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Ultrasound Imaging in Vascular Diseases

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1. Introduction

Ultrasound scanning has become one of the most important noninvasive investigations used in the assessment of vascular diseases. Duplex ultrasound is currently the main diagnostic modality used in deep venous thrombosis and carotid disease. It enables monitoring of bypasses for patency and neointimal hyperplasia as well as transcranial examination of brain vessels in subarachnoid hemorrhage.

Nowdays, the role of the vascular laboratory is continuously changing with the introduction of new technology. New interventions such as carotid stenting and endovascular aneurysm repair have necessitated the use of duplex ultrasound for detecting in-stent restenosis or endoleaks. Ultrasound is also used intra-operatively in evaluating endovenous procedures such as laser and radiofrequency ablation and the patency of in situ vein bypasses. Arterial mapping of the lower extremity by duplex ultrasound has replaced contrast angiography (CA) and magnetic resonance angiography (MRA) for lower extremity bypass procedures.

Most recently, a variety of new applications for vascular ultrasound has arisen. Contrast-enhanced ultrasound imaging allows the assessment of microcirculation and can be used for delivery of drugs and genetic therapies. Physicians use three-dimensional ultrasound to assess carotid plaque volume and monitor its evolution with time and its response to various treatments. In the era of atherosclerosis, ultrasound has provided a non-invasive way of assessing the elastic properties of an artery and to evaluate the patient's risks of adverse cardiovascular events. Finally, intravascular ultrasound has opened new frontiers in the measuring of intimal thickness and assessing vulnerable plaques.

2. Ultrasound in the era of atherosclerotic disease

2.1 Intravascular ultrasound (IVUS)

Intravascular ultrasound is a promising and rapidly evolving technique that provides high-quality images of the vessel's wall and lumen (Houslay & Uren, 2005) (Fig. 1).

Angiography, the traditionally used "gold-standard" in the imaging of vascular morphology (Liu & Goldberg, 1999) has multiple disadvantages, such as depiction only of

contrast agent filled lumen and not the vessel wall, as well as the risk of contrast-induced renal failure. Moreover, it underestimates the plaque burden, especially for the detection of concentric lumen narrowing (Liu & Goldberg, 1999).

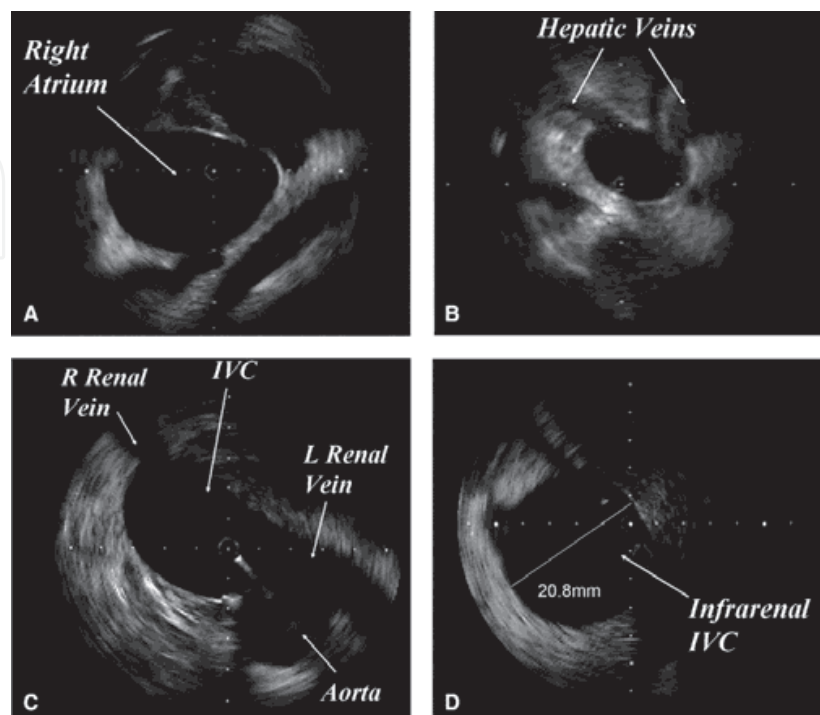


Fig. 1. Intravascular ultrasound (IVUS) advancing via the inferior vena cava (IVC) at various levels depicting the right atrium (A), the hepatic veins (B), the renal veins (C), and the infrarenal IVC (D)

With the use of high-frequency catheter based transducers, all basic components of the vessel are identified: the cross sectional luminal size, shape and vessel wall, as well as the various layers of the wall such as the intima, media, adventitia and perivascular structures (Liu & Goldberg, 1999).

In conventional gray-scale intravascular sonography arteries can be classified as elastic (lying centrally in the arterial tree) or muscular (peripherally distributed). Calcifications are demonstrated as hyperechoic areas, whereas hemorrhage or fat deposition inside an atheromatic plaque is hypoechoic. Subsequently, the plaque is subclassified as lipid, calcified and fibrous, according to its differential acoustic properties (Liu & Goldberg, 1999). Furthermore, the concomitant use of colour-flow intravascular sonography allows for a real-time dynamic assessment of plaque morphology and provides a better understanding of the blood flow, the lumen size and the success of endovascular treatment (Zacharatos et al., 2010). Hence, the physician can obtain a realistic virtual histology map of the patient's arteries, visualize the atheroma without the need of true histologic sections of the diseased coronary arteries and tailor his treatments (Fayad & Fuster, 2001; Martin et al., 1997).

The correlation of IVUS plaque characteristics and histopathologic specimens is well validated in literature (Potkin et al., 1990). The CAPITAL study showed a strong correlation of IVUS findings with histologic specimens from endarterectomy (Diethrich et al., 2007) while Potkin et al compared IVUS with coronary histopathologic specimens, to show that fibrous and calcified plaques were identified with good precision (Potkin et al., 1990).

In patients with coronal artery stenosis IVUS can act as a prognostication tool, as vulnerable plaques, heavy in fat deposition are considered at higher risk for cardiovascular events and might need more aggressive treatment. In addition, plaque regression in respond to lipid lower therapies with statins has been successfully monitored by the use of serial IVUS (Crouse et al., 2007; Nissen, 2005; Nissen et al., 2008). Many dynamic phenomena in the setting of an atheroma, such as positive and negative remodeling or restenosis after angioplasty and stenting are timely demonstrated and treated accordingly (Liu & Goldberg, 1999).

The concomitant use of intravascular elastography (Fayad & Fuster, 2001) (images obtained from cardiac IVUS images associated with intraluminal pressures during the cardiac cycle) expands the frontiers of the IVUS technique, as it illustrates the mechanical properties of the vessel wall and provides strain information. IVUS allows a direct visualization of the processes associated with lumen expansion by balloon dilation. It is believed that about 80% of the post-dilation increase in the lumen area is due to an increase in vessel size, and 20% is due to a reduction in plaque area, due to axial plaque redistribution (Liu & Goldberg, 1999).

IVUS can be utilized as a means of planning and evaluating the effects of vascular brachytherapy in the treatment of post-stent restenosis (Carlier et al., 2000). Apart from coronal artery disease, it is a safe method of choosing the appropriate intervention procedure in peripheral vascular disease (Fig. 2) and carotid stenting (Liu & Goldberg, 1999). It's only risk, the disruption of a plaque and release of embolic material, seems minor compared to it's numerous advantages.

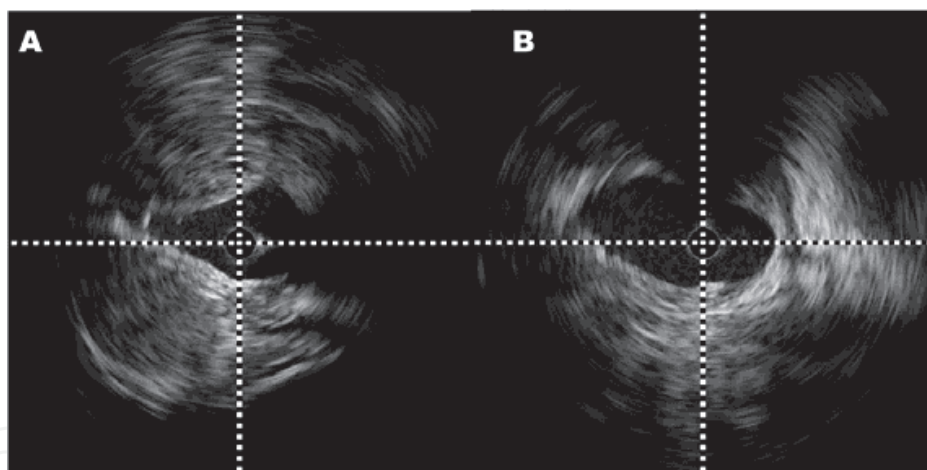


Fig. 2. Obstruction of the iliac vein: pre-intervention imaging (A) and post-intervention result (B) by intravascular ultrasound (IVUS)

2.2 3D ultrasound

Three-dimensional ultrasound is a recent development that came as an answer to the multiple problems inherent to 2D ultrasound images, leading to incorrect quantification of plaque morphology, difficult localization and significant operator dependence (Fenster et al., 2004) (Fig. 3).

3D imaging of atherosclerotic plaques can allow reproducible quantitative monitoring of plaque progression and regression and provide important information regarding the plaques' response to therapy, as its morphology and geometry is accessed (Weyman, 2009). With this technique vascular branches, accessory vessels and their intimate relationships can

be easily demonstrated (Liu & Goldberg, 1999). Arterial dissections, aneurysms and aortic dissections and flaps are depicted with 3D IVUS much better than conventional angiography.

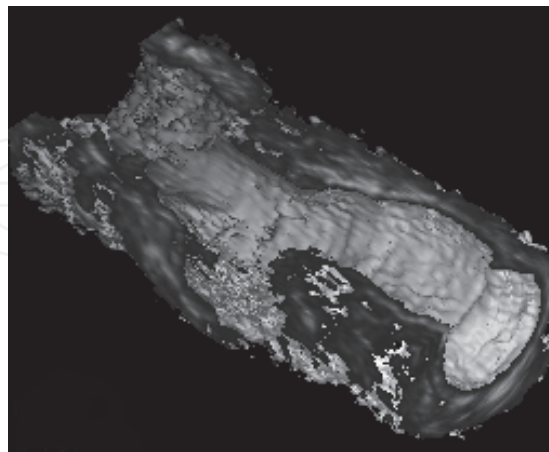


Fig. 3. 3D IVUS of an iliac artery

Although the importance of 3D imaging has been demonstrated in several studies, the widespread use of this technique has been prevented by inherent disadvantages, such as the slow frame rate, the lengthy analysis time and the limited spacial resolutions (Weyman, 2009). The combination of contrast with 3D ultrasound will likely compensate for the latter and should enhance its value in areas such as stress echocardiography (Liu & Goldberg, 1999).

2.3 Flow mediated dilatation (FMD) and carotid intima-media thickness

Endothelial dysfunction and its effect on modulation of vascular tone is considered to play an important role in the pathogenesis of the atherosclerotic process (Ghiadoni et al., 2008). The degree of vasodilation is a measure of endothelial function; the greater the vasodilation, the higher the endothelial function.

A novel non invasive technique called the “flow-mediated dilation” (FMD) of the brachial artery is nowadays widely used in current clinical practice to assess the function of the endothelium and its relationship to coronary artery disease. Ischemia of the brachial artery is induced by the inflation of an arterial cuff for five minutes. After cuff deflation brachial artery flow increases and this also increases shear stress of the artery resulting in vasodilation. It is believed that the endothelium locally produces NO in response to stress induced phosphorylation of the endothelial NO synthase (Ghiadoni et al., 2008). In arteries with impaired NO production, due to decreased endothelial function the above response is diminished.

Decreased brachial artery FMD has been associated with all the major risk factors for cardiovascular disease, such as smoking, diabetes, advanced age and hypercholesterolemia. Faulx et al have demonstrated that FMD was almost as sensitive and more specific in detecting coronary artery disease in comparison to stress electrocardiography (Faulx et al., 2003). Lerman et al showed that FMD significantly predicted cardiovascular events, independently of traditionally used cardiovascular risk factors (Lerman & Zeiher, 2005).

Limitations of this promising technique are the potential small vessel size of the brachial artery that often renders the measurement erroneous and the ambiguity in image timing after cuff deflation (Faulx et al., 2003).

Another marker used to quantify atherosclerosis by B-mode ultrasound is the measurement of carotid intima-media thickness (CIMT) (de Groot et al., 2008; Labropoulos et al., Dec 2005). A simple distance measurement between the leading edges of the lumen-intima and media-adventitia ultrasound interfaces is performed and this measurement can be used to measure the degree of existing atherosclerosis and future cardiovascular disease risk (de Groot et al., 2008; Bots et al., 1997; Chambless et al., 1997). Furthermore, several studies in literature have proved the efficacy of CIMT in monitoring the patient's response to lipid lowering therapies (Blankenhorn et al., 1993; de Groot et al., 1998; Furberg et al., 1994; Smilde et al., 2001).

3. Pre-operative ultrasound use

In patients with lower extremity ischemia, angiography has traditionally been considered the "gold standard" of arterial mapping. However, in recent years, duplex ultrasonography (DA) has gained a major role in the pre-operative evaluation of patients undergoing lower extremity bypass (Ascher et al., 1999; Grassbaugh et al., 2003; Ligush et al., 1998; Pemberton et al., 1996; Proia et al., 2001). Mazzariol et al reported that the use of duplex ultrasonography can provide enough information for surgery in more than 83% of patients with arterial stenosis and that an abnormal femoral artery waveform was 100% predictive for detecting stenosis greater than 80% (Mazzariol et al., 2000) Proia et al have also confirmed these results (Proia et al., 2001).

In comparison with conventional angiography or MRA, DA has a lower sensitivity for detecting arterial disease of the lower extremity. Moreover, it is often cumbersome and time-consuming to scan the entire arterial tree from the aorta to the pedal vessels. Imaging can also be obscured in obese patients or heavily calcified vessels. Nevertheless, the simplicity and safety of this technique underlines its importance as a first-line examination before planning a bypass surgery (Pearce & Astleford, 2004).

4. Intra-operative and post-operative ultrasound

Completion angiography has been traditionally used as an adjunctive technique after bypass procedures to scan the graft for anatomic and flow abnormalities. Nowadays, duplex scanning is used as a safer alternative to visualize these abnormalities (Johnson et al., 2000). Defective grafts are identified by direct measurement of PSV and ratio at the lesion divided by proximal velocity (Johnson et al., 2000).

Moreover, surveillance Duplex ultrasound has acquired an important role in the post-operative assessment of patients following lower extremity revascularization. It enables prompt detection of hemodynamically significant lesions and early intervention (Bandyk, 2002, Mills et al., 2001). Patients undergoing EVAR (endovascular aneurysm repair) are also monitored by serial ultrasound examinations (Bendick et al., 2003; Carter et al., 2000; McWilliams et al., 1999; Pearce & Astleford, 2004). The value of duplex ultrasound scanning in this group of patients is that repeated studies can be performed frequently to detect an endoleak or a restenosis, without the risk of contrast-induced nephropathy or the presence of adjacent metal artifacts.

Carotid artery stenting (CAS) is currently being clinically evaluated as an alternative to conventional carotid endarterectomy (CEA). Duplex ultrasound is commonly used to monitor restenosis in patients following CEA. Several authors in literature begin to report

their experience in the use of ultrasonography as a follow-up tool in CAS too (Lal et al., 2004).

5. Ultrasound in venous disease

In the field of deep venous thrombosis ultrasound is nowadays the sole diagnostic modality in most centers and has contributed extensively in our understanding of the natural history and the pathophysiology of the disease (Labropoulos et al., Feb 2005; Labropoulos et al., Jan 2010; Apr 2010) (Figures 4, 5).

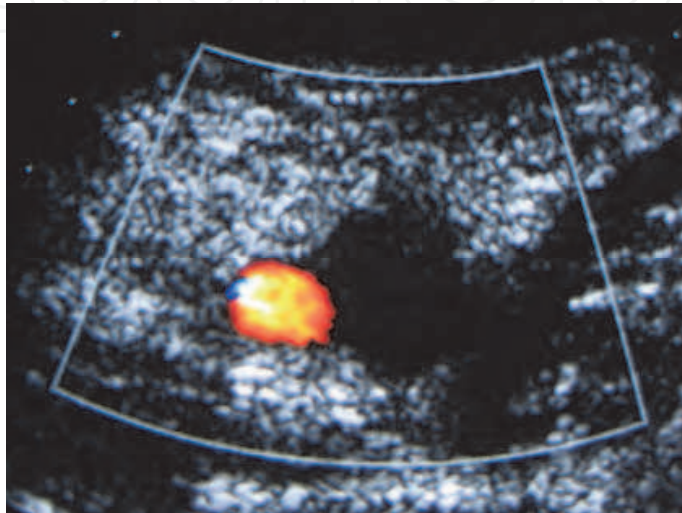


Fig. 4. Acute thrombosis in the common femoral vein. There is absence of color, the vein is dilated (twice the size of the adjacent common femoral artery in red) with homogenous echolucent texture

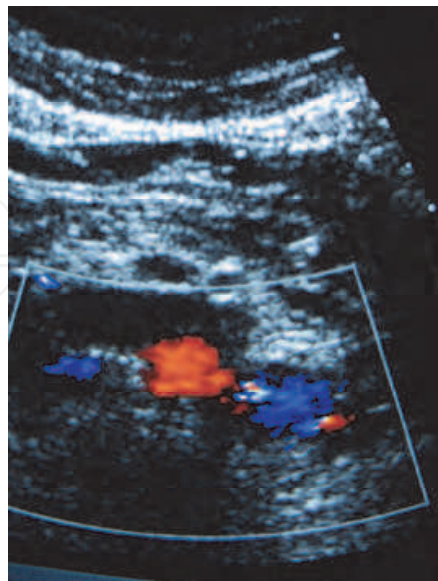


Fig. 5. Chronic inferior vena cava (IVC) obstruction with partial recanalization. The lumen of IVC is smaller compared to the adjacent aorta. The azygos vein is dilated and larger than the aorta.

Duplex ultrasound is also used as a follow-up tool to detect venous reflux up to six months after treatment (Labropoulos et al., Feb 2005) (Fig. 6) and to investigate conditions such as thrombus neovascularization (Labropoulos et al., Sep 2005).

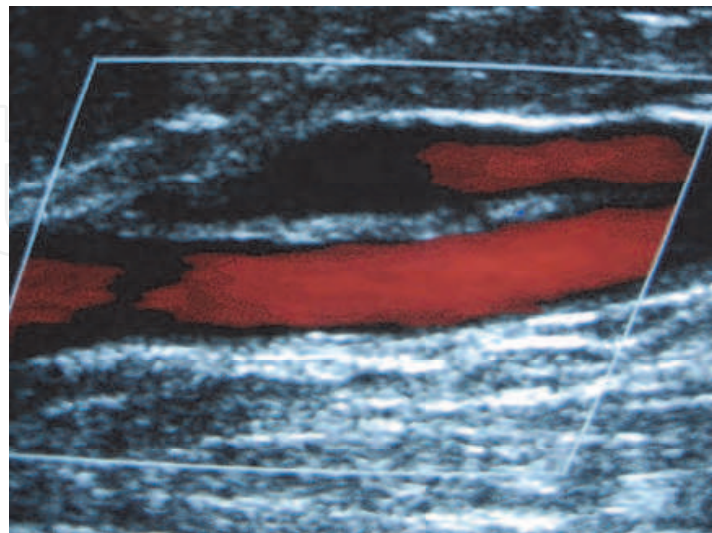


Fig. 6. Chronic thrombus with partial recanalization in great saphenous vein. Flow channels with reflux are seen over the old thrombus that is seen as an echogenic band in the lumen

Patients undergoing varicose vein stripping and venous ablative surgery routinely undergo preoperative ultrasound scanning to assure that the deep venous system is clot-free and to identify the location of perforators and accessory veins as well as the presence of lesser saphenous reflux. Intraoperatively, the use of ultrasound allows for placement of a catheter under direct guidance close to the sapheno-femoral junction, and then the anesthesia agent is injected (Min et al., 2001; Pichot et al., 2004). Successful ablation is then established by monitoring venous occlusion by means of ultrasonography.

6. Contrast-enhanced ultrasound

Gramiak was the first to describe contrast enhanced ultrasound in 1969, using air bubbles in the aorta (Gramiak et al., 1969). In modern clinical practice contrast agents for ultrasound use are microbubbles of different gases, 1-7 μ m in diameter (Cosgrove, 2006). The gas can be air, which unfortunately dissolves quickly in water or blood, or newer agents such as sulphur hexafluoride, perfluocarbons or heavy gases, which minimally dissolve in water (Cosgrove, 2006). In order to reach and persist in systemic circulation the microbubbles are stabilized with albumin, simple phospholipids micelles, bilayered membranes and biocompatible polymers (Cosgrove, 2006). Inside the vessels microbubbles expand and contract in the alternating pressure waves of the ultrasound beam, while tissues are almost incompressible. Special software using multiple pulse sequences enhances this blood-tissue border detection (Weyman, 2009). Adverse effects of contrast agents are headache, bruising, injection site pain, paresthesias and burning.

Microbubbles are currently used to improve Doppler studies especially when flow information makes conventional imaging difficult, a technique called "Doppler rescue" (Cosgrove, 2006). Common applications include imaging of the basilar and vertebral arteries, transcranial ultrasound examinations in patients with severe hyperostosis of the

skull, measurement of internal carotid stenosis in calcified arteries (Cosgrove, 2006) and differentiation of subtotal stenosis from occlusion in acute stroke (Seidel & Meairs, 2009). Moreover, contrast enhanced ultrasound has been used in renal artery stenosis, portal and hepatic artery examinations (e.g. in cirrhosis, tips shunts or after liver transplantation) (Furlow, 2009) and in liver oncology (Wilson & Burns, 2006) (Fig. 7).

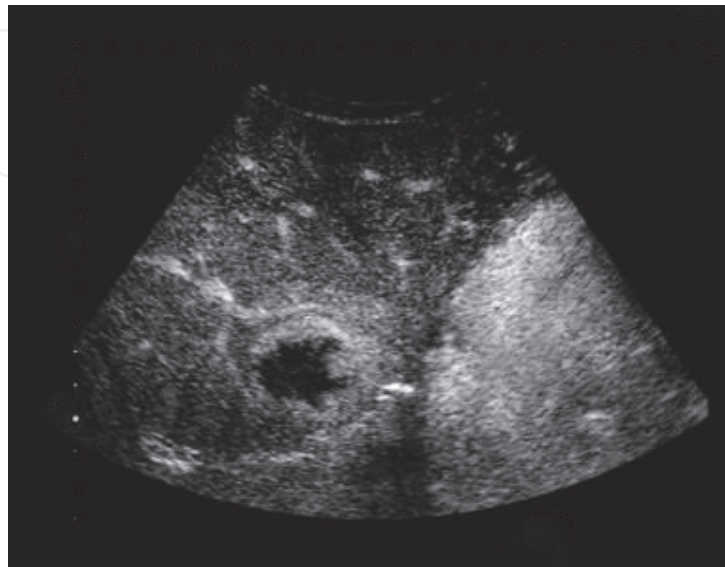


Fig. 7. Contrast-enhanced ultrasound of an hepatic hemangioma

Neurosurgeons can intra-operatively assess vascular pathologies such as middle cerebral artery aneurysms and arteriovenous malformations in real time and make appropriate surgical planning (Hölscher et al., 2007).

The microbubbles used in contrast-enhanced ultrasound techniques after attachment of antibodies or other ligands to their shell can bind to specific cell receptors in areas of disease (Voigt, 2009), thus provide information about the stage of the disease (Lindner, 2009). Several promising studies have targeted pathologic processes with contrast-enhanced ultrasound (Lindner, 2009; Voigt, 2009), such as angiogenesis (by targeting endothelial integrins) (Lerman & Zeiher, 2005), thrombus (by targeting IIbIIIa receptors or fibrinogen) (Alonso et al., 2007), inflammation (by targeting ICAM-1, VCAM-1 P- and L- selectin) and plaque (by targeting ICAM-1, VCAM-1 and several angiogenesis markers) (Voigt, 2009). In fact, it is believed that by targeting plaque inflammation and neovascularization we could identify patients at high risk for cardiovascular events well before angiography (Lindner, 2009; Voigt, 2009) or even recognise “vulnerable plaques” and begin early treatment (Vicenzini et al., 2009).

Several future promising therapeutic applications of microbubbles are under research. Therapeutic agents, genes, siRNAs, drugs and molecules can be attached to or dissolved within the surface shell or deposited within the bubbles themselves (Hernot & Klibanov, 2008; Hynynen, 2008; Weyman, 2009).

Local cavitation due to microbubble destruction can produce clot fragmentation and enhance thrombolysis (Medel et al., 2009; Trübestein et al., 1976). Continuous transcranial Doppler has been shown to augment the t-PA induced arterial recanalization in stroke victims (Alexandrov et al., 2004). Future studies need to be performed in order to improve the safety profile and therapeutic indexes of these challenging techniques.

7. Conclusion

Ultrasound imaging in vascular diseases has evolved during the past years due to new challenging technologies. Virtually all peripheral arterial and venous structures can be visualized with color duplex ultrasound. In the era of atherosclerosis, the use of intravascular ultrasound, contrast-enhanced ultrasound, 3D ultrasound, flow mediated dilatation and carotid intima media thickness techniques allow for more precise and localized diagnosis, treatment and follow-up. Ultrasound techniques routinely performed before, during or after surgical procedures are nowadays commonplace. The low cost and noninvasive aspect of most ultrasound methods make it the technique of choice in studying the human vasculature.

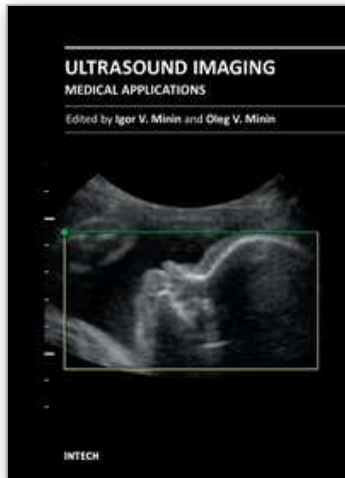
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