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The Evolution of Ultrasound Technologies; from Anatomic to Physiologic, Histologic, and Molecular Imaging

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Introduction

Ultrasound imaging has long since been used for visualization of anatomic structures for disease diagnosis and guidance during therapeutic procedures. Benefits of Ultrasound include a lack of ionizing radiation and real-time dynamic imaging. It is also the least expensive, most widely available imaging technology. In gray scale ultrasonic imaging, the signals which form the image result from reflection and scattering of soundwaves where there are differences in the characteristic tissue impedances. Ultrasonography has changed little since the 1970s. Only basic anatomic information is obtained with the modality such as: organ length, cortical thickness, collecting system or ductal dilatation are assessed. Doppler Ultrasound allows assessment of vascular physiology including blood flow velocity, which in addition to anatomic images can be used to determine the hemodynamic physiologic significance of stenosis. Resistive Index (peak systolic velocity - end diastolic velocity)/peak systolic velocity) a quantitative measure of blood flow, vascular resistance/compliance, is commonly used in the diagnosis of renal dysfunction [1].

Contrast Enhanced Ultrasound

Contrast enhanced MRI and CT have been primary cross sectional imaging modalities. Recently, dynamic contrast enhanced (DCE) MRI and CT has been utilized to evaluate perfusion/permeability and vascular physiology [2]. However, this capacity has not been available for ultrasound. With the introduction of microbubble contrast agents, diagnostic ultrasound has evolved to allow dynamic detection of tissue perfusion for assessment of the macro and microvasculature. Microbubble contrast agents contain gases that are compressible, such that they expand and contract in the alternating pressure waves of the ultrasound beam producing echogenic signal, while the surrounding tissue is relatively incompressible [3]. Contrast enhanced Ultrasound (CEUS) scanning is continuous, dynamic and in real time. Furthermore, ultrasound has greater spatial and temporal resolution when compared to MRI or CT.

Numerous applications of CEUS allow improved anatomic and physiologic imaging. In echocardiography endocardial border detection and myocardial perfusion assessment is possible [4]. Unfortunately, ultrasound contrast agents are currently only FDA approved for use in echocardiography in the USA. In Europe and Asia CEUS is being developed for a number of applications. CEUS is particularly well suited for visualization of Neovascularization, seen in all malignancies and inflammatory processes. For example, ultrasound imaging of hepatic lesions is significantly improved allowing evaluation of small lesions that can be indeterminate on CT [5]. This is because microbubbles linger in the extensive sinusoidal space of normal liver for several minutes whereas they wash out rapidly from malignancies. Thus, dynamic enhancement patterns aid in the diagnosis of these lesions. This real time perfusion imaging is also being proven to be particularly useful for evaluating anti-angiogenicbiologic anti-neoplastic therapies [6]. as well as image guided local-regional therapies such as chemoembolization [7] and radiofrequency ablation [8] were intra-procedural dynamic imaging of tumor perfusion can be used to determine the completeness of therapeutic vascular embolization and tumor destruction [9]. Furthermore, CEUS might allow sensitive and specific evaluation of abdominal trauma. Injury to the liver, spleen and kidneys can be assessed rapidly and repeatedly with excellent visualization. Parenchymal infarcts, ischemia and vascular injury resulting in dissection, psuedoanuerysm or frank extravasation can be visualized [10].

CEUS applications in vascular imaging are also extremely important. The vascular lumen, wall and vasa vasorummicrovascular perfusion is well evaluated. A particularly useful area of development is CEUS imaging of the carotid with assessment of the vasa vasorum and the ectopic vascularization of atherosclerotic plaque (intraplaque neovascularization). This approach improves identification of "vulnerable" plaques prone to rupture causing stroke [11,12]. CEUS is also emerging for evaluation of aortic pathologies and for the detection of endoleaks following endovascular treatment of abdominal aortic aneurysms [13]. Furthermore, a real-time CEUS method has recently been developed to assess the skeletal muscle microcirculation which could be used to study patients with peripheral arterial disease (PAD) or diabetic microangiopathy. CEUS techniques can be used to assess the severity of PAD by measuring muscle flow reserve during either contractile exercise or pharmacologic vasodilation and thus may provide a measure of the effects of large- and small-vessel PAD, and the influence of collateral perfusion. PAD patients have a significantly longer time to peak contrast concentration. CEUS can also be used in evaluation of myositis, and diabetic microvascular disease [14].

Elastography

The emerging technology of ultrasonic imaging of soft tissue strain and elasticity aims at providing information about the mechanical properties of tissues, stiffness. The relative constituents oft tissue components; cells, connective tissue, interstitial fluid, and vascular structures affect elastography. Techniques for imaging strain and elasticity (i.e. Young's or shear modulus) provide unique information. The elasticity of a material describes its tendency to resume its original size and shape after being subjected to a deforming force or stress. The change in size or shape is known as the strain. The force acting on unit area is known as the stress. Properties reflecting organ anatomy, physiology and pathology can be quantified with Elastography [15].

Elastography is being developed for applications in all aspects of medical diagnosis. Investigations suggest diagnostic accuracy, sensitivity and specificity in detection of malignancies of the breast [16], prostate [17], liver [18], thyroid [19] and pancreas. Furthermore, Elastography changes during treatment. For example, elastography changes during radiofrequency ablation reflect areas of resultant tumor necrosis [20]. Hepatic elastography is being utilized for evaluation of cirrhosis [21]. Regional ultrasonic myocardial strain and strain rate measurements have been in clinical use for more than 10 years [22] to evaluate myocardial ischemia, motion and contractility. Muscle elastagraphy is being applied to the diagnosis of polymyositis, dermatomyositis and inclusion body myositis [23] as well as ischemia and compartment syndrome. Applications in vascular imaging include assessment of hard, soft and vulnerable plaque as well as vessel wall thickness and compliance affected in carotid and peripheral vascular disease.

Molecular Imaging

The development of microbubbles, or other acoustically active nanoparticles, specific for molecular targets has lead to ultrasound based molecular imaging. These agents can be targeted to specified sites by either manipulating the chemical properties of the microbubble shell or through conjugation of disease/molecule-specific ligands or antibodies to the microbubble surface. Microbubbles cannot leave the intravascular space due to their size, therefore only molecular targets in the vascular compartment can be imaged. Targets related to Inflammation, angiogenesis and thrombus formation allow for molecular imaging of atherosclerosis, transplant rejection and tumor-related angiogenesis and thrombosis [24,25]. Up-regulation of endothelial adhesion molecule 1 (VCAM-1) and intercellular cell adhesion molecule 1 (ICAM-1) is detected on endothelium of atherosclerotic plaques [26]. Selectins are also upregulated in inflammation [27].

Angiogenesis is a hallmark of tumor growth. Vascular endothelial growth factor receptor 2 (VEGFR-2) and αvβ3 integrins are prominently expressed angiogenesis markers. Targeted CEUS allow specific visualize of tumors and evaluation of response to therapy. αvβ3 integrin, cyclic arginine-glycineaspartic acid (RGD) peptide and knottin peptides have been targeted with microbubbles [28,29]. Clot imaging is important for myocardial infarction, deep venous thrombosis/pulmonary embolism and stroke assessment with Microbubble targeting to glycoprotein IIb-IIIa receptors and P-selectin ligand [30].

Ultrasound Backscatter Microscopy (Ultrasound Biomicroscopy)

Conventional ultrasonic imaging systems typically use frequencies from 2 to 15 MHz and millimeter spatial resolution. 40-60-MHz clinical ultrasound systems, with high resolution on the order of 20 to 100 micron, are being developed with applications in ophthalmology, oncology, intravascular ultrasound, dermatology, and rheumatology. However, resolution comes at the expense of a shallower depth of penetrationof about 8-9 mm [31].

"Ultrasound biomicroscopy" allows real time in-vivo visualization of histologic structures seen with microscopy of resected sectioned tissue. For example, oral mucosal lesions including hyperplasia, dysplasia and malignancy are well differentiated with assessment of the dermis, mucosa, connective tissue, epithelium and microvasculature. Malignant invasion of the underlying stroma is well visualized [32]. Thus, non-invasive imaging previously requiring biopsy, staining and microscopy is possible allowing for real time, dynamic and repeated histologic evaluation.

Conclusion

Ultrasound has lagged behind MRI and CT with respect to functional/physiologic imaging. Furthermore, the field of molecular imaging is rapidly expanding. Relatively recent advances in ultrasound technology are opening the door to real time dynamic physiologic imaging never before possible. Furthermore, compared to CT and MRI, ultrasound imaging is more cost effective, widely available globally and without ionizing radiation.

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