Ultrasound in Med. & Biol., Vol. 41, No. 6, pp. 1570–1576, 2015

0301-5629/$ - see front matter

http://dx.doi.org/10.1016/j.ultrasmedbio.2015.02.004

● *Original Contribution*

ROLE OF CONTRAST-ENHANCED ULTRASOUND ARTERIAL MAPPING IN SURGICAL PLANNING FOR PATIENTS WITH CRITICAL LIMB ISCHEMIA

Xavier Martí Mestre, Ramon Vila Coll, Antoni Romera Villegas, and Carlos Martínez Rico
Hospital Universitari de Bellvitge, Barcelona, Spain

(*Received* 15 *October* 2014; *revised* 6 *February* 2015; *in final form* 10 *February* 2015)

Abstract—The goal of the study described here was to evaluate the role of contrast-enhanced ultrasound (CEUS) arterial mapping in surgical planning in cases of critical limb ischemia. From March 2007 to December 2012, 565 consecutive patients with critical limb ischemia of the lower limbs were treated and initially examined with only ultrasound (US) arterial mapping. For 479 of the 565 patients, basic US examination results were deemed sufficient for surgical planning (group A). That is, US examination provided sufficient information to decide a surgical plan to treat those patients. In the remaining 86 patients, basic US examination was insufficient for revascularization planning, and CEUS examination was performed (group B). In 5 cases, CEUS results were also insufficient for surgical planning, as a suitable outflow vessel was not visualized. In these cases, a pre-operative arteriogram was performed. To assess the usefulness of CEUS, we compared results of examinations with and without contrast administration, surgical findings and angiographic findings when available. Data were collected prospectively. Examinations were compared by establishing the degree of agreement between results of paired examinations and degree of agreement between CEUS results and surgical findings. Clinical, hemodynamic (ankle–brachial index) and duplex follow-up was performed at 1 and 3 mo to evaluate cumulative patency of the procedures in each group. Within group B, degree of agreement between basic US and CEUS was 46.5%. CEUS resulted in a change in the surgical plan in 46 of 86 patients. Among all 565 patients, degree of agreement between surgical decision based on basic ultrasound arterial mapping and final decision based on surgical findings was 87.1%, and improved to 95.2% with CEUS ($p = 0.00001$, κ index = 0.823). Degree of agreement between the ultrasound-based decision and surgical findings was 97.5% in group A (κ index = 0.818) and 94.2% in group B ($\kappa = 0.848$). There was no significant difference between groups ($p = 0.784$). Within group B, of the five arteriograms performed, results of only one matched well the US mapping findings. Vessel patency at 1 and 3 mo did not significantly differ between patients whose surgical planning was based on basic US and patients whose planning was based on CEUS ($p = 0.418$ and $p = 0.489$, respectively). US arterial mapping is an excellent tool for surgical planning in critical limb ischemia. CEUS arterial mapping improves the accuracy of ultrasound examination in patients with critical limb ischemia, especially in patients with inconclusive non-enhanced exams. (E-mail: xamame@hotmail.com)

Key Words: **Duplex, Ultrasound, Contrast enhanced ultrasound, Critical limb ischemia, Surgical planning.**

INTRODUCTION

For patients with critical limb ischemia (CLI), the use of ultrasound (US) mapping as the sole pre-operative examination is increasingly becoming accepted (Cao et al. 2011; Norgren et al. 2007). Most angiographic methods provide only simple morphologic information on lumen reduction and reconstitution sites; duplex ultrasound, however, can reveal much more. Doppler analysis allows the collection of hemodynamic data regarding blood flow inside these vessels. Furthermore, duplex is an affordable test, has no adverse effects and can be repeated and extended until an adequate diagnosis is obtained. However, duplex has also been criticized as being highly user dependent and time consuming. Another drawback is the difficulty in obtaining reliable results in cases with obese patients, severe arterial calcifications or very low flow in the studied vessels (Cao et al. 2011; Mazzariol et al. 1998). Patients with CLI usually have multilevel disease and low-flow perfusion of the vessels and very frequently exhibit vessel wall calcification caused by diabetes (Cao et al. 2011; Norgren et al. 2007). Hence, arterial US mapping is especially troublesome in CLI. The use of contrast

Address correspondence to: Xavier Martí Mestre, Hospital Universitari de Bellvitge, C/Felip II, 133, Barcelona 08027, Spain. E-mail: xamame@hotmail.com

enhancement has been proposed to improve performance of duplex exams in these difficult situations.

A contrast ultrasound agent is defined as a substance capable of enhancing the intravascular ultrasound signal in B-mode and color Doppler mode, allowing better visualization of vascular flow. The contrast agent consists of gaseous microbubbles that act as non-linear reflectors of ultrasonic waves. When encountered by ultrasound waves, these microbubbles compress and dilate in all directions of space, readily breaking and releasing harmonic energy that enhances ultrasonic signal. To be suitable for clinical use, a contrast agent must be easy to prepare, non-toxic, effective after intravenous administration, persistently stable, with good hematopulmonary diffusion for clearance, and capable of enhancing ultrasonic signal in specific contrast imaging modes (Rose and Nelson 2004). SonoVue (Bracco International, Amsterdam, Netherlands) is a second-generation contrast agent that meets all of these above; it consists of a gas molecule of sulfur hexafluoride encapsulated in a lipid shell to form the microbubble. When an ultrasound wave encounters a microbubble, it causes it to compress and expand. Bubbles resonate at classic harmonic frequencies, enabling discrimination between bubble, tissue and artifact (Harvey et al. 2001; Lindner 2004). Figure 1 is an example of the images provided by contrast-enhanced US (CEUS).

The aim of the present study was to evaluate the role of sulfur hexafluoride as an enhancer in arterial duplex studies of critically ischemic limbs.

METHODS

We performed an observational, comparative and prospective study in patients diagnosed with CLI according to TransAtlantic Inter-Society Consensus II criteria (Norgren et al. 2007). Patients were recruited consecutively from those treated in our institution between March 2007 and December 2012. Patients who only received management with medical treatment or primary amputation because of the extent of lesions were excluded. All patients signed an informed consent to participate in the study; furthermore, those included in the ultrasound contrast enhancement group signed an additional consent for the off-label use of the product. This observational study received the approval of the ethics committee of our institution (Registry No. PR347/14).

All patients were examined using the same US machine (Acuson Antares Premium Edition, Siemens Medical Solutions USA, Malvern, PA, USA). During examination, the patient was placed supine with slight flexion and external rotation of the hip and knee. We evaluated the arteries from the aorta to the popliteal artery below the knee in the cranial-to-caudal direction. Distal arteries, including the anterior and posterior tibial artery and peroneal artery, were studied in the caudal-to-cranial direction. We used a 7.5-MHz linear array probe (Siemens Acuson Antares VF 10-5 Transducer, Siemens Medical Solutions USA) to study femoropopliteal and distal vessels and a 3.5-MHz curved array probe (Siemens Acuson Antares CH4-1 Transducer, Siemens Medical Solutions USA) to study aorto-iliac vessels. The examination began in B-mode to evaluate vessel wall lesions; this was followed by color Doppler mode to evaluate arterial flow characteristics, and finally, pulsed-Doppler was used to evaluate flow velocity waveform. A lesion was considered significant when the ratio of peak systolic velocity at the stenosis to that before was ≥ 3, which is consistent with a stenosis $\geq 70\%$ (Mestre et al. 2009). A vessel was considered occluded when no color signal was obtained in the vessel lumen in color Doppler mode or when there was no Doppler signal in the lumen of the vessel in pulsed Doppler mode (Mestre et al. 2009).

When a scan was insufficient for use in determining the arterial anatomy of the limb to re-vascularize, contrast agent was employed. Criteria for non-diagnostic scans were those in which an experienced sonographer was unable to identify an outflow vessel or a treatable lesion, despite a thorough search. Such scans were basically characterized by severe calcification, poor visualization of vessels or inability to detect flow in runoff vessels. Patients with CLI may have very slow, non-pulsatile flow in below-knee vessels that is not detected with non-enhanced US. We considered that a scan was insufficient when it did not allow us to decide on a surgical plan. This means that the US test did not reveal appropriate vessels for revascularization. This was determined by the sonographer who performed the US.

Contrast agent was prepared by diluting 25 mg of sulfur hexafluoride in 5 mL of 0.9% saline solution (SonoVue, Bracco International). This dilution was injected into a peripheral vein in two pulses of 2.5 mL each. In these examinations, segments of the arterial tree that had not been properly visualized with conventional duplex were specifically focused with specific software to detect contrast agent in the lumen of the vessels in B-mode (Advanced SieClear spatial compounding with Dynamic TEC tissue contrast enhance technology). Vessels were defined as *patent* when contrast agent was visualized in the lumen and as *occluded* when it was not. All US arterial mapping exams were performed by an accredited sonographer (X.M.M.).

If contrast-enhanced mapping ultrasound was insufficient for surgical planning, an arteriogram was used (IGS Descubrimiento 730, General Electric Healthcare, Spanish Division, Barcelona, Spain). CEUS was deemed insufficient when it did not improve the findings of the