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Review

The New Face of Ultrasound Imaging: A Gift by Nanotechnology

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ABSTRACT: The search for novel ultrasound contrast agents has now led to the use of nanoparticles due to their ability to generate contrast, amalgamation of numerous properties, adequate circulation times and satisfactory safety issues. Experiences with these nano particles promise not only in-depth knowledge of disease processes but also the early effects of therapy. In this review we discuss how nanoparticles have evolved for use as ultrasound contrast agents.

KEY WORDS: ***Ultrasound Contrast Agents; Nanotechnology; Nanoparticles***

INTRODUCTION

Ultrasound imaging involves the use of high frequency ultrasound beams to non-invasively visualize the inner structures of human body. Thus, gross findings of a pathology that is merely suspected on clinical examination or confirmed after appropriate laboratory investigations can further be validated by directly visualizing it in vivo with the help of ultrasound. Often it is difficult to differentiate between what is normal from what is abnormal particularly in the early stages as the differences on ultrasound imaging might be very subtle. This is particularly important when a malignant lesion is involved in differential diagnosis. To a novice in this field both the conditions might appear similar at early stages. It is then, that there arises a need for some agent that can enhance visualization.

HISTORY

To solve this dilemma, contrast agents were introduced in sonographic imaging. The history dates back to 1960`s when the heart and the aortic root[1] could be better visualized sonographically by injecting agitated liquid containing air bubbles simultaneously while performing the scans. Since then, efforts are being made to develop optimum ultrasound contrast agents.

MECHANISMS INVOLVED

The enhanced difference in acoustic impedance on grey scale imaging, between the contrast agent and surrounding tissue helps in better visualization and characterization of lesion[2]. Microvasculature as well as parenchymal vascularity is also better detected on colour and power Doppler following contrast usage[3].

EXAMPLES AND INDICATIONS OF CURRENTLY AVAILABLE CONTRAST AGENTS

- Albunex consisted of air filled human albumin microspheres of size 1-8 μ for use in myocardial contrast echocardiography[4]. Now Albunex is no longer in circulation.
- Echogen is a dodecafluopentane droplet emulsion to better visualize enhancement in Heart, Liver and Renal system.[5]
- Perflubron emulsion for lymphography.[6]
- Simethicone-coated cellulose based suspension used as an oral gastrointestinal contrast agent.[7]

LIMITATIONS OF CURRENTLY AVAILABLE CONTRAST AGENTS

The main limiting step has been the very short useful life span of the bubbles in the contrast once they are introduced in the vascular system, because

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the contrast agents act by enhancing the backscatter of reflected ultrasound echoes in the tissues that bear them. Other factors which limit the usage of the currently available contrast agents are artifacts like colour blooming, spectral bubble noise and increase in maximum Doppler shift[8]. Adverse effects like flushing of upper half of body and face, shortness of breath, chest heaviness, dizziness etc are also been reported.

NANOTECHNOLOGY ENABLED NEW ROAD OF NANOBUBBLES

Nanoparticles[9] are made from natural proteins and polymers, artificial polymers, dendrimers, fullerenes and other carbon-based structures, lipid-water micelles, viral capsids, metals, metal oxides, and ceramics. Signal generators incorporated into nanoparticles include iron oxide, gadolinium, fluorine, iodine, bismuth, radionuclides, quantum dots and metal nanoclusters.

Tumour blood vessels have open pores that permit entry and retain nanoparticles in the tumour vasculature, so that they can be effectively used as ultrasound contrast agents. Nanoparticles can have multiple bioadhesive sites and share functionalities with many subcellular organelles like ribosomes, proteasomes, ion channels and transport vesicles. Use of imaging for sentinel node localisation and stem cell tracking is therefore also possible[9]. Both the contrast medium as well as therapeutic drug can be delivered, by the same nanoparticles.

Nano-sized ultrasound contrast agents are being investigated by using Poly (D, L-lactic acid)[10] as a platform material. Sublimable porogens such as camphor make the nanoparticles hollow , which are then filled with hydrophobic and dense bioinert gas Sulfur hexafluoride gas (SF_6), is then introduced which increases echogenicity by enhance backscattered signals. These nanoparticles have approximately 200 nm size with a unimodal distribution and spherical shape and can be accumulated at solid tumor sites passively via well known EPR (Enhanced Permeability and Retention) effect.

Polyoxyethylene 40 stearate[11] is being increasingly used as an alternative surfactant for generating nanobubbles because it is biocompatible, degradable and non-toxic.

Poly (Lactic-co-glycolic) acid[12] can be used as a carrier for imaging contrast agents. The nanocage of elemental silver surrounding a therapeutic core consisting of the biodegrade polymer poly (Lactic-co-glycolic) acid with encapsulated chemotherapeutic drugs provides the contrast property for better imaging.

ADVANTAGES OF NANOPARTICLES AS ULTRASOUND CONTRAST AGENTS

- Echogenicity of blood and surrounding tissues is almost similar as human body is composed mostly of water. This makes it difficult on non contrast ultrasound to clearly visualize the interface between the tissue and blood, degree of blood flow, and perfusion or the using traditional ultrasound. These contrast agents improve visualization.[13]
- They allow real-time blood flow assessment.[14]
- Radiation free nature makes it safer than other imaging.[14]
- Sonography is very cost-efficient and widely available as against other imaging modalities, such as MRI, PET and SPECT.[15]
- Less amount of intravenous dosage of sonography contrast is needed, than for other imaging modalities such as MRI contrast agents.[15]

DISADVANTAGES

- The ultrasonic frequency needs more careful monitoring as ultrasound produces more heat with increase in frequency.
- Microvasculature rupture can result from simultaneous large number of nanobubble destruction.[16]
- Targeting ligands can be immunogenic, since current targeting ligands used in preclinical experiments are derived from animal culture.[16]
- Low targeted microbubble adhesion efficiency, which means that only a small fraction of injected microbubbles bind to the area of interest.[17]

CONCLUSION

Nanoparticles are thus unleashing newer power of imaging towards uncharted frontiers. This will surely lead to early diagnosis and prompt treatment. Nanotechnology thus holds a new promise for better health and longevity.

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