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Review

New sonographic techniques for harmonic imaging—Underlying physical principles

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Abstract

In this paper, modern harmonic imaging techniques are reviewed and their physical principles are explained. The clinical advantages of these new techniques that are generally used in conjunction with ultrasound contrast agents are highlighted and compared to conventional flow imaging methods. Low/high mechanical index (MI) methods are discussed as well as emerging technologies for future transducer or beamformer generations. Finally the latest safety issues concerning applications of modern (harmonic) imaging techniques with contrast agents are given.

Keywords: Diagnostic ultrasound; Harmonic imaging; Transducer technology; Ultrasound contrast agent; Safety

Contents

1. Introduction

Nowadays it is almost impossible to write a review of new sonographic techniques without being selective. At the same time the state of the art of ultrasound imaging is so widespread in hardware and software developments – even compared to only a decade before – where digital beamformers were introduced and advantageous innovations in clinical practice could be focused on 3D-imaging and colour flow ultrasound applications [1–10]. However, today the numerous software-based ultrasound evaluation methods and real-time transducer array concepts could not have come about without the development of powerful and fast computers in the last decade.

In this review, the focus will be on modern signal generation and evaluation techniques for ultrasound imaging with or without contrast agents. A large number of different acronyms for these techniques are marketed, e.g., THI, CHI, PI, PS, CPS, ADF, and CBI [11]. This paper is intended to clarify and explain the meaning, the physical basics, and techniques behind these abbreviations and to highlight clinical advantages of some modern US system, transducer tech-

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nologies, and beamforming concepts compared to classical ones. Finally some leading-edge technologies will be presented.

2. Physics of signals

2.1. What are harmonics?

To understand the basics of modern US systems and transducer technologies it is essential to know a little of the fundamental wave physics of the emitted signals and the way in which they are modified as they travel through a medium or interact with ultrasound contrast agents (UCA). A continuously emitted sinewave can be characterized as a single frequency f (Fig. 1(a)) in the spectrum and is known as the fundamental frequency of this wave. A transducer of an ultrasound system emits short pulses, i.e., a pulse with N sinusoidal cycles results in a spectrum of a range of frequencies with a centre frequency f_c and a 3 dB bandwidth (bw) (Fig. 1(b)). Additionally the emitted pulses are neither perfectly sinusoidal nor the cycles are equal in amplitude or duration. Such real pulses consist of a number of different harmonic spectra with individual centre frequencies f_c, $2f_c$, $3f_c$, respectively (Fig. 1(c)). In ultrasound imaging it is common to talk about the fundamental frequency f_c rather than about the fundamental spectrum. Higher frequency components are called second ($2f_c$) or third ($3f_c$) harmonic frequencies. Frequencies lower than the fundamental frequency (f_c) are called sub-harmonics.

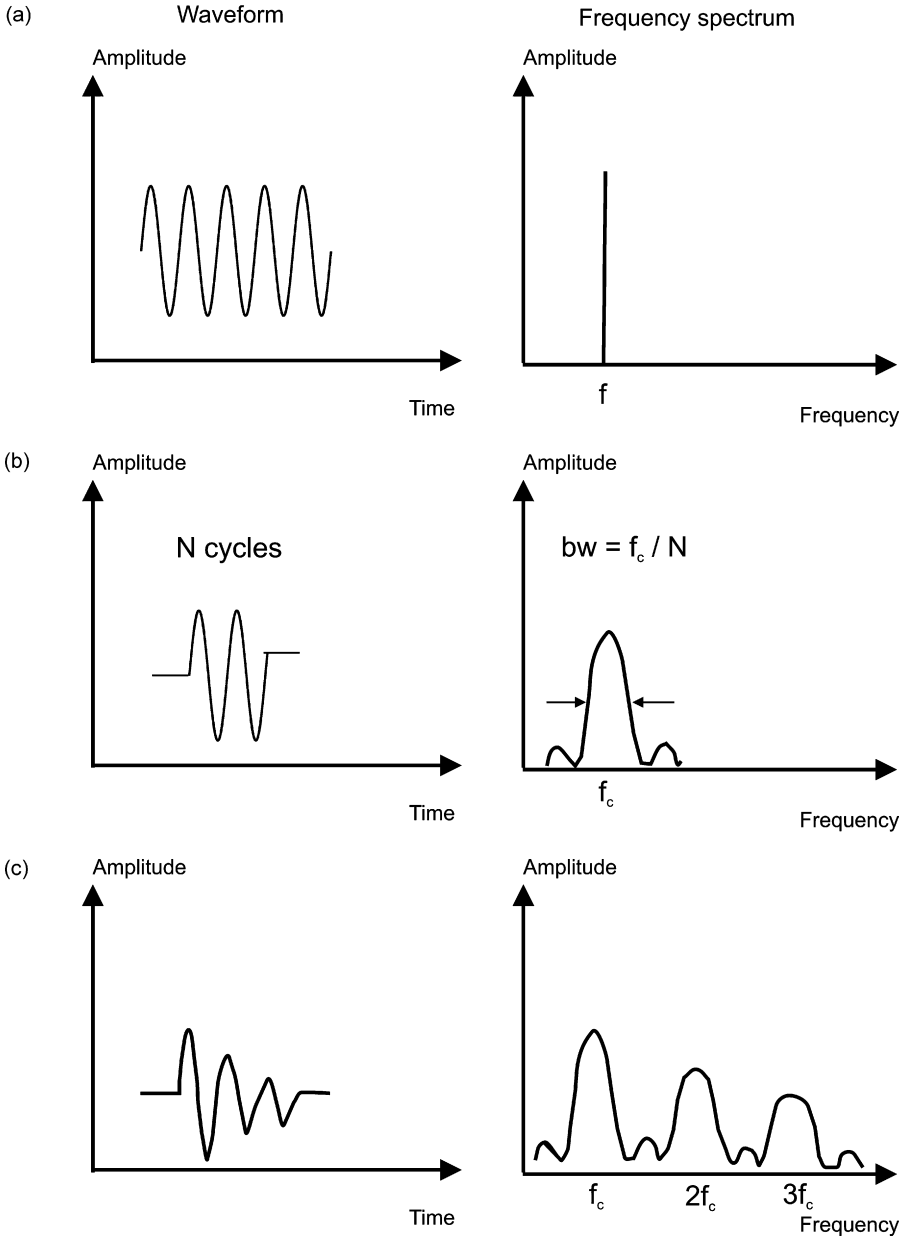

Fig. 1. Waveforms and its corresponding frequency spectrum. (a) A sinewave is characterized by a single frequency. (b) A short ideal pulse is characterized by different frequencies around a centre frequency (f_c) with bandwidth (bw). (c) A real pulse with different amplitudes is characterized by different harmonic frequencies (fundamental and higher harmonic frequencies).

In general as can be seen in Fig. 1 the amplitude of the fundamental frequency is higher than the amplitudes of the harmonic frequencies, which has an important impact on transducer technology regarding sensitivity, bandwidth, and filter design for modern systems [12].

2.2. Harmonics in tissue

Before introducing harmonic imaging techniques into clinical practice, it was assumed that ultrasound propagation through tissue is linear. But this is not true; it is obvious that a second harmonic component exists within the tissue echo, too. The ultrasonic pulse travelling through tissue is distorted with time, as a result of non-linear propagation. The peaks within the pulse wave propagate with a higher speed than the troughs of the waveform. This is because the speed of propagation is a little bit greater in the regions of tissue, which are compressed than in the regions, which are expanded by the passing pressure wave. The resulting waveform distortion in tissue depends on the emitted pulse amplitude and distance it has travelled in tissue. For low amplitude pulses the distortion may be negligible but significant for large amplitude pulses (mean/high MI).

In practice the echoes returning from tissue interfaces contain a second harmonic frequency component that can be processed in modern imaging systems. These kinds of techniques are known as native or (differential) tissue harmonic imaging (dTHI) or harmonic grey-scale imaging. In some circumstance second harmonic images of tissue can be superior to those formed from the fundamental frequency. The images can provide greater clarity, contrast, and details, because of the greater lateral resolution and the reduction of the acoustic noise (clutter) due to reverberations, grating, and side lobes. Additionally patients who were imaged poorly with fundamental frequency ultrasound could be examined by second harmonic imaging [12,13].

An important impact on this technique has new concepts for beam generation, forming, and processing and are presented in a later section.

2.3. Harmonics and ultrasound contrast agents (UCA)

Today almost all modern UCA consist of a gas-filled kernel encapsulated by a phospholipid or albumin shell (~2 nm thick) with a total bubble radius of 1–10 μm [14–16]. The microbubbles act as Rayleigh scatterers, i.e., their geometric scattering cross-section increases with the 4th power of applied frequency and the 6th power of the bubble radius; a technical feature of objects that are very small compared to the ultrasonic wave length (1–0.1 mm at 1.5–15 MHz).

The fragile and viscoelastic UCA reacts with a flexible and unique acoustic signature to an ultrasound pulse caused by the microbubble's structure, the external pulse amplitude and frequency.

In diagnostic imaging an index, the mechanical index MI, is displayed on the monitor that can be used to characterize the microbubble's behaviour (Fig. 2): the higher the MI-value the higher the incident ultrasound pulse amplitude that interacts with the microbubbles:

- very low MI: stable linear scattering;
- low/mean MI: stable non-linear scattering;
- high MI: transient non-linear scattering and destruction.

While the ultrasonic wave is passing a microbubble, the bubble contracts and expands in the rhythm of the positive and negative pressure phase of the wave. Depending on the amplitude of the incident ultrasonic wave the bubbles can oscillate in a symmetrical (linear) or in an asymmetrical way (non-linear). These oscillations lead to a specific effect called resonance. The resonance frequency f_{Renc} of an encapsulated microbubble of radius r and a total bubble mass m that is surrounded by a liquid with a density ρ and ambient pressure p is

$$f_{\mathrm{Renc}} = \frac{1}{2\pi r}\sqrt{\frac{3\gamma p}{\rho} + \frac{S_{\mathrm{shell}} r^2}{m}} \tag{1}$$

with γ is the ideal gas constant and S_{shell} is the stiffness of the bubble shell.

In the case of a low incident wave amplitude there is a linear response of the UCA according to Eq. (1), increasing wave amplitudes (mean MI) show a non-linear (asymmetrical) behaviour of the UCAs response, the bubbles can expand but not contract in phase any longer, which leads to a harmonic frequency spectrum f_{harm}:

$$f_{\mathrm{harm}} = n f_{\mathrm{Renc}} \quad \text{with } n = 1, 2, 3, \ldots \tag{2}$$

This bubble effect of generating a second harmonic frequency ($n = 2$) is evaluated for imaging and used within modern harmonic imaging or contrast harmonic imaging techniques (e.g. HI, CHI).

Besides this microbubbles' asymmetrical oscillations can also produce harmonic frequency components (Eq. (2)) that are called sub-harmonics ($n = 1/2, 1/3, \ldots$) and ultra- or super-harmonics ($n = 1.5, 2.5, \ldots$). While the evaluation of the sub-harmonics frequency spectrum is under current development for imaging purposes, the first ultra-harmonic frequency is used in clinical practice and known as 1.5 harmonic imaging [14,17].

Because UCA are used as a tracer within the blood pool, the harmonic imaging technique is not restricted to detect higher harmonics of static objects (tissue, stationary microbubbles) but can be used for Doppler-mode applications as well. In this case the equipment detects and evaluates the shifted harmonic frequency components Δf_{harm} of the Doppler signal coming from the moved and oscillating microbubbles:

$$\Delta f_{\mathrm{harm}} = \frac{n f_{\mathrm{Renc}} v}{c} \cos(\alpha) \tag{3}$$

with $n = 1, 2, 3, \ldots$, $c = 1540$ m/s, v the velocity of tracer (UCA), and α is the Doppler angle.

If the incident wave amplitude is increased further (high MI), another effect occurs: the microbubble collapses, i.e., the bubble is mechanically destroyed or fragmented by the instantaneous high peak pressure of the wave (stable/inertial cavitation). In ultrasound imaging, this bursting is manifested by a very strong echo followed by a complete destruction within the region-

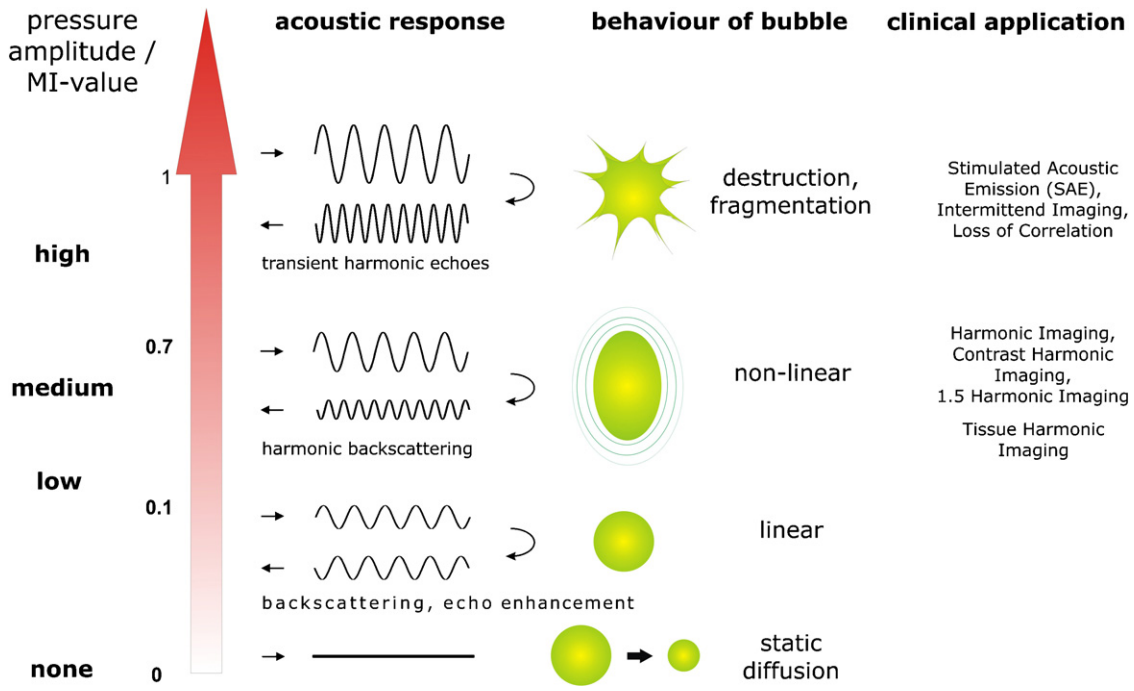

Fig. 2. Schematic view of the behaviour of microbubbles (UCA) at different ultrasonic amplitudes of the propagating pulse (MI values) and corresponding clinical applications.

of-interest on the display. Techniques using regular high MI values for destroying UCA or a single activated high amplitude pulse ("big bang") are known as intermittent imaging, stimulated acoustic emission (SAE), loss of correlation (LOC) or flash echo imaging (FEI) techniques (Fig. 2). The cavitation of the bubble, as well as related secondary effects [14,18] represents a source for induced bioeffects and application of these techniques should be performed under safety aspects [19].

3. Methods of pulse generation and detection for imaging

Both tissue and UCA have a second harmonic frequency spectrum and it is necessary to distinguish between both structures to improve the image contrast. Some techniques such as THI, CHI, harmonic power Doppler (HPD) or harmonic greyscale imaging use large amplitude pulses and high-pass filters to suppress the fundamental echoes but leave the second harmonic frequency components (Fig. 3). The amplitude of the transmitted pulses are chosen in a way that the UCA is not destroyed, nor the second harmonic tissue echo is too dominant to ensure a relevant strong echo from the bubbles. The resulting images show brighter vessels against a darker tissue background. Additionally HPD show reduced flash artefacts, and smaller blooming artefacts compared to conventional Doppler methods [16].

But this method has its limitations in practice: the overlap between the fundamental and second harmonic spectrum of the echoes is not as small as possible, and the filter cannot separate the components successfully. Strong tissue echoes containing high frequency parts of the fundamental echo can overwhelm low second harmonic signals detected from UCA (Fig. 3), resulting in tissue clutter. Also the bandwidth of transducers is sometimes not large enough to cover the total range of the fundamental spectrum and second harmonic spectrum, which leads to a poorer axial resolution.

To overcome these limitations in more recent techniques two different approaches combined with sophisticated pulse schemata were developed, the low MI and the high MI method.

3.1. *Low MI*

The low MI method seeks to minimize the destruction of the UCA by using low amplitude pulses. Techniques using this method are fully dedicated to the detection of the non-linear scattering of the microbubbles. The echoes returning from the microbubbles have a greater second harmonic component than the echoes of tissue and sophisticated binary pulse coding and/or pulse emission shapes as, e.g., pulse inversion (PI), pulse subtraction (PS) or contrast pulse sequences (CPS) are used to separate the UCA from tissue optimally.

Techniques to generate longer pulse transmission pulses, which carry identifying codes in the form of frequency or phase changes are used to improve the signal-to-noise ratio (SNR) up to 20 dB and leave the side lobes below 60 dB and enhance the sensitivity as well as the penetration. These techniques are known as "chirp" and "binary coding" techniques. The detected echo sequences are decoded by autocorrelation. Because of the longer pulse length of coded pulses, more acoustic power is transmitted into the patient for a given peak intensity; temporal peak intensity and tissue heating are therefore greater [13].

A second generation of techniques developed uses different pulse shapes during emission and involves interrogating each scan line twice: short pulses (2–3 cycles) are transmitted with

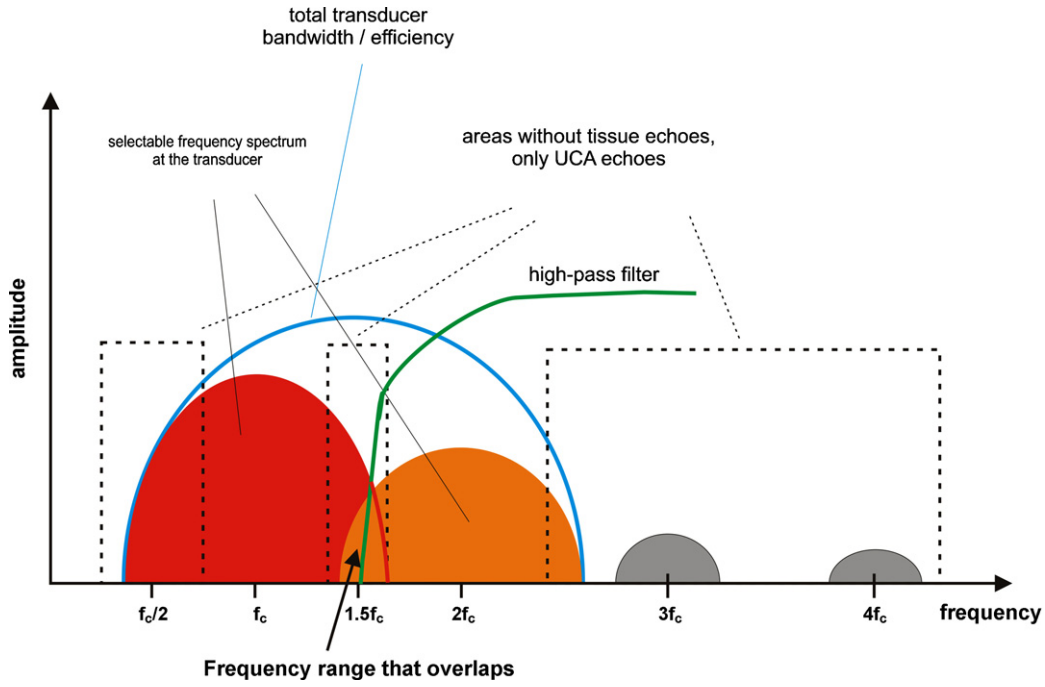

Fig. 3. Schematic view of the frequency spectrum used for second harmonic imaging. A modern transducer must be capable of covering the full frequency range of the fundamental and second harmonic spectrum (blue line) and makes it possible to switch between both frequency bands within operation (red and orange area). In general a high-pass filter (green line) is not able to separate the frequency components successfully. The dotted areas represent areas that contain no tissue echo within the sub- and super-harmonic frequency spectrum.

the waveform of the second pulse being inverted (i.e. 180° phase shifted) with respect to the first (Fig. 4(a) and (b)). The echoes from tissue on both pulses are identical versions but inverted with different amplitudes which will be cancelled when the two echo sequences are summed, sometimes named pulse subtraction (PS). The echo of an UCA representing non-linear scatterers is not cancelled on addition (Fig. 4(c)). Other variations of this technique are using alternate scan lines, three pulses or two pulses having different amplitudes (amplitude modulation) or combinations of two variations, e.g., pulses having different

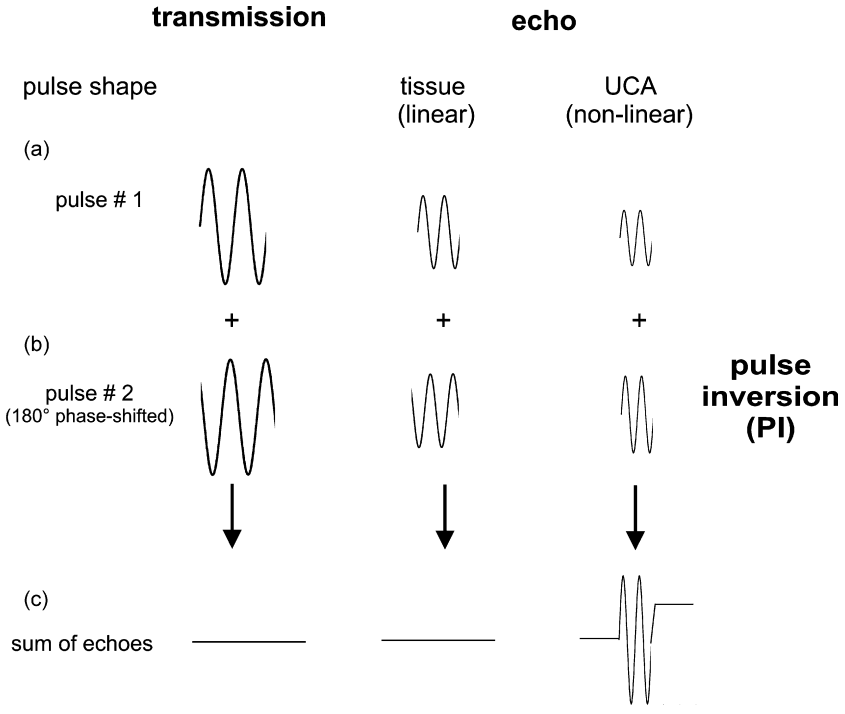

Fig. 4. Method of pulse inversion. Short pulses are transmitted with the waveform of the second pulse being inverse (i.e. 180° phase shifted) in respect to the first (a and b). (c) The echoes from tissue on both pulses are identical versions but inverted with different amplitudes, which will be cancelled when the two echo sequences are summed. The echoes of microbubbles (UCA) do not cancel and give a signal at summation.

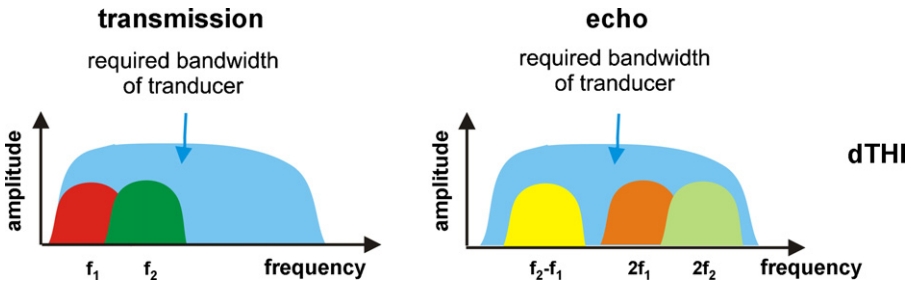

Fig. 5. Method of differential tissue harmonic imaging (dTHI). Simultaneous transmission of two pulses at different frequencies and reception of signals at harmonic and differential frequencies. This technique requires a large bandwidth of the transducer.

amplitudes and phases like contrast pulse sequence (CPS) or cadence imaging.

These techniques can be used for fundamental as well as for harmonic echo waveforms because they eliminate the odd harmonic frequencies ($1f_c$, $3f_c$) and double the amplitudes of the even harmonic frequencies ($2f_c$, $4f_c$). Although these techniques have a disadvantage of a lower frame rate (at least 2 or more pulse emissions per line), they show an improved visualization of macro-/micro-vasculature, an enhanced sensitivity, and detail as well as spatial and temporal resolution compared to conventional techniques.

Finally another advanced approach is utilized for differential tissue harmonic imaging (dTHI). This technique transmits simultaneously two pulses with different frequencies and receives echo signals at the harmonic and differential frequencies. The cancellation of the fundamental signals is then performed by pulse subtraction (Fig. 5). Modern broadband transducers and fast signal processing are essential for this kind of technique, which benefits in a superior border and tissue definition, increased penetration with unchanged spatial and contrast resolution compared to conventional THI [20].

3.2. High MI

The second is the high MI method transmitting pulses with large amplitude (MI > 0.7, Fig. 2) to evaluate the difference in echo signal before and after UCA destruction or the energy released. This method achieves higher sensitivity and is an option for those UCA whose microbubbles are not flexible enough to give sufficient non-linear signal when insonated with low MI amplitudes or to detect stationary or very slow moving microbubbles.

After transmitting a high amplitude pulse the microbubbles are oscillating vigorously or are collapsing and therefore sending strong non-linear echoes back. These echoes are evaluated for imaging (LOC) in B-mode and/or Doppler-mode (Fig. 6) and are diagnostically useful in large vessels and the chambers of the heart where blood velocity is high. In smaller vessels or the capillary bed the blood flow is low and it takes a while to replenish and to visualize the region again with UCA after destruction. By using ECG to trigger one image frame each 2–4 cardiac cycles or by using intermittent imaging techniques (FEI, SAE) with low frame rates visualizing this kind of vessels is possible nevertheless.

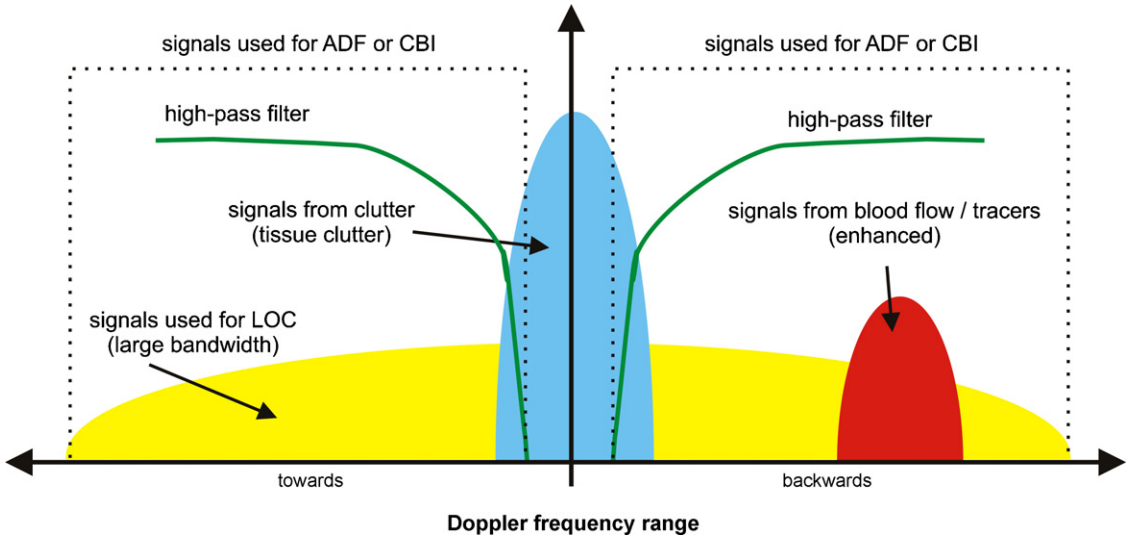

Fig. 6. Doppler frequency range used for LOC, ADF, and CBI techniques using UCA. The enhanced signals from blood flow or tracers (red area) and used in ADF, CBI are well separated from the clutter signal (blue area) but are only a small part of the signal components used for LOC (yellow area).

The echoes produced by collapsing microbubbles contain a wide range of harmonics, but because of the high amplitude pulse desisted from safety issues generates a high level of second harmonic component from tissue (clutter, Fig. 6) in the echo, too, that can reduce the contrast resolution to only a few decibels but can be improved by off-line subtraction of a non-contrast-enhanced image from the contrast-enhanced image of the same area.

Generally the high MI method suffers from poor spatial resolution and more recent developments use short broadband high amplitude pulses to overcome this limitation. Additionally, the number of pulses transmitted down each line has also been reduced to improve temporal resolution.

Because the bandwidth of the received signals is large, a high-pass filter can eliminate most of the tissue clutter signal and leaves the Doppler spectrum mainly unchanged. The filter performance can be improved by using a high pulse repetition frequency (PRF) that means also a greater tolerance of tissue movements since there is less phase shift between consecutive tissue echoes. Besides no blood or tracer (i.e. UCA) velocity is measured with this technique, and therefore higher PRF sequences can be used (Fig. 6). Techniques working on this principle are marketed as contrast burst imaging (CBI) or advanced dynamic flow (ADF) and use typically 2–6 large or slightly lower amplitude short pulses per line for transmission. Clinically relevant advantages of these techniques are the high sensitivity and spatial resolution as well as the high PRF, highly reduced blooming artefacts and the display of the flow direction but with the lack of missing velocity information [12,13,16,21,22].

3.3. *Imaging techniques beyond second harmonic*

As shown in Fig. 3 higher (and lower) harmonics than the second one are also produced as a consequence of the non-linear propagation of the transmitted pulse. The super-harmonics (i.e. $3f_c$, $4f_c$) are relatively weak, but can be acquired with a modern composite broadband transducer. They are characterized by a high spatial and temporal resolution, the minimization of clutter, and what is most important the absence of harmonic tissue signal content (Fig. 3). With ongoing new and innovative transducer developments (Section 4) new clinical applications can be expected in the coming years where these kind of frequency spectra are involved.

One technique that is already in clinical use is known as 1.5 harmonic imaging (1.5 HI). This technique detects and visualizes signals that are a factor of 1.5 times higher than the fundamental centre frequency of the transducer and are intermediate between the fundamental and the second harmonic frequency spectrum [14,16,17]. The benefit is that this frequency range is almost free of tissue echoes and only contains microbubble echoes (Fig. 3). Therefore the technique is featured with a contrast improvement between tissue and microbubbles of 20 dB or more compared to the second harmonic technique. Because of the slightly higher frequency distribution of 1.5 HI, the technique provides a higher lateral resolution than the fundamental one and because of the slightly lower frequency distribution has greater depth sensitivity than the second harmonic techniques in general. However, the frequency band can be easily set to the centre frequency of modern digitally driven transducers, that helps to improve the signal-noise ratio (SNR). An innovative transducer and console technology is necessary for this imaging technique to suppress higher frequency components of the fundamental signal which can disturb the 1.5 HI signal by using digitally processed pulses and controlled waveforms as well as by optimizing the filter performance within the post-processing steps.

4. Emerging techniques of transducers and systems

Over the past 30 years piezoelectric materials, mainly the ferroelectric ceramics containing lead zirconate titanate (PZT), have been developed to produce high sensitive and efficiency transducers with a wide dynamic range and frequency bandwidth. For PZT ceramics the high acoustic impedance compared to the human body is a problem that has been solved with matching layers or by embedding small particles of PZT in a plastic to form a composite that has a reduced acoustic impedance compared to PZT alone; but both lead to more complex and expensive transducer manufacturing. Another plastic, polyvinylidene difluoride (PVDF) is used because of its low acoustic impedance and wide frequency bandwidth. It is fairly sensitive in receiving but rather inefficient in transmission [23].

Transducer technology is therefore the most prominent and critical component in ultrasonic imaging: the performance of the transducer determines the sensitivity, resolution, efficiency, and quality of the information coming out of the human body. Especially in harmonic imaging, transducers should cover a large frequency bandwidth; present a high efficiency in transmission and a high sensitivity or dynamic range for receiving.

In the last years a new type of piezocrystals discovered in the 1970s has now been marketed as Purewave Crystal or XBT technology [24]. The new piezocrystal material is more uniform and exhibits fewer defects, which leads to a dramatic enhancement of the electromechanical properties: the efficiency is improved by 68–85%, the frequency bandwidth and sensitivity enlarged compared to PZT ceramics. With precisely engineered multiple matching layers, backing materials, and advanced acoustic lens design, it is now possible to cover the frequency range of current two best-in-class broadband transducers with a single one. This will lead to new harmonic imaging applications because the clinician can select from a wide harmonic frequency range to address different imaging needs. Additionally these lightweight transducers offer significant performance increase in penetration and imaging resolution, as well as remarkable clarity and fine detail with greater uniformity throughout the entire field of view.

Another promising technology appearing recently is capacitive micromachined ultrasonic transducers (cMUTs), which are typically mounted on a silicon substrate and with a thin electroded membrane as the other plate of the capacitor acting as the active surface of the transducer. The membrane transmits an oscillatory force if a dc voltage is applied between the plates

of the device, which is superimposed additionally with an ac voltage, while a received wave causes a corresponding change in the spacing between the plates [23].

The available cMUT transducers are quite sensitive receivers with good resolution but will need high voltages for transmission. Their potential lies in its fabrication as arrays using the same lithographic processes as for microchips, which reduces weight and costs and provides the opportunity to combine them with integrated circuits. The first prototypes of linear or ring arrays for abdominal and intravascular/intracardiac applications have been tested [25,26].

Simultaneously with new transducers the development of digital beamformers and post-processing is essential to handle the demands of harmonic imaging technology in the way of multi-element arrays and wide frequency bandwidth range that results in very high and precise sampling frequencies as well as in rapid signal processing to get the information in real-time. Concepts and implementations for new digital beamformers and receiving technologies are already published to fit with clinical needs [23,27].

5. Safety issues associated with harmonic imaging

Normally no gas bodies are present within the blood but with the application of UCA many gas-filled microbodies are introduced into the body that, of course, interact with the propagating pulses for imaging and are capable of inducing microscale bioeffects: fluid jets, sonochemical activities and as initial nuclei cause inertial cavitation. The possibility of occurrence of these non-thermal mechanisms depends on the ratio of the insonated negative pulse amplitude (p_r) and acoustic working frequency or centre frequency of the transducer (f_c) and is subsumed in the mechanical index (MI):

$$\mathrm{MI} = \frac{p_r}{\sqrt{f_c}} \quad (4)$$

The MI informs the user about possible mechanical damages or hazards to tissue and is originally derived for a homogenous medium with an attenuation coefficient of 0.3 dB cm^{-1} MHz^{-1} and linear pulse propagation without the presence of UCA and some other simplified assumptions. Therefore the MI values for high MI imaging techniques are easily capable to reach or exceed the threshold for inertial cavitation (MI > 0.7) or microstreaming [14,28]. Small animal models have shown that micro-vascular damage or rupture is possible [19]. But there are also some indications that low MI techniques could increase the risk of potential hazards because of the non-linear propagation of the pulse, some non-valid simplified assumptions and the calculation method used for MI that can differ up to a factor of 5 in some cases [28].

Another mechanism is a thermal one that is related to the ratio between the transmitted ultrasonic energy to the absorbed ultrasonic energy in the tissue. The user is again informed of potential thermal hazards on-screen in terms of the thermal index (TI). Three different models are developed (TIS, TIC, TIB) depending on the tissue involved and are calculated automatically. But many clinicians are not aware that in diagnostic imaging the main thermal increase can occur at or within the skin, due to direct heating of the transducer.

The European Committee of Medical Ultrasound Safety (ECMUS) states within its safety update for 2007 related to UCA applications that caution should be considered for its use in tissue where damage to micro-vasculature could have serious clinical implications, such as in the brain, the eye, and the neonate. Additionally high MI and end-systolic triggered techniques can induce premature ventricular contractions in contrast-enhanced echocardiography and users should take precautions in these circumstances. As in all diagnostic ultrasound methods the MI and TI values should be continually checked and kept as low as reasonable achievable (ALARA-principle) [19].

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