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● *Review*

ULTRASOUND CONTRAST IMAGING: CURRENT AND NEW POTENTIAL METHODS

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Abstract——For 10 years, it was thought that ultrasound (US) contrast agents could be sufficiently detected and imaged with the conventional imaging techniques, now referred to as fundamental imaging. However, it turned out that fundamental imaging was not sensitive enough to detect the contrast agents in the presence of tissue. New imaging techniques that are based on specific properties of the contrast agents, such as nonlinear and transient scattering, proved to be more sensitive. US contrast imaging modalities used today are fundamental, second harmonic, harmonic power Doppler, and pulse inversion; new modalities, such as release burst and subharmonic imaging are emerging. Second harmonic imaging is still not optimal for perfusion imaging applications. However, in combination with Doppler techniques such as power Doppler, it is one of the most sensitive techniques currently available. A complete understanding of the US-contrast agent interaction is essential for further improvements of current detection methods, and the development of new imaging techniques. © 2000 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Ultrasound imaging, Contrast agents.**

INTRODUCTION

The diagnostic applications of ultrasound (US) imaging have been expanded enormously for the last decades. It has been recognized as a well-established diagnostic technique for clinical decision making. Significant improvements in equipment have contributed to the understanding of anatomy and function of different organs. With the introduction of real-time two-dimensional (2-D) imaging, different anatomical structures in the body could be imaged noninvasively. Also, blood flow measurements in large vessels and the heart became feasible using Doppler imaging. Nevertheless, new applications, as well as technological innovations, are continuously being developed. Real time 3-D imaging, for example, provides volumetric information, rather than cross-sectional information like that obtained with conventional 2-D imaging. Additionally, with the utilization of US contrast agents, perfusion imaging of, for example, the myocardium or tumors, has become possible, and will provide meaningful physiological and pathological information for clinical decision making.

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Ultrasound contrast agents

Ophir and Parker (1989) gave a summary of the use of US contrast agents (UCA) in medical imaging. Five types of agents with different physical properties were classified: free gas bubbles, encapsulated gas bubbles, colloidal suspensions, emulsions and aqueous solutions. In those days, it was a main challenge to produce small microbubbles that could pass through the lung capillary circulation and that were stable enough to reach the left heart after an IV injection. Now, all the UCA are able to reach the left ventricle cavity of the heart, and are based on free-gas bubbles or are stabilized by encapsulation to avoid rapid disappearance. They are either air-filled or contain gases that dissolve poorly in the blood, and have mean diameters smaller than 7 μm. More than 10 UCA are currently under investigation and tested in clinical trials (Table 1). However, there are only three transpul-

Table 1. Status of pulmonary us contrast agents that are currently under investigation or being evaluated in clinical trails, and commercially available

Name	Manufacturer	Type (shell/gas)	Status	Available
Albunex®	MBI/Mallinckrodt	Sonicated HSA*/air	Approved	USA/Europe
Levovist®	Schering AG	Galactose/air	Approved in Europe	Europe/Japan
Echogen™	Sonus/Abbot	Dodecafluoropentane (DDFP) in a sucrose solution	Approved in Europe	
SonoVue™	Bracco	Phospholipid/sulfur hexafluoride	Phase II/III	
Optison®	MBI/Mallinckrodt	Sonicated HSA*/perfluorocarbon	Approved	USA/Europe
Quantison™	Quadrant Ltd.	Spray-dried HSA*/air	Phase II Europe	
Definity™	Dupont Merck/ImaR_x	Liposomes/perfluorocarbon	?	
Sonazoid™	Nycomed	Polymer/sulfur hexafluoride	Phase II Europe	
Imagent®	Alliance/Schering	Surfactant membrane/perfluorohexane-air	Phase III USA	
Bisphere®	Point Biomedical	Polymer-HSA*/air	Phase I	
AI-700	Acusphere Inc.	Polymer (PLGA)/low solubility gas	Phase I USA	

* Human serum albumin.

monary agents commercially available: Levovist® (Schering AG, Berlin, Germany), Albunex™ and Optison™ (Mallinckrodt, St. Louis, USA).

Ultrasound-contrast agent interaction

When a gas bubble is insonified by a US wave, it generates two kinds of responses. First, the wave will be reflected at the surface of the bubble because of the large difference in acoustic impedance between the surrounding medium and the gas inside the bubble. More importantly, however, when the bubble size is much smaller than the wavelength of the US wave, it is forced into volume pulsation (for a 3-MHz US wave, the wavelength in water is 0.5 mm). In the simplest situation, the size of the bubble decreases in the positive half cycle of the US wave, and the bubble expands in the negative half cycle. The volume pulsation of the bubble is frequency-dependent and shows a clear maximum at a specific frequency, which is referred to as the resonance frequency, and is inversely related to the bubble size (Medwin 1977). The resonance phenomenon is an important effect because a resonating bubble behaves as a source of sound, rather than as a passive reflector and, therefore, yields an enhancement of the backscatter signal compared to the off-resonance behavior of the bubble.

The response of a gas bubble to a US wave depends on the acoustic pressure amplitude and can be divided into three regimens. For small amplitudes of the US wave, the relative compression and expansion of the bubble is the same and, therefore, the bubble size is linearly related to the applied acoustic pressure. For higher amplitudes, however, compression generally retards relative to expansion and nonlinearity occurs. Consequently, the bubble size is not linearly related to the applied acoustic pressure (de Jong et al. 1994), and the bubble vibration contains second and higher multiples of the transmitted frequency. In this way, the backscatter signal from the bubble not only contains the fundamental (transmitted) frequency, but also harmonic frequencies, most notably at twice the fundamental frequency. This effect is not shown so markedly by tissue and it, therefore, offers the possibility of separating the response of the bubble from that of surrounding tissue.

If the amplitude of the acoustic wave is increased more, the scattering level of most of the contrast agents increases abruptly for a short time. This has been associated with bubble rupture and release of free gas bubbles (Frinking et al. 1999). The irreversible effect is transient and lasts until the released free-gas bubbles are dissolved in the surrounding liquid at a rate that depends on the type of gas and its dissolvability in the liquid. Furthermore, the scattered signal becomes highly nonlinear.

In this article, an overview is given of US contrast imaging methods that are currently available or under investigation. They all exploit one of the bubble signatures that are demonstrated in one of the regimens of the applied acoustic pressure. Specific properties of each method are emphasized, and are given from a technical point of view, illustrated with some clinical examples. The following methods are described: fundamental B-mode imaging, harmonic B-mode imaging, harmonic power Doppler imaging, pulse inversion imaging, release burst imaging and subharmonic imaging.

Fundamental B-mode imaging

With the introduction of UCA, it was thought that it would be sufficient to detect and image them with conventional imaging methods now referred to as fundamental imaging. In this mode, UCA simply enhance the backscatter signal, which is demonstrated by an increase in grey-scale level (Fig. 1a). This has been employed in combination with conventional 2-D B-mode imaging to create images of greater clarity. For example, left ven-

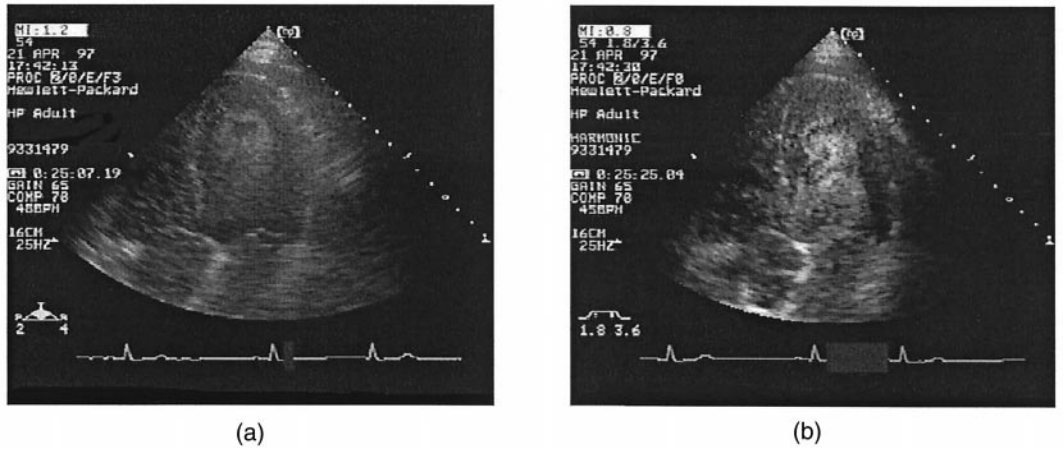


Fig. 1. Apical four-chamber view of a human heart after an IV administration of Levovist®. (a) Fundamental imaging (*i.e.*, transmitting and receiving at 3 MHz). (b) Second harmonic B-mode imaging (*i.e.*, transmitting at 1.8 MHz and receiving at 3.6 MHz.

tricular opacification improves endocardial border detection, which results in a better assessment of wall motion abnormalities (Kasprzak et al. 1999). However, for the myocardium, the ratio of blood volume and tissue is approximately 10% (Kaul and Jayaweera 1997). Consequently, for concentrations used in clinical studies, the increase from UCA in the myocardium will only be several decibels. Therefore, fundamental B-mode imaging results in poor contrast agent detectability in the presence of tissue, generally expressed as agent-to-tissue ratio (Frinking et al. 2000).

More recently, it appeared that, for high acoustic amplitudes (high mechanical index, MI), (Uhlendorf and Hoffman 1994) transient enhanced scattering may occur (Frinking et al. 1999). The amplitude of the US wave is indicated on US scanners by the MI, which is defined as the ratio of the peak negative pressure, in MPa, and the square root of the frequency, in MHz (Abbot 1999). In conventional B-mode imaging, the enhanced scattering may be visualized as bright echogenic areas. Although the increase in echogenicity can be substantial, in hyperechoic regions or very small vessels where the number of bubbles is low (*e.g.*, the myocardium), echoes from surrounding tissue can easily mask this increased echogenicity.

The transient enhanced scattering effect is most effective when the US wave insonifies the bubbles for the first time. This has led to the development of triggered imaging (Porter and Xie 1995) as a new modality. In the triggered mode, single scans are made at reduced frame rates (*e.g.*, 0.1–1 Hz), resulting in an increased efficacy of the agent. However, US imaging looses its real-time character in this mode. This is not only limited to fundamental imaging, but applies to all contrast imaging methods that use the transient characteristic of UCA.

Harmonic B-mode imaging

New imaging techniques are continuously being developed, and are based on contrast agent-specific properties. By utilizing these properties, it is possible to detect UCA in tissue, even if the fundamental backscatter component is low compared to the scattering of surrounding tissue. Second harmonic (B-mode) imaging, for example, is a method where the US system separates the harmonic frequencies of the received signal from the fundamental frequencies and then processes the harmonic signal alone. In Fig. 1, fundamental (a) and second harmonic (b) images are shown after an intravenous injection of Levovist®. In the second harmonic mode, a complete opacification of the left ventricle cavity is obtained.

To increase the sensitivity of the system in detecting the agent, the spectral overlap between the fundamental and harmonic frequencies has to be reduced (Fig. 2). This is achieved by transmitting narrow-band signals that, in return, deteriorate the imaging resolution. Consequently, system optimization consists of finding the optimal balance between these two aspects, and generally is called the contrast detectability and imaging resolution trade-off.

For US waves transmitted at high acoustic pressures, slight nonlinearities in sound propagation through tissue occur that gradually deform the shape of the waves (Fig. 3a) (Bouakaz et al. 1999). This results in the development of harmonic frequencies that were not present in the transmitted wave, close to the transducer (Fig. 3b). The harmonic frequencies will linearly be reflected by

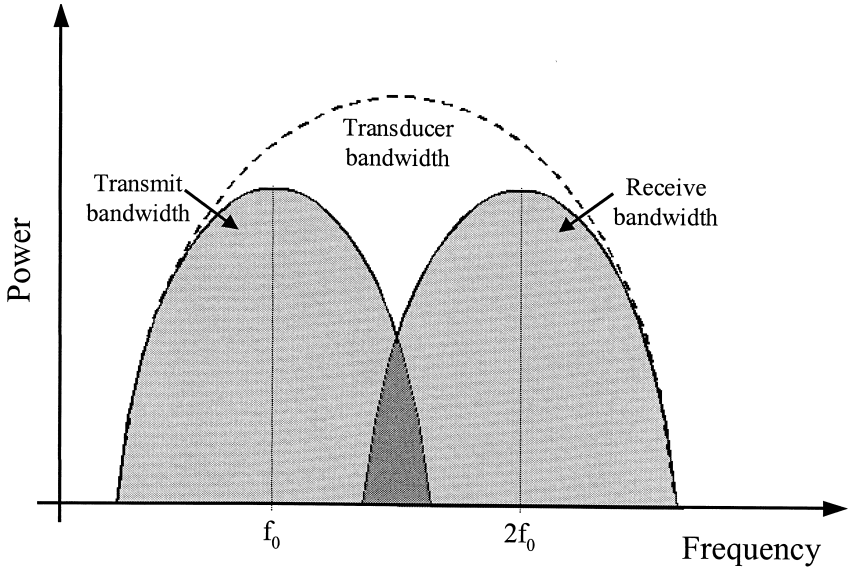


Fig. 2. Overlap between transmit (f_0) and receive ($2f_0$) passbands (dark grey area) results in a residual signal of the fundamental image in the filtered harmonic image.

surrounding tissue and, therefore, can mask the nonlinear response from UCA. Consequently, all imaging methods that exploit harmonic filtering for improved contrast agent detection are obscured by a residual tissue component due to nonlinear propagation. Therefore, the maximal obtainable agent-to-tissue ratio is limited.

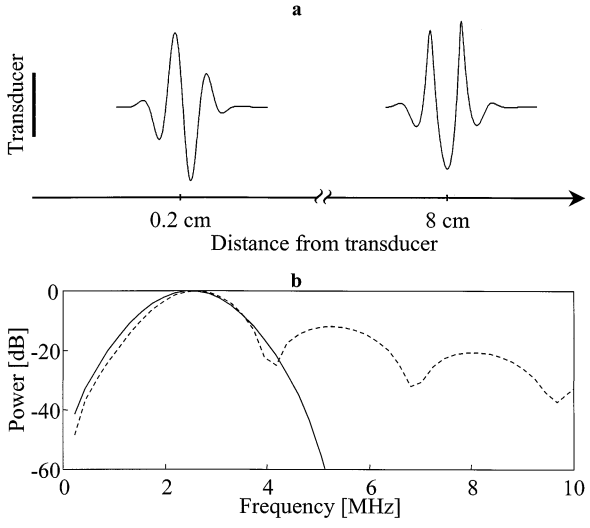


Fig. 3. Simulation results for a propagating US wave transmitted by a focused single-element transducer at 2.5 MHz and 100 kPa. (a) Change of shape of the US wave as it propagates through water. (b) Corresponding (normalized) spectra at 0.2 cm (solid line) and 8 cm (dashed line) from the transducer. The transducer diameter was 28 mm, the frequency was 2.5 MHz, the focus was 75 mm and the peak negative pressure was 100 kPa.

Although harmonic imaging was originally developed for UCA, it turned out that also, without UCA, the image quality improved considerably compared with fundamental imaging. This is generally called *native harmonic* or *tissue harmonic* imaging to distinguish it from UCA-generated harmonics. There are two aspects that are critical for the improvement of tissue harmonic imaging (Ward et al. 1997). First, harmonic frequencies are absent at the transducer face and they build up progressively. Consequently, there is hardly any harmonic energy in the near field and most of the harmonics develop beyond the chest wall (Fig. 4a). Therefore, selective display of the harmonic frequency will show less near-field artefacts. Second, the harmonic component has a quadratic relationship to the fundamental one. Thus, most of the harmonic energy originates from the strongest part of the beam, whereas the weaker parts of the beam, (*i.e.*, side lobes and grating lobes) give rise to a small contribution (Fig. 4b). Because side lobes and grating lobes are sources of noise and artefacts, selective harmonic imaging improves the signal-to-noise ratio and, thus, results in cleaner images. Another consequence of the quadratic relationship between the harmonic and fundamental components is that the lateral beam width is narrower for the second harmonic beam compared to the fundamental beam (Fig. 4b). This translates in a better lateral resolution of the second harmonic image compared to the fundamental image.

The aforementioned improvements explain why, for example, a better endocardial border definition can be

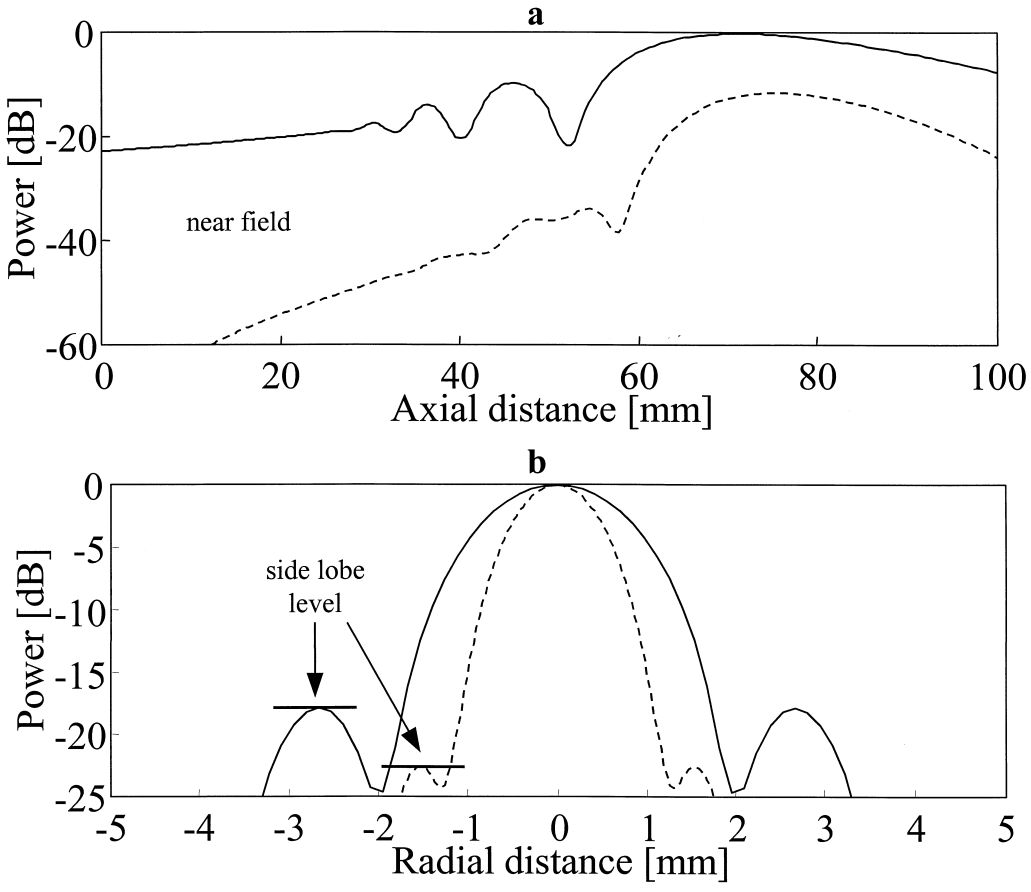


Fig. 4. Same simulation as used for Fig. 3. (a) Normalized axial beam profile of the fundamental (solid line) and second harmonic (dashed line) beam. (b) Normalized lateral beam profile of the fundamental (solid line) and second harmonic (dashed line) beam at the focus of the transducer.

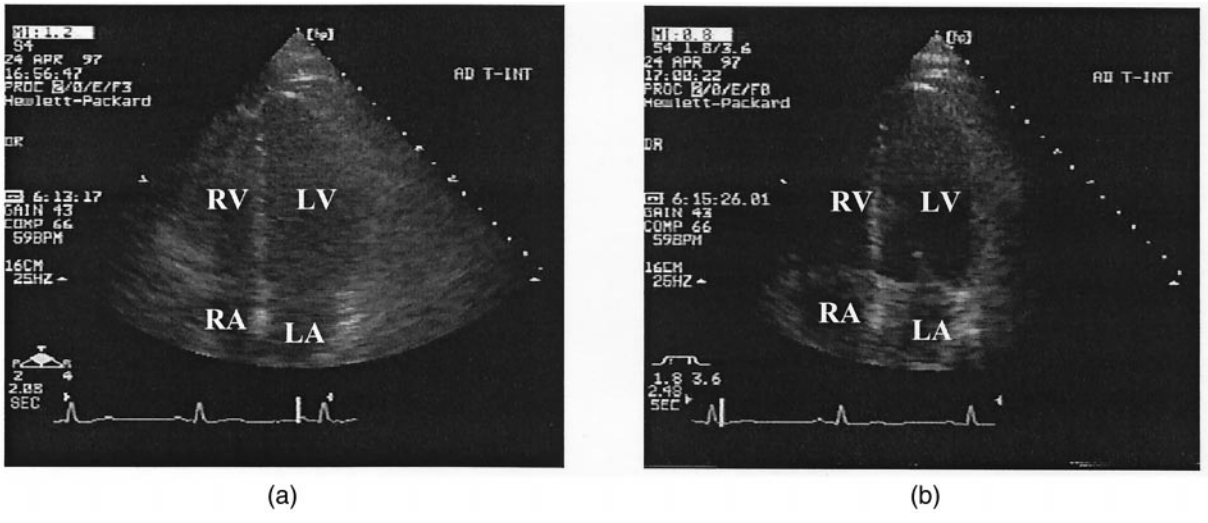


Fig. 5. Apical four-chamber view of the human heart. RV = right ventricle; LV = left ventricle; RA = right atrium; LA = left atrium. (a) Fundamental imaging (*i.e.*, transmitting and receiving at 3 MHz). (b) Tissue harmonic imaging (*i.e.*, transmitting at 1.8 MHz and receiving at 3.6 MHz).

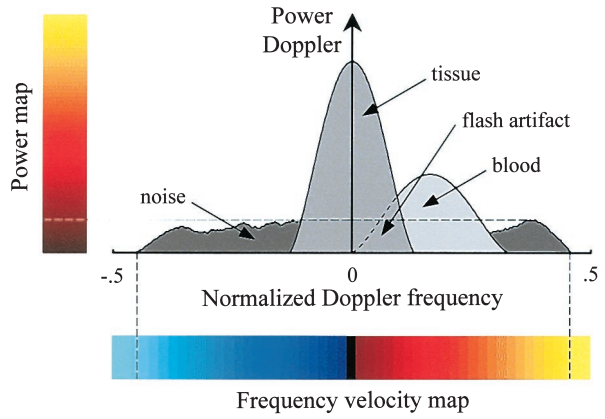


Fig. 6. Diagram showing the advantage of power Doppler over color Doppler (velocity mode) (Powers et al. 1997). In the power Doppler mode, the power of the Doppler signal is displayed instead of the frequency. Consequently, noise from the Doppler receiver at high gain settings is mapped to a single color, instead of many colors as in the velocity mode, resulting in an effective increase of the dynamic range. The *tissue* signal overlapping the *blood* signal causes a flash artefact.

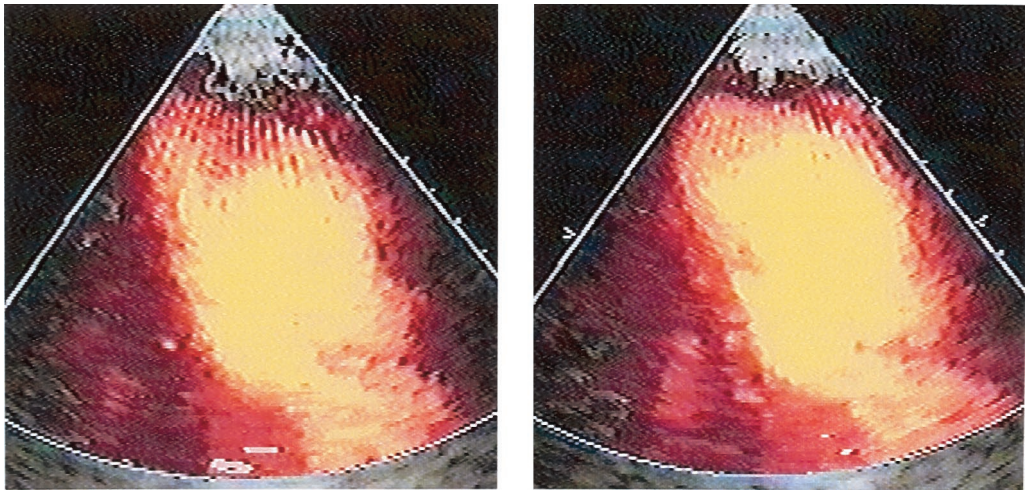
obtained in harmonic mode. This is described by Kasprzak et al. (1999), and shown in Fig. 5a and b.

Harmonic power Doppler imaging

With conventional Doppler imaging, blood velocity can be measured by tracking scattering objects in a region of interest. Unlike conventional Doppler, power Doppler does not provide information about the direction of the flow but, instead, displays the power of the Doppler signal (Fig. 6). This has proven to be a more sensitive method in terms of signal-to-noise ratio and low flow detectability (Powers et al. 1997). With the addition of a UCA, the signals received from blood containing contrast are enhanced and the detectability of flow from small vessels is increased further. However, because most of the Doppler techniques are multipulse techniques (*i.e.*, a packet of pulses is transmitted in the same line of sight), they are susceptible to tissue motion that is not eminent in B-mode imaging. Tissue motion generates Doppler signals (clutter) that can be even stronger than the contrast-enhanced signals with the same Doppler shift frequencies, such as the signals from blood. This results in a flash artefact, which is a severe problem in Doppler applications. The flash artefact or clutter can be reduced by the combination with second harmonic filtering. This makes harmonic power Doppler an effective tool for the detection of flow in the small vessels of organs, which may be moving with cardiac pulsation or respiration. It is currently considered as one of the most sensitive techniques available in terms of agent-to-tissue ratio.

Another imaging technique for UCA arises for US waves transmitted at a high MI. Every time a pulse (in the same direction) is transmitted, transient enhanced scattering occurs (*i.e.*, the contrast agent is disrupted or modified). In this way, changes in the scattering of the contrast agent are induced. This effect can be detected very accurately with current Doppler techniques because Doppler is sensitive to changes between backscatter signals from successive pulses.

An example of a harmonic power Doppler study performed on a patient is given in Fig. 7, where a constant IV infusion of Levovist® was administered. By



(a) (b)

Fig. 7. Two-chamber view of a heart with an inferior infarction after thrombolysis. (a) Harmonic power Doppler imaging, triggered every heartbeat. (b) Harmonic power Doppler imaging, triggered every fifth heartbeat.

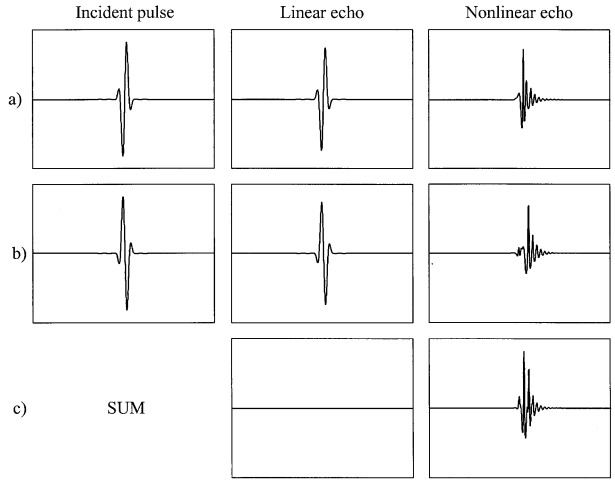


Fig. 8. Principle of pulse-inversion imaging (Hope Simpson et al. 1999). (a) An acoustic pulse is transmitted and echoes from linear and nonlinear scatterers are detected. (b) An inverted copy of the same pulse is transmitted and echoes are again detected. (c) When the two echoes are added, only the nonlinear echoes are retained.

changing the triggering interval from every heartbeat (Fig. 7a) to every fifth heartbeat (Fig. 7b), the myocardium appears to be enhanced. This is explained by the low flow rate in the myocardium. The reappearance rate of the UCA provides a measure of the mean myocardial blood velocity, and is sometimes called the *microbubble destruction/reperfusion method* (Wei et al. 1998).

Pulse-inversion imaging

The limited bandwidth of current transducers forces the transmit bandwidth to be narrow, to minimize the spectral overlap between the fundamental and second harmonic parts of the received spectrum (see Fig. 2). A new technique, called pulse inversion, has been developed and largely overcomes the contrast detectability and imaging resolution trade-off (Hope Simpson et al. 1999). In pulse-inversion imaging, a sequence of two US waves is transmitted into tissue (Fig. 8). The second wave is transmitted after a suitable delay and is an inverted replica of the first wave. For a linear medium, the response of the second wave is an inverted copy of the response from the first wave, and the sum of the two responses is zero. For a nonlinear system (*e.g.*, gas bubbles), the responses will not be inverted copies. The sum is not zero and the remainder is related to the degree of nonlinearity. The main advantage of pulse-inversion over harmonic imaging and harmonic power Doppler imaging is that it can function over the entire bandwidth of the received echo signal and, therefore, achieves superior imaging resolution. It has been shown that pulse-inversion imaging can be performed at low MI, prolonging the lifetime of the contrast agent and, perhaps, obviating the need for intermittent imaging (Hope Simpson et al. 1998). In radiology, where continuous imaging is common, the method has improved the image quality substantially. Nevertheless, pulse inversion is susceptible to motion because it is a multipulse technique. This implies that the method is less suitable for cardiology. Therefore, pulse-inversion detection and Doppler detection have been combined into one technique called pulse-inversion Doppler. It exploits the advantages of both detection schemes (Hope Simpson et al. 1999), which means that more than two pulses are transmitted and special Doppler filters are applied to remove tissue motion. However, nonlinear propagation effects still limit the maximal obtainable agent-to-tissue ratio.

An example of pulse-inversion imaging is shown in Fig. 9 (Moriyasu 1999). Figure 9a shows a baseline recording of the liver of a patient with a hepacellular carcinoma (HCC). After the administration of Optison™, a tortuous and irregular hypervascular pattern appears, penetrating to the central area of the tumor, which can be an indication of a malignant tumor (Fig. 9b). Additionally, malignant liver tumors often show a pulsatile blood flow because they are supplied by the hepatic artery. In contrast, benign tumors will show a regular vascular structure with a steady regular blood flow. Therefore, continuous high-resolution contrast imaging (*i.e.*, a high temporal and spatial resolution such as can be obtained with pulse inversion), is of great diagnostic value in tumor imaging applications.

Release-burst imaging

Release-burst imaging is a novel contrast imaging approach that optimally employs the transient characteristic of UCA. It is based on a combination of multiple high-frequency, broadband-detection pulses and a separate release burst. The detection pulses are used to survey the target before and after transient enhanced scattering, which is forced by the release burst. In this way, both processes (*i.e.*, imaging and transient enhanced scattering) can be optimized separately. Therefore, this method circumvents the need to sacrifice either contrast sensitivity or imaging resolution (Frinking et al. 1998). The presence of the contrast agent is simply detected by correlating or subtracting the signal responses from the imaging pulses. The time-interval between the two detection pulses is minimal (approximately 200–400 μs, depending on the scan depth, size of the region, etc.). In static situations, the two detection pulses can be simply subtracted, which can be performed in real-time. In dynamic situations, this new method can be combined with a Doppler kind of processing scheme to remove residual clutter signals from moving tissue (Kirkhorn et al. 1999).

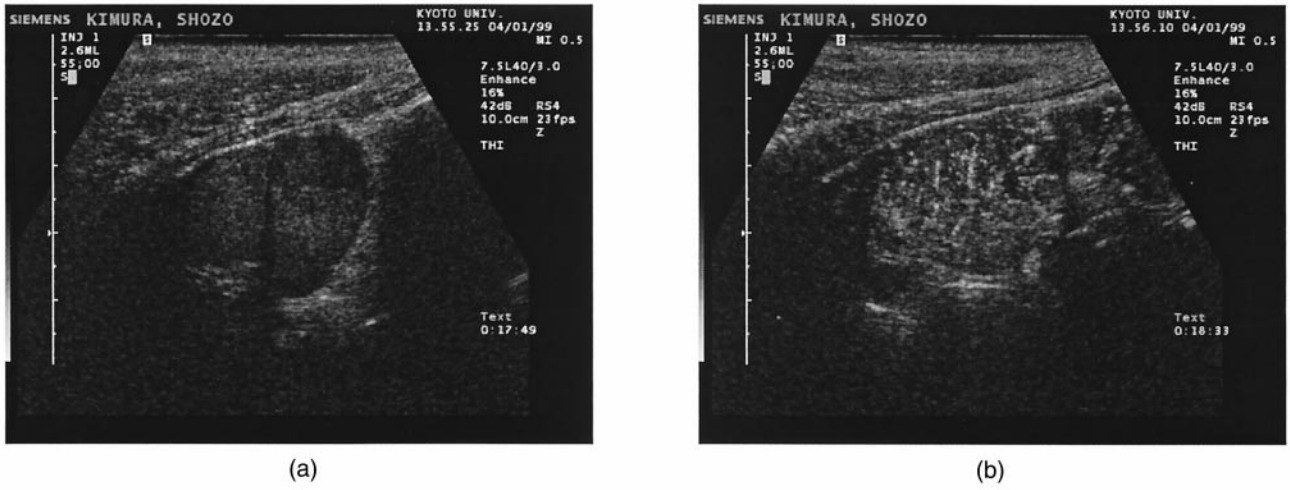


Fig. 9. Example of pulse-inversion imaging of a human liver with a hepacellular carcinoma (Moriyasu 1999). (a) Baseline recording; (b) after Optison™ has been administered. Note that the images were recorded in continuous mode (Courtesy F. Moriyasu, Kyoto, Japan).

In Fig. 10, the first experimental *in vivo* release burst images are presented. Digital radiofrequency (RF) data were recorded with a System Five US scanner (GE Vingmed Sound, Horten, Norway) with a customized software version. All the data were processed and visualized off-line using Matlab® (The Mathworks Inc., Natick, MA). Triggered imaging was used at the end-diastolic phase of the heart cycle every third beat. Figure 10a shows the baseline recording before Levovist® was administered. The left panel shows the B-mode image for orientation with the *release burst sector* indicated in blue. The quality of the B-mode image was suboptimal because the transmitted pulses were designed so that as little as possible of the UCA was disrupted by the B-mode scan. The middle panel shows the processed release burst data superimposed on the B-mode image. The right panel shows the power profile of the processed release burst data, corresponding to the cross-section, as indicated by the dashed red line in the left and middle panels. Blooming artefacts may be excluded by using the additional information provided by the power profile. The baseline image shows that gain settings and clutter filtering were sufficient to suppress most of the motion of the myocardium. The signals from the left ventricular cavity were due to high blood flow velocities.

During infusion of Levovist® (Fig. 10b), a clear opacification of the left ventricular (LV) cavity and a part of the right ventricle (RV) was obtained. Especially at the interventricular septum (IVS), the LV cavity was clearly delineated. In this example, it was more emphasized because of the poor quality of the B-mode image. Additionally, an enhancement of the IVS was obtained, which is confirmed by the power profiles in Fig. 10a and b, and was approximately 10–15 dB.

Great care needs to be taken, however, to interpret the enhancement of the septum as perfusion. As with power Doppler, release burst imaging is a multipulse technique, because a number of pulses are transmitted in the same line of sight. Therefore, motion artefacts originating from moving tissue can be interpreted as signals originating from contrast (flash artefact). However, a powerful utility of release burst imaging is that the release burst can instantaneously be switched on and off. The release burst modifies the UCA, which only occurs in a region where the contrast agent is present. Therefore, blooming and flash artefacts from clutter can be discriminated from real contrast-enhanced signals. By displaying the images simultaneously in a dual image mode, contrast-rich areas can be accurately depicted. Figure 10c is an example where the release burst was switched off, which is actually equal to power Doppler at low MI. Indeed, the RV is less opacified and the IVS is hardly enhanced. The residual signals can be caused by motion artefacts or contrast agent disruption by the detection pulses. The clear opacification of the LV is due to high blood flow and agent disruption.

The increased agent-to-tissue ratio for release-burst imaging is clearly demonstrated. It should be remarked, however, that the MI was 0.4. At maximal MI, the agent-to-tissue ratio for harmonic power Doppler imaging obviously will increase. Nevertheless, there are some limitations. Because a number of pulses are transmitted in the same direction, a high MI will result in a high disruption rate of the UCA. Decreasing the number of

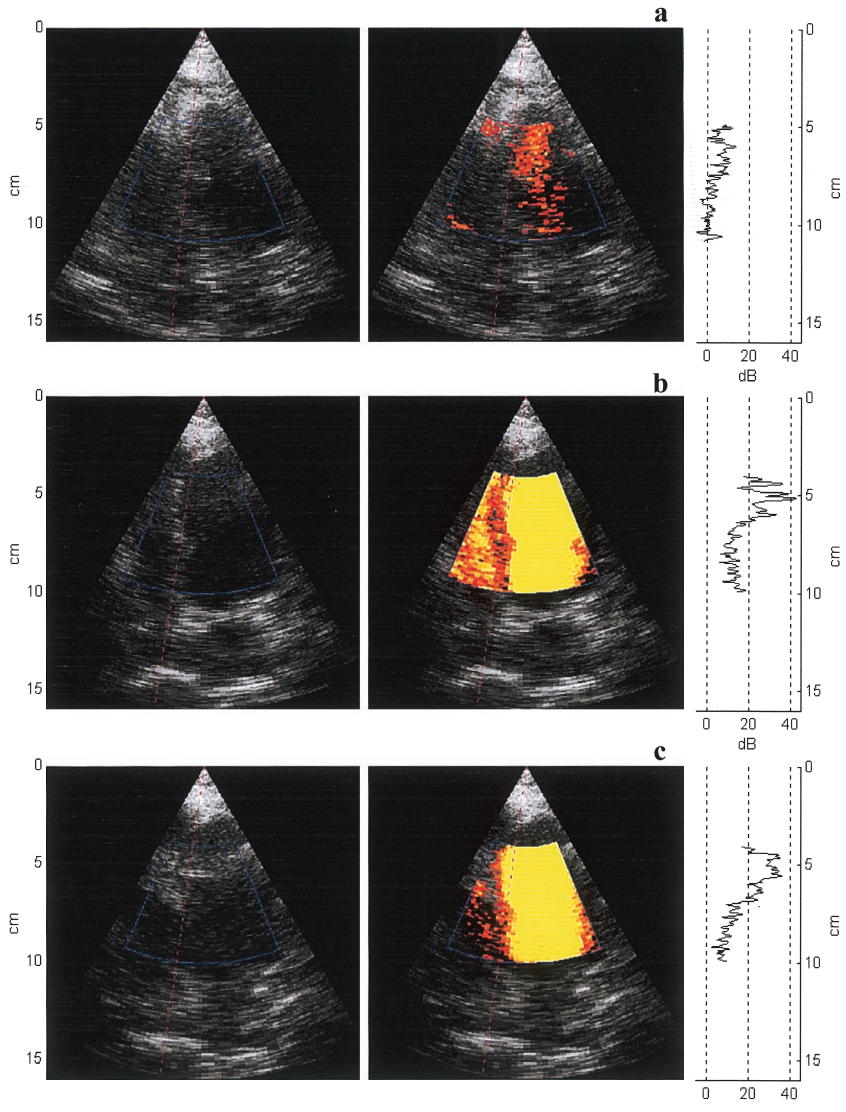


Fig. 10. *In vivo* result of release-burst imaging. Left panel: B-mode image of an apical four-chamber view of the heart, with ROI for orientation. Middle panel: the processed release-burst data are superimposed on the B-mode image. Right panel: power profile of the processed release-burst data corresponding to the dashed red line in the left and middle panels. (a) Baseline recording without Levovist® and with the release burst; (b) with Levovist® and with the release burst; and (c) with Levovist® and without the release burst.

pulses will have a lower limit because of clutter removal performances. Additionally, in harmonic power Doppler, the sample volume (*i.e.*, the length of the transmitted pulses) is generally increased to 3 to 5 cycles to get a more efficient disruption of the contrast agent (Frinking et al. 1999). But, this results in a degradation of the imaging resolution. Therefore, with harmonic power Doppler, a compromise between contrast sensitivity and imaging resolution has to be made. With release-burst imaging, the release burst and imaging pulses are separated and, consequently, will be less susceptible to this trade-off.

Release-burst imaging is very sensitive for UCA detection in fundamental mode and, therefore, nonlinear propagation effects do not limit the maximum obtainable agent-to-tissue ratio. However, due to the disruption of UCA, it has to operate in an intermittent way, as all imaging methods depending on bubble disruption. In the intermittent mode, US imaging loses its real-time character, which can make it difficult to determine the position of the scanning plane.

Nevertheless, a combination of continuous imaging and release-burst imaging can be implemented. Real-time imaging can be displayed on one part of the mon-

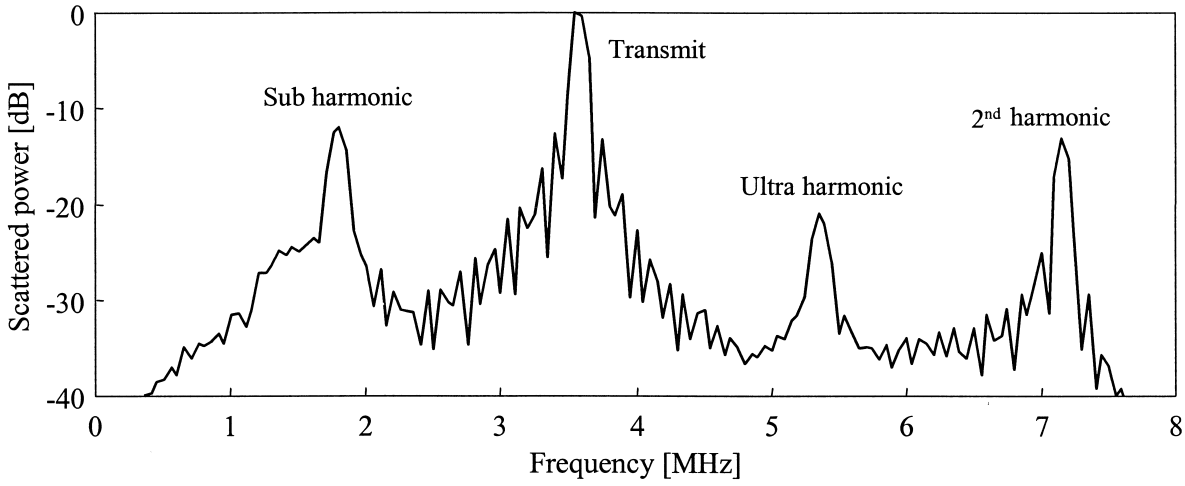


Fig. 11. Scatter spectrum of SonoVue™, showing the fundamental, second harmonic, subharmonic and ultraharmonic components. The transmitted burst had a frequency of 3.5 MHz, 40 cycles and a peak negative pressure of 75 kPa.

itor, and the information of contrast-rich areas will be updated after every scan of release bursts and displayed on another part of the monitor, as with flash echo imaging (Kamiyama et al. 1999).

Subharmonic imaging

The harmonic nature of oscillating gas bubbles has been exploited extensively with second harmonic imaging applications such as harmonic B-mode, harmonic power Doppler and pulse inversion. Nevertheless, new opportunities arise by exploiting the subharmonic component of an oscillating gas bubble. Under specific conditions, gas bubbles generate subharmonics, which occur mainly at half the transmitted frequency. A potential advantage of subharmonic imaging is that, unlike with (second) harmonic imaging, the contribution of tissue is minimal at acoustic pressures currently used in diagnostic US, which will result in a high agent-to-tissue ratio (Shankar et al. 1998). Several investigators have described the possibility of subharmonic imaging for UCA (Lotsberg et al. 1996; Shankar et al. 1998). Recently, Shi et al. (1999) described the implementation of subharmonic imaging in a US scanner and showed *in vivo* images.

According to theory, the onset of subharmonic scattering for a free gas bubble depends on the transmitted frequency and the applied acoustic pressure (Eller and Flynn 1969). The acoustic pressure for the onset is minimal at twice the resonance frequency of the gas bubble. Additionally, narrow-band signals are needed because the generated subharmonic components will be more dominant when the number of periods increase.

Figure 11 shows the scatter spectrum for SonoVue™ (Bracco Research SA, Geneva, Switzerland). Apart from the transmitted (fundamental) and second harmonic components at 3.5 MHz and 7 MHz, respectively, the subharmonic and ultraharmonic components are clearly present at 1.75 MHz and 5.25 MHz, respectively. The measurement was corrected for the sensitivity of the receiving transducer and, as can be appreciated from Fig. 11, the corrected subharmonic component is higher than the second harmonic component. The subharmonic signals in the received echoes can be extracted using filtering techniques, as with second harmonic imaging. This gives subharmonic imaging a great potential. On the other hand, the narrow-band character, necessary for optimal generation of subharmonics, will limit the spatial resolution.

The application of subharmonic imaging is currently in its infancy. The development of a new transducer design and imaging strategy will be essential to exploit optimally the advantages of subharmonic imaging.

CONCLUSIONS

UCA have unique signatures that differ from surrounding tissue. Imaging methods like harmonic imaging, harmonic power Doppler imaging and pulse-inversion imaging have improved the image quality of US contrast imaging considerably. New methods, such as release-burst imaging and subharmonic imaging, are being developed and have to prove their additional value for US contrast imaging in the future. For further improvements of the current imaging methods and for the development of the new techniques, a complete understanding of the US-contrast agent interaction is essential. It is expected that new technical improvements will lead to a further step forward in US contrast imaging. For

example, specific machine settings and detection methods for different agents (*i.e.*, agent-specific imaging templates) will probably be available on future US scanners.

REFERENCES

Abbot JG. Rational and derivation of MI and TI: A review. Ultrasound Med Biol 1999;25(3):431–441.

Bouakaz A, Frinking P, de Jong N. Ultrasound imaging based on nonlinear pressure field properties. 15th International Symposium on Nonlinear Acoustics, Gottingen, Germany, 1999. Nonlinear acoustics at the Turn of the Millenium. Proceedings of the ISNA15, W Lauterborn, T. Kurz (eds.), Melville, New York: AIP, 2000, 487–490.

de Jong N, Cornet R, Lancee CT. Higher harmonics of vibrating gas filled microspheres. Part one: Simulations. Ultrasonics 1994;32: 447–453.

Eller A, Flynn HG. Generation of subharmonics of order one-half by bubbles in a sound field. J Acoust Soc Am 1969;46(3II):722–727.

Frinking PJA, Cespedes EI, de Jong N. Multi-pulse ultrasound contrast imaging based on a decorrelation detection strategy. S Shneider, M Levy, B McAvoy (eds). Milwaukee, IEEE. 1892. IEEE Ultrasonics Symposium, Sendai, Japan, 1998:1787–1790.

Frinking PJA, de Jong N, Cespedes EI. Scattering properties of encapsulated gas bubbles at high ultrasound pressures. J Acoust Soc Am 1999;105(3):1989–1996.

Frinking, P, Cespedes, E, Kirkhorn, J, Torp, H and de Jong, N. A new Ultrasound Contrast Imaging Approach Based on the Combination of Multiple Imaging Pulses and a Separate Release Burst. Accepted for publication in IEEE Trans Ultrason Fer Freq Con; 2000.

Hope Simpson D, Chin CT, Burns PN. Perfusion imaging with pulse inversion Doppler and microbubble contrast agents: in vivo studies of the myocardium. S Shneider, M Levy, B McAvoy (eds). Milwaukee; IEEE; 1892. IEEE Ultrason Symposium, Sendai Japan, 1998.

Hope Simpson D, Chin CT, Burns PN. Pulse inversion Doppler: A new method for detecting nonlinear echoes from microbubble contrast agents. IEEE Trans Ultrason Ferr Freq Cont 1999;46(2): 372–382.

Kamiyama N, Moriyasu F, Mine Y, Goto Y. Analysis of flash echo from contrast agent for designing optimal ultrasound diagnostic systems. Ultrasound Med Biol 1999;25(3):411–420.

Kasprzak JD, Paelinck B, Ten Cate FJ, Vletter WB, de Jong N, Poldermans D, Elhendy A, Bouakaz A, Roelandt JR. Comparison of native and contrast-enhanced harmonic echocardiography for visualization of left ventricular endocardial border. Am J Cardiol 1999;83(2):211–217.

Kaul S and Jayaweera R. Coronary and Myocardial blood volumes. Noninvasive tools to assess the coronary microcirculation. Circulation 96: 719–724; 1997.

Kirkhorn J, Frinking PJA, de Jong N, Torp H. Improving the sensitivity of power Doppler for ultrasound contrast imaging by using a high power release burst. 4th Heart Centre European Symposium on Ultrasound Contrast Imaging, Rotterdam, The Netherlands, 1999: 56–60 F. Ten Cate and N. de Jong (eds). Delft: JB&A; 85.

Lotsberg O, Hovem JM, Aksum B. Experimental observation of subharmonic oscillations in infoson bubbles. J Acoust Soc Am 1996; 99(3):1366–1369.

Medwin H. Counting bubbles acoustically: a review. Ultrasonics 1977; 1:7–13.

Moriyasu F. In vivo behavior of microbubbles observed using harmonic grey-scale imaging. 4th Heart Centre European Symposium on Ultrasound Contrast Imaging, Rotterdam, The Netherlands, 1999:24–25. F. Ten Cate and N. de Jong (eds.) Delft: JB&A; 85.

Ophir J, Parker KJ. Contrast agents in diagnostic ultrasound. Ultrasound Med Biol 1989;15(4):319–33.

Porter TR, Xie F. Transient myocardial contrast after initial exposure to diagnostic ultrasound pressures with minute doses of intravenously injected microbubbles. Demonstration and potential mechanisms. Circulation 1995;92(9):2391–2395.

Powers JE, Burns PN, Souquet J. Imaging instrumentation for ultrasound contrast agents. Advances in echo imaging using contrast enhancement. In: Nanda N, Schlief R, Goldberg B, eds. Dordrecht, The Netherlands: Kluwer Acedemic, 1997:139–170.

Shankar PM, Dala Krishna P, Newhouse VL. Advantages of subharmonic over second harmonic backscatter for contrast-to-tissue echo enhancement. Ultrasound Med Biol 1998;24(3):395–399.

Shi WT, Forsber F, Hall AL, Chiao RY, Liu J, Miller S, Thomenius KE, Wheatley MA, Goldberg BB. Subharmonic imaging with microbubble contrast agents: Initial results. Ultrasound Imag 1999;21: 79–94.

Uhlendorf V and Hoffmann C. Nonlinear acoustical response of coated microbubbles in diagnostic ultrasound. IEEE Ultrason Symp, Cannes, France: 1559–1562; 1994.

Ward B, Baker AC, Humphrey VF. Nonlinear propagation applied to the improvement of resolution in diagnostic medical ultrasound. J Acoust Soc Am 1997;101(1):143–163.

Wei K, Jayaweera AR, Firoozan S, Linka A, Skyba DM, Kaul S. Quantification of myocardial blood flow with ultrasound-induced destruction of microbubbles administered as a constant venous infusion. Circulation 1998;97(5):473–483.