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● *Part I: Science and Technology*

NONLINEAR IMAGING

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INTRODUCTION

It was Lord Rayleigh who first described the nonlinear radial motion of a gas bubble in an acoustic field. His theory, subsequently elaborated by a series of investigators, predicted that a bubble, driven into nonlinear resonant oscillation by an incident sound field, gives rise to a scattered signal that contains higher harmonics of the incident frequency (Fig. 1). This observation led, nearly 100 years later, to the development of a method that forms an image from the components of the echoes around the second harmonic of the transmitted frequency. These first harmonic images were made as part of an attempt to improve sensitivity to microbubble contrast agents in very small vessels (Burns et al. 1996). They have, however, stimulated fresh investigation of nonlinear acoustic phenomena in tissue and an interest in nonlinear imaging methods, which is sure to be sustained into the new millennium.

CONTRAST HARMONIC IMAGING

For microbubble contrast agents, harmonic imaging led to the first contrast-enhanced images of blood at the microvascular level, including myocardial perfusion. Harmonic Doppler imaging, in which Doppler detection is performed on the second harmonic component of the echo, provides an entirely new method of tissue motion (or "clutter") rejection that combines radio-frequency and Doppler-frequency filtering. The specificity of such a method to bubbles over moving tissue led to the detection of vessels down to the diameter of about 40 μm (Burns et al. 1996). At the same time, some unanticipated properties of these images became apparent. First, with high incident sound pressure, the harmonic signals from microbubbles were found to be transient in nature. This was subsequently shown to be a result of bubble destabilisation and fragmentation caused by successive pulses of the incident ultrasound field. Echoes from the first few pulses are strong and particularly rich in harmonics. These echoes, which can be detected by Doppler schemes even when the microbubbles are almost stationary in tissue, now provide the basis for perfusion imaging of the myocardium (Porter and Xie 1995). Second, ordinary tissue could be seen on a gray-scale harmonic image, even if the bandwidth of the image was restricted to a narrow region around the second harmonic. First considered as an artifact in harmonic contrast imaging, these "tissue harmonic" images have since been shown to have peculiar characteristics that render them in many cases superior to conventional ultrasound images.

TISSUE HARMONIC IMAGING

Harmonic imaging for microbubble contrast agents was originally developed under the assumption that tissue is linear and all harmonic echoes are generated by the bubbles. In fact, tissues, like bubbles, are nonlinear systems. Whereas the harmonic echoes from bubbles have their origins in nonlinear scattering, those from tissue are a result of nonlinear propagation and subsequent linear scattering. In nonlinear propagation, the propagation speed of a wave, c, is not constant as is assumed in linear acoustics. It is a function of the particle velocity owing to the wave disturbance, $c = c_0 + \beta u$, where u is the particle velocity and β is the coefficient of nonlinearity of the medium (Hamilton and Blackstock 1998). Thus, the positive peak of the wave where the particle velocity is high has a faster propagation speed than the negative peak of the wave where the particle velocity is low. This variation of the propagation speed results in a waveform distortion, also referred to as wave "steepening," which shifts energy from the fundamental to the higher harmonic components (Fig. 2a and b).

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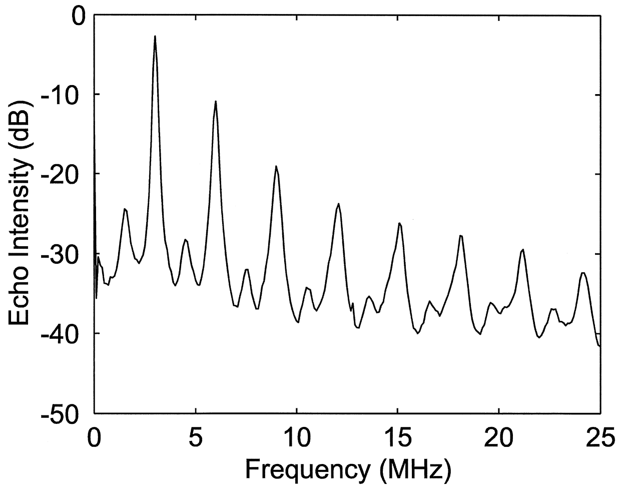


Fig. 1. Measured spectrum of echoes from a perfluorocarbon contrast agent in response to narrowband sound transmission at 3 MHz. Harmonics, subharmonics and ultraharmonics of the incident frequency are seen.

Nonlinear propagation of sound waves from focused beams in tissue has some interesting properties that contribute to the characteristics of tissue harmonic images. The fundamental beam is generated at the transducer whereas the harmonic beam is generated continuously along the propagation path as a consequence of the local instantaneous amplitude. The harmonic beam can be considered as a volume source that starts at the transducer and extends out to the point of interest. Because it has double the frequency, the harmonic beam is narrower than that of the fundamental energy. Its sidelobes, responsible for degradation of image contrast, are lower than those of the fundamental, as shown in Fig. 2c for a phased array transducer. These properties result in increased lateral resolution, reduction of the multiple reflections because of a poor acoustic window, and overall "clutter" reduction. Inhomogeneities of the speed of sound in superficial tissue layers causes phase aberration in the

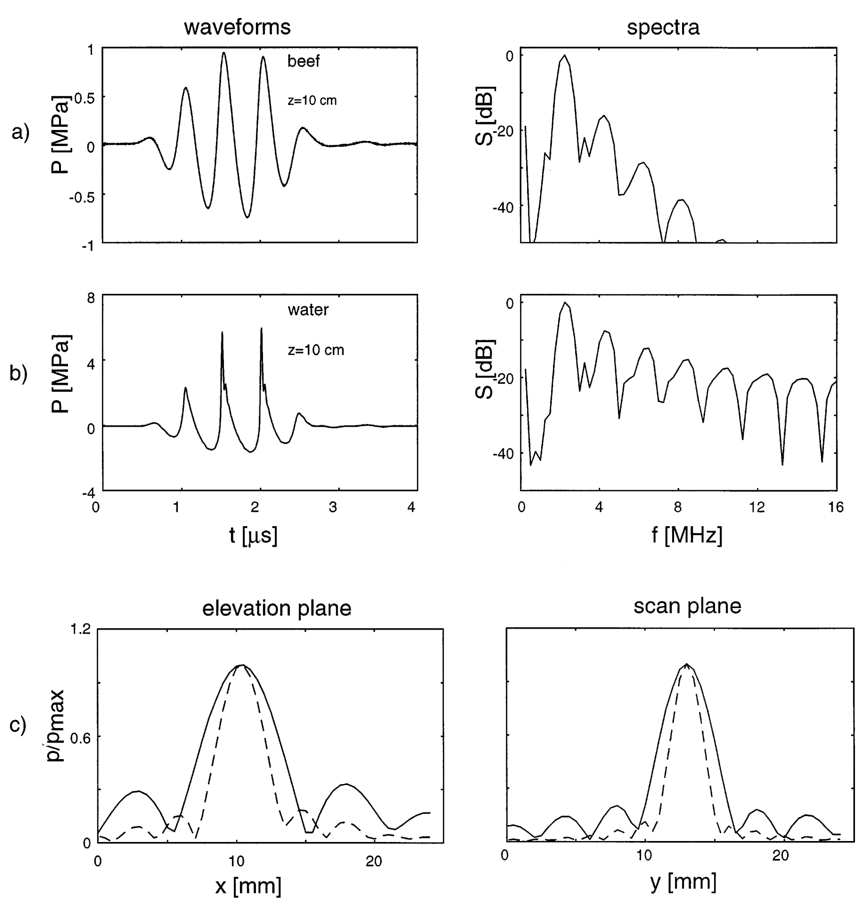
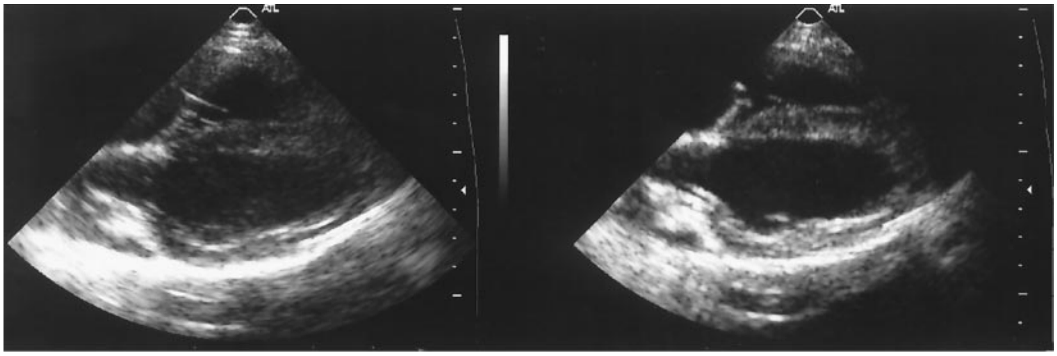


Fig. 2. Nonlinear propagation: (a) measured pressure waveform and spectrum of a 1.67-MHz sound pulse transmitted 10 cm through beef, (b) waveform and spectrum following transmission through water and (c) measured focal beam profiles of the fundamental (solid lines) and nonlinear second harmonic beams (dashed lines). The harmonic beam has a narrower main lobe and weaker sidelobes than the fundamental beam.



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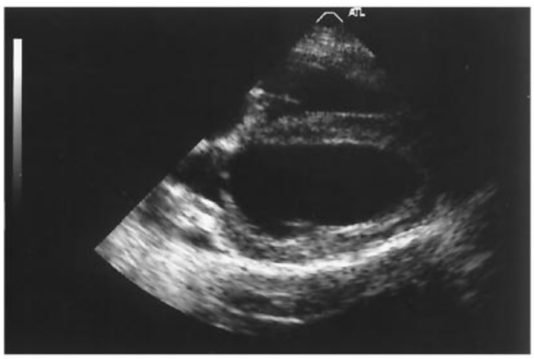

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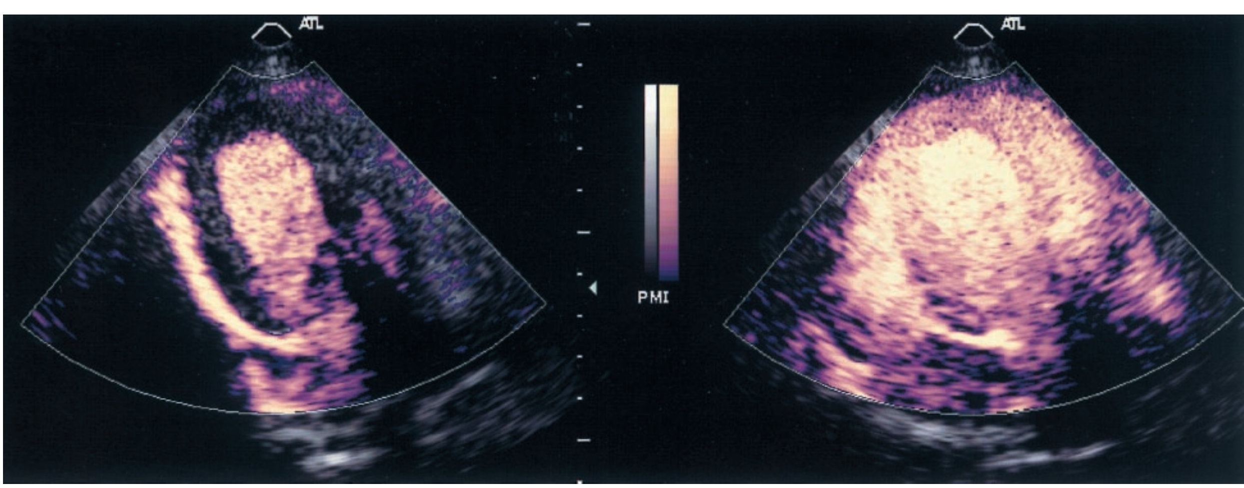
Fig. 3. Parasternal long axis images of a heart made with (a) fundamental imaging, (b) harmonic imaging and (c) pulse inversion harmonic imaging. Nonlinear imaging reduces artifacts, improving contrast and resolution of echocardiography images.

fundamental beam, distorting the resulting image. The harmonic beam is not fully generated until the focus and beyond, and consequently suffers less from aberration in superficial tissue. This explains the reduction of "haze" in abdominal images and the improved border delineation in echocardiography (Fig. 3a and b).

In tissue harmonic imaging, we have a volume source that extends from the transducer to the point of interest. Progress in this area hinges on our ability to understand and control the formation of this source. The image improvements realised so far may well herald the beginning of a new era in beam forming in tissue.



a b

Fig. 4. Real-time imaging of myocardial perfusion with pulse inversion Doppler at MI = 0.1. (a) In an apical view, contrast is seen in the right and left ventricles immediately following a high-intensity "destruction frame." (b) Five seconds later, the myocardium has refilled with fresh contrast. The frame rate is 10 Hz.

PULSE INVERSION IMAGING

Harmonic imaging of tissues or bubbles forces an inherent compromise between image resolution and contrast that limits its sensitivity to nonlinear signals. Overlap in frequency between the fundamental and harmonic echoes results in linear echoes being detected in the harmonic signal, reducing contrast. Narrowing both the transmit and receive bandwidths reduces these effects, but at the expense of image resolution. This compromise limits both the resolution and contrast of harmonic imaging, and is especially significant at low transmit pressures when harmonic echoes are weak.

Pulse inversion imaging overcomes these limitations of harmonic imaging by detecting nonlinear echoes over the entire transducer bandwidth (Hope Simpson et al. 1999). It exploits the fact that second harmonic nonlinear echoes from both microbubbles and tissue are caused by an asymmetric response to regions of high and low pressure in the transmitted sound. In pulse inversion, two ultrasound pulses are transmitted down each line of sight, with the phase of the second pulse inverted. When the corresponding echoes are added together, the linear component cancels but the nonlinear even harmonic components reinforce to produce a strong signal. By exploiting differences between echoes rather than within a single echo, pulse inversion imaging removes the fundamental component (and other odd harmonics) even when the fundamental and second harmonic overlap, thus overcoming the limitations of harmonic imaging. In particular, it allows microbubbles to be detected with high resolution at low transmit intensities, making possible real-time contrast perfusion imaging. At higher transmit pressures, pulse inversion imaging also offers benefits for tissue harmonic imaging (Fig. 3c).

Target motion between pulses results in incomplete removal of the fundamental echoes, introducing a fundamental component into the pulse inversion signal that is approximately proportional to target velocity. Although motion sensitivity aids in the detection of moving or disrupting microbubbles, it may introduce artifacts from moving tissue in cardiac applications.

The principles of pulse inversion imaging may be extended by transmitting more than two pulses of alternating polarity along each line of sight, a generalisation that we call pulse inversion Doppler (Hope Simpson et al. 1999). Doppler frequency filters can now be applied to the detected echoes to provide improved suppression of moving tissue compared to the two-pulse method. Filters can be tailored for specific applications, such as contrast perfusion imaging, tissue harmonic imaging or bubble disruption imaging. At low incident pressures, pulse inversion Doppler has provided the first real-time perfusion images of the myocardium (Fig. 4).

FUTURE PROSPECTS

For bubble imaging, nonlinear imaging methods have opened diagnostic ultrasound to the detection of blood at flows at least an order of magnitude below that previously achievable. In addition, exploitation of the nonlinear propagation of sound in tissue has provided a powerful new tool to manipulate beam properties and tackle tissue aberration problems. Yet the understanding of these phenomena and their associated imaging techniques is still at an early stage. Future developments will focus on segmentation of specific components of bubble and tissue echoes, such as the sub- and ultraharmonics, which may be present in bubble echoes but not from tissue propagation. Imaging of higher order harmonics and novel pulse shaping and pulse sequences may lead to a more effective use of bubble and tissue nonlinearities. It is not unreasonable to predict that progress in nonlinear imaging will dominate that in linear imaging in the next decade of biomedical ultrasound.

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