenously via a cannula in the upper extremity. The examination was then repeated as before.

Patency in this study was defined as compressibility, combined with the presence of flow on colour Doppler if there is clinical uncertainty. Patency in CEUS relates to contrast visibility and compressibility if there is clinical uncertainty.

All ultrasound examinations were performed using a Toshiba Aglio XG (Toshiba Medical Systems, Crawley, UK) or Philips IU22 (Philips Healthcare, Guildford, UK), and a 3–5 MHz curvilinear array transducer. A standardised mechanical index (MI) setting of 0.08 was applied as recommended by the vendor. Images were produced in a contrast agent sensitive harmonic imaging mode, together with corresponding B-mode images and stored in the hospital Agfa Impax PACS system (Agfa Healthcare, Mortsel Belgium) (Figure 1).

Identification of the deep veins using CEUS was correlated with B-mode imaging. Real time images allowed differentiation of arterial and venous flow from observation of the directionality of flow of the microbubbles. The improved visualisation due to opacification of the deep veins allows targeted compression to be performed to aid differentiation. A filling defect in the opacified deep vein would indicate the presence of a DVT. Statistical analysis was performed with Graphpad Prism statistical software package (GraphPadTM Software, La Jolla, CA).

Results

Twelve of the 15 patients (12 limbs) recruited were included in this study (male $n=6$; female $n=6$).

Figure 1. Contrast enhanced images utilising harmonic imaging. The images demonstrate the improved visualisation of the peripheral lower limb venous system with administration of contrast utilising harmonic imaging. (a) demonstrates improved visualisation of the CFV (left image) compared to simultaneous B-Mode imaging (right image) in the transverse plane. (b) The femoral vein can be difficult to visualise at the adductor hiatus, but this is easily demonstrated post contrast administration. (c and d) further demonstrate the improved delineation of the venous anatomy in the popliteal vein and calf veins, respectively.

Of the three excluded, one was excluded due to failure to obtain IV access, another was withdrawn from the study as there was optimal visualisation of the leg veins on the initial B-mode imaging and the third patient was excluded due to extensive dressing on the lower leg due to overlying soft tissue damage precluding ultrasound scanning of the region. A Wilcoxon signed rank test was performed to analyse the pre- and post-contrast data in the calf vessels (Table 1). A single bolus of 5ml Sonovue was sufficient in all cases to provide good venous opacification. No new DVT was identified on the follow-up studies.

For the proximal lower limb, the common femoral vein (CFV) was visualised in 100% of cases pre contrast with no additional benefit gained with contrast

administration. The femoral vein (FV) and the popliteal vein (Pop V) demonstrated a pre-contrast observation of 67% ($n=8$) and 83% ($n=10$) along their whole lengths, respectively. Contrast administration improved visualisation to 100% for both veins.

Contrast administration provided statistically significant improvement in calf vein visualisation extent with a maximum gain of 39cm in a single case (Figure 2). There was improved visualisation of the posterior tibial vein in all of the candidates, with a mean gain in the distance visualised of 18.8cm ($p=0.0005$). Increased full visualisation of peroneal veins was demonstrated, improving from 25% ($n=3$) to 58% ($n=7$). Statistically significant gains in distance were demonstrated in these patients with a mean gain

Table 1. The number of veins (*n*) fully visualised and distances observed pre- and post-contrast administration in the lower limb

	B-mode	CEUS	<i>p</i> value
CFV, <i>n</i> (%)	<i>n</i> = 12 (100%)	<i>n</i> = 12 (100%)	
FV, <i>n</i> (%)	<i>n</i> = 8 (67%)	<i>n</i> = 12 (100%)	
Pop V, <i>n</i> (%)	<i>n</i> = 10 (83%)	<i>n</i> = 12 (100%)	
PTV mean [range] (cm)	12.2 [0–20]	30.9 [12–59]	0.0005
Per V mean [range] (cm)	7.5 [0–20]	20.1 [0–30]	0.02

Figure 2. Bar chart showing the mean visualisation distances pre- and post-contrast in the PTV and Per V with 95% CI.

of 10.6 cm ($p = 0.02$). In total, 60 veins (5 veins in each of 12 patients) were followed along the whole leg from groin to distal calf in the completed study. Of these, 43 were fully visualised pre-contrast and 55 post-contrast, corresponding to an improvement in full visualisation from 71.6% to 91.6%.

No anatomical variants or DVTs were identified on B-mode/colour Doppler imaging or CEUS.

Discussion

The use of CEUS to detect DVT is not a novel idea. A previous study by Bucek et al.¹⁸ showed the efficacy of CEUS in improving the diagnostic quality of Doppler images in DVT in 20 patients. They showed that the image quality of Doppler ultrasonography improved in 65% of scans and the specificity of detecting a calf vein thrombosis improved from 25% to 67% without compromising the sensitivity. However, the contrast agent

used in their study, Levovist (Berlex, Canada Inc.), a first generation air-based microbubble contrast agent, is a poor real-time agent and requires high output harmonic modes.¹⁹ To overcome the problems of the contrast agent's pharmacokinetics, the authors used a continuous IV infusion throughout ultrasound scanning to allow optimal enhancement.²⁰ As giving a continuous IV infusion during ultrasound examination is cumbersome and time consuming, let alone requiring additional nurses or doctors, it is impractical in everyday clinical practice. Furthermore, Levovist requires a high MI for optimal visualisation. Although the majority of the microbubbles remain within the vascular compartment, it has been demonstrated that microbubbles can be taken up by hepatic and splenic tissue.¹⁹ Using high MI ultrasonography can potentially cause tissue and organ damage.^{21,22}

In our study, a second generation contrast agent was used (SonoVue, Bracco International B.V.). This contrast agent is more suitable for real-time scanning, is responsive at low MI and has an excellent safety profile.¹⁹ Spiss et al.²³ have used this second generation contrast agent on three healthy volunteers and have demonstrated the feasibility of using this contrast agent.

Our study not only confirmed the feasibility of using CEUS for imaging the deep veins of the lower limb in a larger cohort, but we have also demonstrated that CEUS is superior to conventional B-mode and colour Doppler imaging. Unlike Spiss' study, we have opted to use the low frequency 3–5 MHz curvilinear probe rather than the 9–3 MHz broadband linear probe. This is because the 3–5 MHz curvilinear probe provides better penetration and is particularly advantageous because many patients with suspected DVT have clinically oedematous legs and the linear probe lacks the capacity to visualise deeper structures. Therefore, in our clinical practice, when looking for DVT in technically difficult lower limbs, we utilise a 3–5 MHz curvilinear probe to good effect.

Although one of the larger feasibility studies to date, this still remains a small cohort of patients and a

further study is required to confirm the efficacy of CEUS in the detection of DVT. Our patients were recruited in a hospital setting and a further population could be accessed in the community where frequent repeat ultrasound studies are performed. At present, the study's ethics approval does not include pregnant patients. As previously stated, this is a high-risk population where this may be potentially useful or of some benefit. To our knowledge, DVT has not been visualised in vivo in humans utilising CEUS.²⁴ DVT has been described in mouse model studies as being visualised as a filling defect or intraluminal negative contrast in the presence of contrast agent. No DVT was identified in our study.

In our experience, there are few technical issues regarding CEUS. However, one limitation in utilising CEUS is the difficulty in differentiating the anatomy of the arterial and venous systems on hard copy images. In real-time it is easy to identify the anatomy due to the direction of microbubble flow and the ability to augment through compression. Another potential pitfall is the presence of normal anatomical variation.²⁵ In the superficial femoral venous system a range of 6–46% of patients has been described as presenting with duplicated systems or multiple vessels. This is also demonstrated in the popliteal vein. This can be a problem even on B-Mode/colour Doppler imaging and there is always the possibility that a parallel deep system may be missed. However, in a single case, visualisation of the peroneal venous system was improved to demonstrate both peroneal veins compared to the single peroneal vein initially observed. Although not the primary motivation of the study, this may suggest CEUS may increase sensitivity of parallel venous systems that may be difficult to visualise with B-mode imaging alone.

Our results demonstrate that CEUS improves visualisation of the venous system in the proximal and distal lower limb and can potentially significantly increase the sensitivity for detecting DVT in patients where traditional B-mode may be unable to, for example in patients with high body mass index, peripheral oedema or diffuse inflammation.¹³ The current NICE guidelines¹³ recommend repeat lower limb ultrasound 1 week after an initial negative scan in high risk patients to look for possible clinically significant DVT propagation. This is to avoid time-consuming whole leg scanning and further unnecessary anticoagulation of patients. It is noted by the NICE guideline development group that proximal DVT scanning in the leg will not identify an isolated calf DVT. CEUS may help prevent serial DVT by providing improved real time visualisation and delineation of proximal venous anatomy with improved visualisation of the calf veins in a single scan.²³ This method, therefore, gives potential to save money to reduce out-patient follow-up for patients who

are high risk for DVT, whilst giving clinicians and the patient peace of mind of increased diagnostic certainty in clinically difficult to examine limbs.

Conclusion

This study has demonstrated that CEUS improves visualisation of the deep veins of the lower limb, thereby increasing the confidence of excluding a DVT. Of the 60 veins studied in total, the number fully visualised increased from 43 (71.6%) to 55 (91.6%). Contrast sonovenography enabled full visualisation of the femoral and popliteal veins in 100% of our cases, whilst improving visualisation of peroneal veins and statistically improving vessel visualisation in all calf veins.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval

The National Research Ethics Service Committee Yorkshire & The Humber-Humber Bridge approved this study (REC Reference 12/YH/0336)

Guarantor

KC

Contributorship

KC and AS researched the literature and provided data analysis. OB gained ethical approval. AS, PP and KC were involved in patient recruitment and data collection. OB, KC and PP were involved in conceiving the project. AS wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Acknowledgements

We are grateful to all of the sonographers at Hull Royal Infirmary for helping identify potential candidates for this study.

References

1. Scarvelis D and Wells PS. Diagnosis and treatment of deep-vein thrombosis. *CMAJ* 2006; 175: 1087–1092.
2. Fowkes FJ, Price JF and Fowkes FG. Incidence of diagnosed deep vein thrombosis in the general population: systematic review. *Eur J Vasc Endovasc Surg* 2003; 25: 1–5.
3. White RH. The epidemiology of venous thromboembolism. *Circulation* 2003; 107: 14–18.

4. Malone PC and Agutter PS. The aetiology of deep venous thrombosis. *QJM* 2006; 99: 581–593.
5. Wells PS, Forgie MA and Rodger MA. Treatment of thromboembolism. *JAMA* 2014; 311: 717–728.
6. Tan M, van Rooden CJ, Westerbeek RE, et al. Diagnostic management of clinically suspected acute deep vein thrombosis. *Br J Haematol* 2009; 146: 347–360.
7. Goodacre S, Sampson F, Stevenson M, et al. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. *Health Technol Assess* 2006; 10: 1–168.
8. Saranteas T. Limitations in ultrasound imaging techniques in anesthesia: obesity and muscle atrophy? *Anesth Analg* 2009; 109: 993–994.
9. Saranteas T, Anagnostis G, Lappas T, et al. Feasibility of ultrasound imaging of the abdominal wall in elderly obese volunteers. *Br J Anaesth* 2010; 105: 549–550.
10. Health & Social Care Information Centre. *Statistics on Obesity, Physical Activity and Diet: England 2015*. Leeds; HSCIC, 2015. See <http://www.hscic.gov.uk/catalogue/PUB16988/obes-phys-acti-diet-eng-2015.pdf> (last checked 12 December 2015).
11. Wells PS, Hirsh J, Anderson DR, et al. Accuracy of clinical assessment of deep-vein thrombosis. *Lancet* 1995; 345: 1326–1330.
12. Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med* 2003; 349: 1227–1235.
13. National Institute for Health and Care Excellence. *Venous Thromboembolic Diseases: Diagnosis, Management and Thrombophilia Testing*. NICE guidelines (CG144). London: NICE, 2012. See <https://www.nice.org.uk/guidance/cg144/chapter/guidance#treatment-2> (last checked 1 December 2015).
14. Schulman S, Beyth RJ, Kearon C, et al. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edn). *Chest* 2008; 133: 257S–298S.
15. Warkentin TE and Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126: 311S–337S.
16. Claudon M, Cosgrove D, Albrecht T, et al. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS) – update 2008. *Ultraschall Med* 2008; 29: 28–44.
17. Sidhu PS, Allan PL, Cattin F, et al. Diagnostic efficacy of SonoVue, a second generation contrast agent, in the assessment of extracranial carotid or peripheral arteries using colour and spectral Doppler ultrasound: a multi-centre study. *Br J Radiol* 2006; 79: 44–51.
18. Bucek RA, Kos T, Schober E, et al. Ultrasound with Levovist in the diagnosis of suspected calf vein thrombosis. *Ultrasound Med Biol* 2001; 27: 455–460.
19. Blomley M, Claudon M and Cosgrove D. WFUMB Safety Symposium on Ultrasound Contrast Agents: clinical applications and safety concerns. *Ultrasound Med Biol* 2007; 33: 180–186.
20. Albrecht T, Urbank A, Mahler M, et al. Prolongation and optimization of Doppler enhancement with a micro-bubble US contrast agent by using continuous infusion: preliminary experience. *Radiology* 1998; 207: 339–347.
21. Vancraeynest D, Kefer J, Hanet C, et al. Release of cardiac bio-markers during high mechanical index contrast-enhanced echocardiography in humans. *Eur Heart J* 2007; 28: 1236–1241.
22. Williams AR, Wiggins RC, Wharram BL, et al. Nephron injury induced by diagnostic ultrasound imaging at high mechanical index with gas body contrast agent. *Ultrasound Med Biol* 2007; 33: 1336–1344.
23. Spiss V, Loizides A, Plaikner M, et al. Contrast enhanced ultrasound of the lower limb deep venous system: a technical feasibility study. Technical innovation. *Med Ultrason* 2011; 13: 267–271.
24. Guenther F, Herr N, Mauler M, et al. Contrast ultrasound for the quantification of deep vein thrombosis in living mice: effects of enoxaparin and P2Y₁₂ receptor inhibition. *J Thromb Haemost* 2013; 11: 1154–1162.
25. Quinian D, Alikhan R, Gishen P, et al. Variations in lower limb venous anatomy: Implications for US diagnosis of deep vein thrombosis. *RSNA Radiol* 2003; 228(2): 443–448.