Contrast Enhanced Ultrasound of the lower limb deep venous system: a technical feasibility study.

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Abstract

Background: A clear diagnosis of deep venous thrombosis (DVT) is still challenging: many patients with unclear compression/duplex-sonography undergo a trial of anticoagulative treatment with the immanent risk of systemic hemorrhagic complications. As contrast enhanced ultrasound (CEUS) has the potential to visualize the blood pool, we conducted this pilot study to determine its potential in the characterization of the deep venous system of the lower limb.

Material and Methods: CEUS was performed with a 9-3 MHz broadband linear transducer (iU22®, Philips, USA) after the standard-application of a second-generation contrast agent (SonoVue®, Bracco, Italy) in three healthy volunteers. Transverse US-scans were performed for depiction of the fibular-, posterior tibial-vein group, the popliteal, femoral, the external iliacal and the inferior caval vein at defined levels.

Results: On our three volunteers the intended segments of the deep venous system of the lower limb were visualized clearly between 45 and 350 seconds by CEUS. The continuous proximal ward scanning demonstrated the venous topography up to the external iliac veins.

Discussion and conclusions: These preliminary results show that the use of CEUS is at least promising in the detection and characterization of the deep venous system of the lower limb. This should be pathbreaking, especially in patients with e.g. high Body Mass Index, local edema, diffuse inflammation etc. undergoing sonographic assessment for suspected deep vein thrombosis not definable by complete compression venous ultrasound or duplex ultrasound.

Keywords: ultrasound, contrast agent, deep vein thrombosis

Introduction

Deep venous thrombosis (DVT) in the lower extremity has an incidence of about 50 per 100,000 person-years signifying a rather common disease. An undiagnosed DVT may lead to potentially fatal complications such as pulmonary embolism [1,2]. To date conventional venography still represents the golden standard for diagnosing DVT, but has become increasingly replaced by complete compression venous ultrasound (CVUS) as the imaging modality of choice during daily routines. CVUS stands for a non-invasive, simple and commonly available diagnostic modality without radiation exposure at a low expenditure of time [2,3]: in an acute setting, the triad of a standardized clinical decision algorithm (i.e. “Wells-scoring”), D-dimer testing and CVUS has proven to be sufficiently safe for the diagnosis of forms of DVT with an inherent risk of pulmonary embolism [2,3]. As sonography is safe and may be performed in bed-side settings, complete compression venous ultrasound (CCVUS), which corresponds to a standardized CVUS including all deep and muscular veins of the lower extremity, is mandatory to replace conventional venography completely and to clarify profoundly the symptomatic patient. If the findings by CCVUS – before all in the calf – are inconclusive though, colour Doppler flow imaging (CDFI) can be used additionally [2,4]. Nonetheless, in a relevant number of
cases the definitive diagnostic assessment before all of the deep venous system remains uncertain due to edema, inflammatory changes and/or obesity of the patient [2-6]. Thus a trial of anticoagulative therapy is often made (before everything in bedfast patients) only based on the clinical suspicion and on laboratory markers alone with the immanent and potentially life-threatening risks of hemorrhagic complications [7]. However, the overall relevance of diagnosis in this field is still in debate as over 50% of DVT diagnosed by CCVUS are estimated to be isolated distal DVT [6,7].

As is known from other admission ranges, 2nd generation ultrasound contrast agents have the potential to depict the blood pool: by their application even very tiny vessels become accessible for sonography, which is clearly beyond any potential of Duplex ultrasound (DU) [8-11]: CEUS enables the visualization of vessels with a diameter as small as about 40 μm [11] which corresponds to the direct pre- and post-capillary vascular system. As (C)VUS presents a rather confined diagnostic yield [12] leading to medical malpractice, this proposed pilot-study was conducted to preliminarily determine the technical feasibility of contrast enhanced ultrasound (CEUS) for assessing the venous system of the lower limb and to establish a new, easy-to-use imaging algorithm for the diagnosis of DVT.

Materials and Methods

Three healthy volunteers aged 28, 29 and 33 years underwent CEUS. Basing on the judgement (Doc. Ref. EMEA/H/C/303) and the public statement of the European Agency for the Evaluation of Medicinal Products (EMEA, Doc. Ref. EMEA/CPMP/212/04) on the indications and contraindications for the use of SonoVue® (Bracco, Italy) informed institutional standardized consent on the utilization of data for study purposes was obtained from each volunteer according to the World Medical Association Declaration of Helsinki (59th WMA Assembly, Seoul, 2008). All images were stored in the institutional Agfa® Impax. All ultrasound examinations were performed on a Philips iU22® (Philips, Bothell, Washington, USA) using a 9-3 MHz broadband linear array transducer and CEUS was performed in contrast harmonic imaging technique. A standard mechanical index (MI) setting of between 0.06 and 0.08 was applied as recommended by the vendor. The sulfur fluoride microbubbles-solution (SonoVue®, Bracco, Italy) was administered as a single 4.8-ml bolus via a 20-gauge cannula in an antecubital vein. The injection was always followed immediately by a single bolus-shot of 10 ml of 0.9% sodium chloride solution. A chronometer displayed on the screen was used to determine the time elapsed after contrast injection. Subsequently axial US-scans were produced in contrast agent sensitive contrast harmonic imaging technique together with a corresponding greyscale image. Beginning at the right distal calf (scanning from medioventral with the patient lying right-sided) continuously upwards to the popliteal fossa (scanning from posterior) up to the thigh (scanning from ventro-medial) heading for the inguinal region. Additionally, the pelvine veins were depicted accordingly (scanning from ventral with an according probe positioning) superior to the inguinal ligament until the confluence to the inferior caval vein.

Results

On our three healthy volunteers the deep venous system of the lower limb could clearly be visualized after the application of a US contrast agent in a time frame between at least 45 and 350 seconds after complete administration:

• When the popliteal vein of each volunteer had clearly presented homogeneously contrast filling, the scanning procedure depicted the two pairs of posterior calf veins (posterior tibial and fibular veins; fig 1).

• The continuous proximal ward scanning demonstrated the confluence of these veins to the popliteal vein (fig 2).

• Also the superficial femoral vein of each volunteer was found to be contrasted homogeneously in its whole extent (fig 3).

• In addition proximally even the influx of the greater saphein vein was depicted homogeneously (fig 4).

Discussion

DVT as an important cause of mortality and morbidity requires an accurate diagnosis. Ultrasound examination, i.e. CVUS, CCVUS and CDFI, has largely replaced the time consuming and ionizing conventional venography during daily routines before everything in order to exclude forms of DVT with immanent risk for pulmonary embolism [12].

Righini et al showed that about 50% of DVT diagnosed by CCVUS are isolated distal DVT [13]. These findings can consist of either true positive small distal DVT, that would resolve spontaneously, or false positive distal DVT. This contains a dispensable risk of associated bleeding complications due to overtreatment not indicated [14].
Fig 1. Scan of the calf, left image in contrast agent sensitive contrast harmonic imaging technique and grey-scale image using: the troika of the two posterior tibial veins (arrow heads) bordering the posterior tibial artery and the troika of the two fibular veins (arrows) bordering the fibular artery; popliteal fossa (asterisk).

Fig 2. Scan of the venous confluens in the popliteal fossa: left image in contrast agent sensitive contrast harmonic imaging technique and corresponding grey-scale image: the more superficial popliteal vein (curved arrow) neighboured by the popliteal artery and differently sized contrasted “dots” of the discharging muscular veins; popliteal “vein confluens” (curved arrow); patella (asterisk).

Fig 3. Scan of the thigh, left image in contrast agent sensitive contrast harmonic imaging technique and corresponding grey-scale image: superficial femoral vein (arrow); patella (asterisk).
Although CCVUS seemed to be promising, some mostly physically based (i.e. due to obesity etc.) rather high rates of inconclusive examinations have been described [2]. The addition of CDFI is a helpful adjunct but as Kearon et al [15] reported in his study, sensitivities of just over 70% for the combination of CVUS and CDFI still remain unacceptably low as the basing physical constraints can not be overcome. About 30% of distal DVT therefore remain uncertain due to impossibilities e.g. local edema, high BMI etc.

In this pilot study we demonstrated the overall technical feasibility and basic potential of CEUS in the visualization of the tiniest vessels of the distal limb after systemic ultrasound contrast administration. The deep venous system of the whole lower extremity and especially the lower leg veins were demonstrated and characterized within an adequate time frame of about 5 minutes.

However, aerated bowel might be seen as a limitation-factor for the demonstration of the pelvic venous segments. Nevertheless, adverse effects on contrast agents have to be taken into account also in the field of venous blood pool imaging even though these effects are estimated to be very low (Doc. Ref. EMEA/H/C/303, Doc. Ref. EMEA/CPMP/212/04): only a rate of 0.0012% of severe events has been documented to date.

**Conclusion**

This time saving, non-ionizing, easy to use and broadly available technique of CEUS could be groundbreaking in the overall diagnosis of DVT, especially in the often non-conclusive and tricky cases seen in patients with bad US conditions. The overall value of CEUS concerning a reliable diagnosis of DVT in the lower limb must be subsequently evaluated in a prospective, randomized clinical trial.

**Conflict of interest:** none

**References**