A Primer on the Physical Principles of Tissue Harmonic Imaging[1]

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Abbreviations: DTHI = differential tissue harmonic imaging, THI = tissue harmonic imaging

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Tissue harmonic imaging (THI) is a routinely used component of diagnostic ultrasonography (US). In this method, higher-frequency harmonic waves produced by nonlinear fundamental US wave propagation are used to generate images that contain fewer artifacts than those seen on conventional fundamental wave US tissue imaging. Harmonic frequencies are integer multiples of the fundamental frequency. The majority of current clinical US systems use second harmonic echoes for THI image formation. Image processing techniques (ie, bandwidth receive filtering, pulse inversion, side-by-side phase cancellation, and pulse-coded harmonics) are used to eliminate the fundamental frequency echoes, and the remaining harmonic frequency data are used to generate the diagnostic image. Advantages of THI include improved signal-to-noise ratio and reduced artifacts produced by side lobes, grating lobes, and reverberation. THI has been accepted in US practice, and variations of the technology are available on most US systems typically used for diagnostic imaging in radiologic practice. Differential THI is a further improvement that combines the advantages of THI, including superior tissue definition and reduced speckle artifact, with the greater penetration of lower frequency US, which permits high-quality harmonic imaging at greater depth than could previously be performed with conventional THI.

Introduction

Tissue harmonic imaging (THI) and differential THI (DTHI) are nonlinear ultrasonographic (US) image-processing technologies designed to improve conventional gray-scale image quality (Table 1). THI was introduced in 1997 (1) when researchers who studied the harmonic frequencies from insonating microbubbles realized that native tissue could also produce diagnostically useful harmonic waves. Harmonic frequencies originate from native tissues during US imaging even without injection of microbubbles, but are weaker than those produced during microbubble imaging (2,3). THI and DTHI are forms of *native harmonic imaging*, which is diagnostic imaging that uses these harmonic waves that arise natively from tissue without microbubbles. DTHI was introduced in 2005 (4) and combines the advantages of conventional fundamental frequency US (increased penetration) with THI (superior border and tissue definition, with reduced speckle) (Fig 1).

In the first part of this article, we explain essential physical concepts, such as fundamental frequency, propagation of US waves in tissue, and harmonic frequency. In the second part, we discuss techniques used to eliminate the fundamental frequency in THI, discuss

TEACHING POINTS

- Linear and nonlinear propagation are terms that describe how soft tissue responds as the US wave propagates. When the pressure of the US wave in a soft tissue is small (<0.5 MPa), tissue behaves in a linear fashion, which means that it becomes completely elastic and that tissue expansion (*rarefaction*) and compression propagate at the same speed. With linear propagation, waves that contain new frequencies are not created during US energy propagation. Nonlinear propagation occurs when high-pressure US waves (>0.5 MPa) propagate through a compressible medium and the transmitted US pulse induces less compression than rarefaction.
- The production of harmonic waves, including those from the edges of the US beam, is proportional to the square of the fundamental intensity. This is greatest at the beam center, where the beam intensity is highest, and at the focal zone, where the beam is most narrow. Little or no harmonics are produced by weaker waves, such as those from the edges of the US beam, and scattered echoes, side lobes, and grating lobes.
- Images produced with THI are often superior to conventional gray-scale images of cysts and abnormalities that contain fat, calcium, or air. Clinically, several advantages are evident.
- In DTHI, two pulses are transmitted simultaneously at different frequencies, referred to as f_1 and f_2. In addition to their harmonic frequencies ($2f_1$ and $2f_2$), the sum and the difference of the transmitted frequencies ($f_2 + f_1$ and $f_2 - f_1$, respectively) are generated within the tissue. The second harmonic signal of the lower frequency (f_1) and the difference frequency ($f_2 - f_1$) are detected by the transducer; other generated frequency components do not fall within the bandwidth of the transducer. Both fundamental frequencies are cancelled by the subtraction technique (a technique similar to pulse inversion) and therefore are not detected in the signal. By receiving the second harmonic $2f_1$ and the differential frequencies ($f_2 - f_1$), the effective bandwidth of the tissue harmonic signals is expanded to between $f_2 - f_1$ and $2f_1$. By using DTHI, higher resolution, better penetration, and fewer artifacts can be achieved.
- DTHI and THI are substantially better than fundamental US imaging for noise reduction, detail resolution, image quality, focal abnormality margin sharpness, and penetration for hepatic imaging. DTHI also performed better than THI regarding detail resolution, image quality, and contrast-to-noise ratio in evaluation of focal hepatic abnormalities.

advantages and limitations of THI, and introduce some current clinical applications of THI. Finally, in the third part, we introduce the physical principles of DTHI, explain how DTHI images are processed, and compare DTHI with THI.

Technical Concepts and Terminology

Fundamental Frequency

The *fundamental frequency* is defined for a continuously emitted sine wave from a US transducer (Fig 1) as the lowest frequency in the pulse spectrum. Diagnostic US systems do not continuously emit waves, as they need to receive returning echoes. Consequently, the US transducer emits short pulses that contain a frequency spectrum with a central frequency. These pulses and their resulting echoes form the US image. In conventional B-mode US, the frequency of the transmitted pulses and of the returning echoes is the same (Fig 2).

Table 1: Glossary of Parameters of US Image Quality

Parameter	Definition
Axial resolution	The ability to resolve objects in the direction of the wave propagation, determined by transmit-pulse length or bandwidth
Lateral resolution	The ability to resolve adjacent objects across the field of view
Contrast resolution	The ability to distinguish between small anatomic structures with similar tissue characteristics
Signal-to-noise ratio	A measure of signal strength relative to background reflections, or noise, and a good predictor of contrast resolution

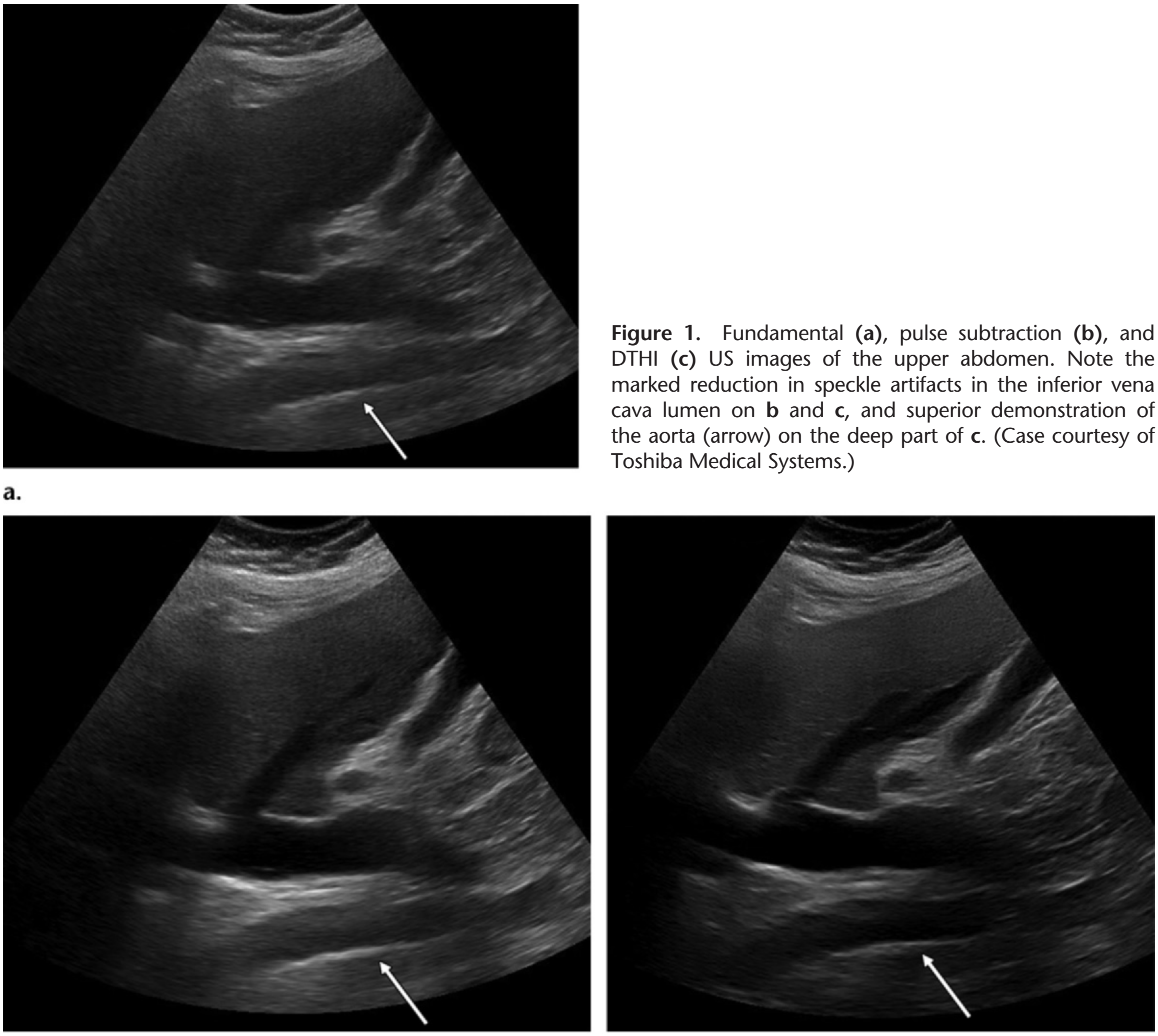
Linear and Nonlinear US Propagation

Linear and nonlinear propagation are terms that describe how soft tissue responds as the US wave propagates (Fig 3). When the acoustic pressure of the US wave in a soft tissue is small (<0.5 MPa) (1), tissue behaves in a linear fashion, which means that it exhibits completely elastic behavior and that tissue expansion (*rarefaction*) and compression propagate at the same speed. With linear propagation, waves that contain new frequencies are not created during US energy propagation (5).

Nonlinear propagation occurs when high-pressure US waves (>0.5 MPa) travel through a compressible medium and the transmitted US pulse induces less compression than rarefaction (1) (Fig 3). The propagation speed of US pulses is not constant because it is slightly faster in compressed tissue and slightly slower in rarefied tissue (5–7). Over time, this difference in propagation speed will distort even an ideal sine wave into a sawtooth wave (Fig 4).

Harmonic Frequencies

Definitions.—Harmonic frequencies are integer multiples of the fundamental frequency (ie, if the fundamental frequency is *f*, the harmonics have frequencies of 2*f*, 3*f*, and so on). The amplitudes of the harmonic waves are almost always lower than those of the fundamental frequency waves. Subharmonic frequencies are integer fractions of the fundamental frequency (eg, *f*/2, *f*/3, and so on). Subharmonic



a.

b.

c.

Figure 1. Fundamental **(a)**, pulse subtraction **(b)**, and DTHI **(c)** US images of the upper abdomen. Note the marked reduction in speckle artifacts in the inferior vena cava lumen on **b** and **c**, and superior demonstration of the aorta (arrow) on the deep part of **c**. (Case courtesy of Toshiba Medical Systems.)

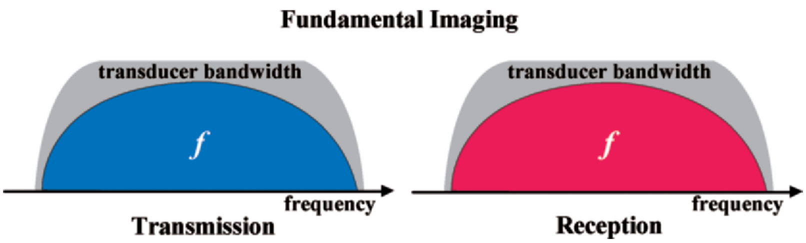


Figure 2. Diagram of the fundamental frequency imaging process. In this method, transmitted and received bandwidths are identical.

imaging is generally suitable for deep imaging because there is less attenuation of lower-frequency subharmonic signals (8,9). Frequency multiples of the subharmonic frequency component (eg, $3f/2$, $5f/2$, $7f/2$, and so on) are called ultraharmonic frequencies (10) (Fig 5).

Mechanism of Harmonic Wave Generation.—Tissue nonlinearity distorts the fundamental sine wave pattern during propagation through tissue; the compressive pulse wave peaks propagate at higher speed than do rarefactive wave troughs. This is because the speed of propagation is slightly greater in the compressed regions of the tissue than in the expanded regions. The resulting waveform distortion depends on the emitted pulse amplitude and distance traveled by the fundamental wave (5,11). For low-amplitude pulses, the distortion is negligible, but at higher amplitudes the effect becomes substantial. At the skin, tissue harmonics are virtually zero; their intensity increases with depth to the point where tissue attenuation predominates and harmonic amplitudes decrease (2) (Fig 6).

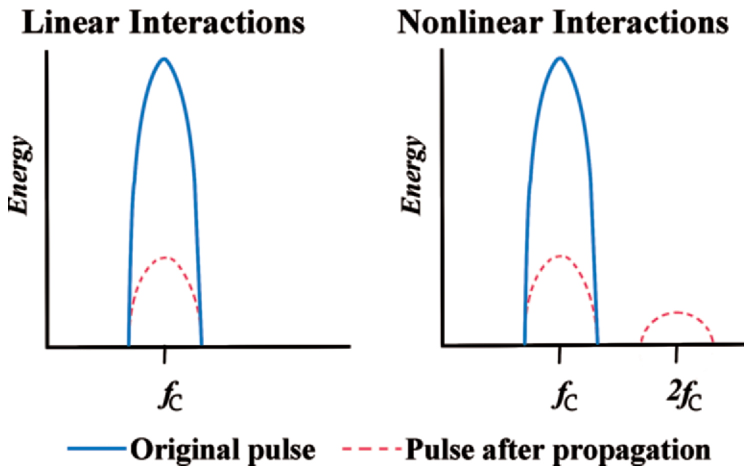


Figure 3. Linear (left) and nonlinear (right) US wave propagation. The transmitted pulse consists of a range of frequencies centered around f_c. In a linear medium, the echo pulse frequency is the same as the fundamental frequency but has lower energy, whereas the nonlinear medium results in harmonic waves of higher frequency and lower energy in addition to the fundamental frequency. f_c = fundamental frequency, $2f_c$ = example of a harmonic frequency.

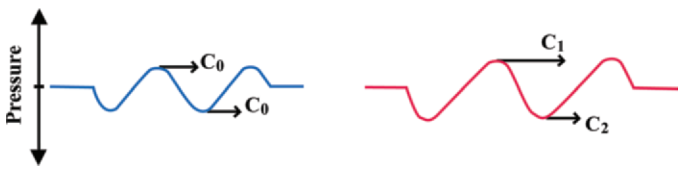


Figure 4. As fundamental frequency waves (left) propagate through medium nonlinearly, harmonic waves (right) are generated. The shape of the wave becomes distorted, and the sharp peaks travel with faster velocity (C_1) than that (C_2) for the rounded troughs.

The production of harmonic waves, including those from the edges of the US beam, is proportional to the square of the fundamental intensity (5). This is greatest at the beam center, where the beam intensity is highest, and at the focal zone, where the beam is most narrow (Fig 7) (12). Little or no harmonics are produced by weaker waves, such as those from the edges of the US beam, and scattered echoes, side lobes, and grating lobes (6,13).

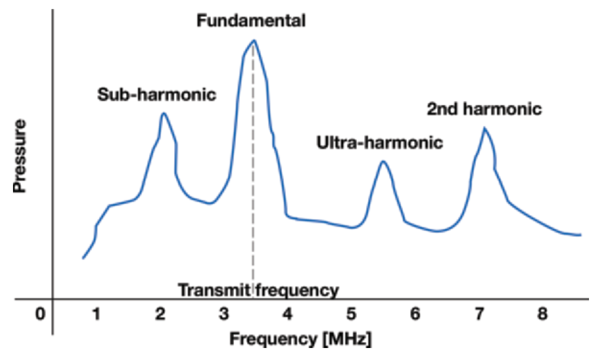


Figure 5. Graph shows fundamental, second harmonic, subharmonic, and ultraharmonic frequencies. The vertical dashed line shows the transmit frequency.

Tissue Harmonic Imaging

The majority of clinical US systems use second harmonic (ie, 2*f*) echoes for THI image formation, with limited use of higher-frequency harmonics. The reasons for this include bandwidth limitations of current transducers, which curtail higher-frequency detection, and the fact that the energy of returning echoes at higher harmonic frequencies is less than the energy of echoes returning at the second harmonic frequency (5). Therefore, for harmonic waves at frequencies greater than 2*f*, tissue attenuation removes the amount of signal available to form an image (9,14).

Fundamental Wave–Elimination Techniques

The fundamental and the second harmonic frequencies are received together in the time domain as a combined distorted wave. High-quality THI primarily depends on achievement of complete elimination of the echoes at the fundamental frequency. Various techniques are used to remove the fundamental wave in THI, including bandwidth receive filtering, pulse inversion, side-by-side phase cancellation, and pulse-coded harmonics.

Bandwidth Receive Filtering.—Bandwidth receive filtering is a signal processing technique in which lower frequencies that are more likely to have emerged from the fundamental beam are filtered out, and higher-frequency harmonic echoes are used to generate the image. In this technique, noise diminishes and enhancement is improved (3,5). However, narrowing the received bandwidth reduces axial resolution because axial resolution can be estimated as the speed of sound in the tissue divided by two times the bandwidth (1,15,16). Selection of an appropriate cutoff frequency is a compromise between harmonic frequency signal loss and contamination by the fundamental frequency

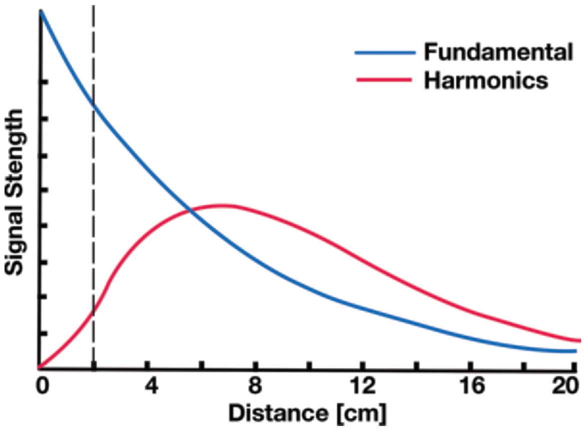


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Figure 6. Graph shows the schematic relationship between fundamental and harmonic frequency wave amplitudes as a function of depth. (Dashed line = sum of skin and subcutaneous thicknesses.)

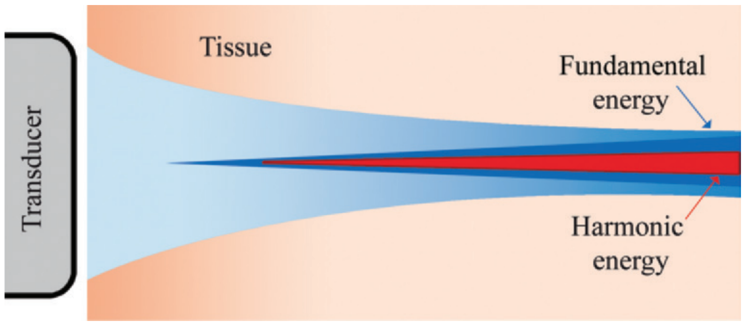


Figure 7. Diagram shows the harmonic energy profile. Higher-amplitude US pulses produce more harmonic waves. Therefore, harmonic waves are predominantly created in the central, most intense portion of the beam, which causes a narrower imaging plane and reduced artifacts because of side lobes and grating lobes. Note the increase in harmonic wave energy with increasing depth. (Courtesy of Jeff Powers, PhD.)

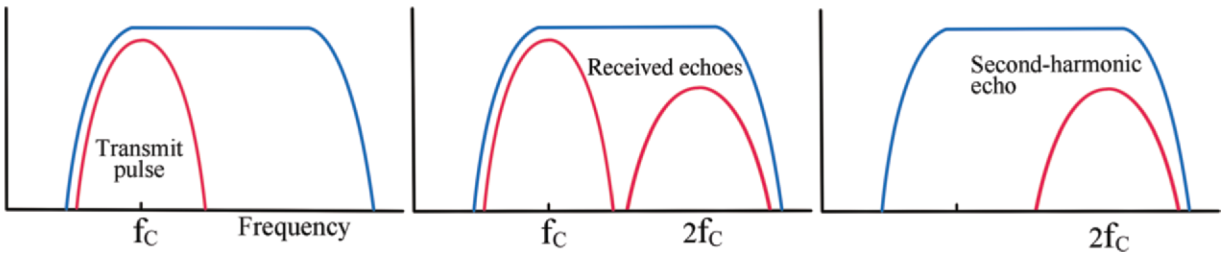


Figure 8. Diagram shows the filtration technique for fundamental frequency removal. Fundamental pulses (left) are emitted by the transducer, which receives both fundamental and second harmonic frequencies (middle), and the fundamental frequency is selectively filtered out and the second harmonic frequency waves are used for image generation (right). Red lines = pulses and echoes, blue lines = transducer bandwidth, f_c = fundamental frequency, $2f_c$ = second harmonic frequency.

signal (13) (Fig 8). To overcome this limitation, pulse-inversion methods were developed.

Pulse Inversion.—Pulse inversion is a technique in which two pulses with a 180° phase difference (ie, opposite phase) are emitted sequentially into the tissue along the same line. The summation of these received pulses results in fundamental echoes canceled out with odd harmonic frequency components, and the retention of harmonic waves at even frequency multiples of the fundamental frequency, with a doubling of the amplitude of even frequency multiple harmonic waves (3,17) (Fig 9). This technique is also termed a *phase cancellation* or a *temporal cancellation* technique. The principal advantage of this technique is that axial resolution is not degraded and tissue contrast is better preserved. However, the insonated tissue must remain stable for the duration of the two opposed-phase pulses for pulse summation to result in phase cancellation only. Consequently, pulse-inversion harmonic imaging is highly dependent on a fixed tissue frame, and tissue motion can markedly degrade the US image (3,18,19). In addition, some reduction in frame rate will occur.

Side-by-Side Phase Cancellation.—Side-by-side phase cancellation is similar to pulse inversion, but two pulses with opposite phase are transmitted along adjacent lines of sight. These adjacent lines are then added to cancel fundamental echoes and odd harmonics. This technique is a spatial cancellation technique. As with pulse inversion, side-by-side cancellation preserves harmonic frequency bandwidth (20).

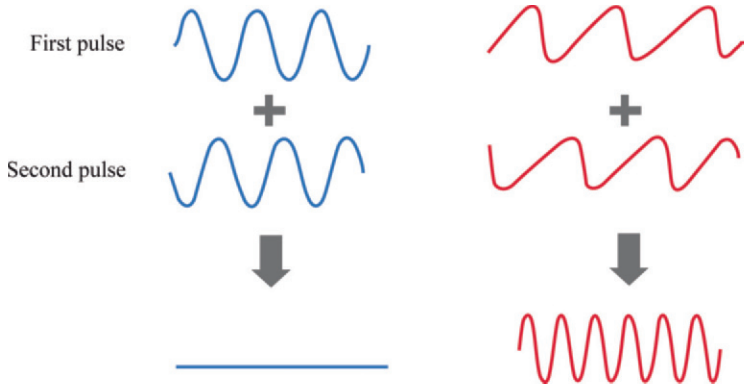


Figure 9. Pulse-inversion technique for fundamental frequency removal. The first pulse (top) is transmitted, and the received echoes are stored. A second pulse with an inverted phase (ie, 180° phase shifted) (middle) with respect to the first is transmitted along the same beam. The echoes from the second pulse are added to those from the first pulse, with a resulting summed waveform (bottom). Low-amplitude echo signals (left) cancel out, whereas distorted high-amplitude signals (right) are retained.

Table 2: US Artifacts Glossary

Artifact Type	Definition
Side lobes and grating lobes	Multiple beams of low-amplitude US energy that project radially from the main beam axis, which may create echoes detectable by the transducer
Reverberation	Echoes repeatedly reflected between two highly reflective interfaces; the display shows multiple equally spaced signals that extend into the deep field
Comet tail	A form of reverberation where the two reflective interfaces are closely spaced; sequential echoes may be so close together that individual signals are not perceivable

Pulse-coded Harmonics.—The pulse-encoding technique transmits relatively complex pulse sequences into the body with a unique and recognizable code imprinted on each pulse. The unique code is then recognized in the echoes (21). Because the fundamental echoes have a specific code, they can be identified and canceled. The remaining harmonic echo is then processed to form the image.

This technique is especially useful in the near field because longer encoded pulses produce harmonics more efficiently in the near field than do conventional THI pulses.

The code can be binary or frequency modulation chirp encoding. Binary encoding uses a sequence of wavelengths transmitted as binary numbers. In frequency modulation chirp encoding, the frequency of the emitted pulse is increased at a known rate during pulse generation. A combination of chirp encoding and pulse inversion improves signal-to-noise ratio (22).

Advantages of THI

Images produced with THI are often superior to conventional gray-scale images of cysts and abnormalities that contain fat, calcium, or air (23). Clinically, several advantages are evident: *(a)* improved contrast resolution: increased signal-to-noise ratio results in better tissue contrast enhancement, which improves the conspicuousness of subtle parenchymal abnormalities; *(b)* improved lateral resolution and reduced section thickness: as noted in this article, harmonic waves are predominantly generated at the center of the US beam, which narrows the imaging plane and improves lateral resolution (16,18,23); *(c)* beneficial effects on artifacts: THI reduces some artifacts (Table 2), including reverberation artifact, side lobe artifact, and grating lobe artifact, which have their origins in weaker beams, produced on either side of the main lobe of the transmitted beam (5,23–26), and enhances other artifacts such as acoustic enhancement deep to fluid (useful for depicting cysts), acoustic shadowing, and comet-tail artifacts (3); *(d)* reduced noise in the near field: harmonic waves are not produced in the superficial part of tissue, which reduces noise in the near field; and *(e)* improved imaging of deeper tissue: preferential generation of harmonic waves in deeper tissue can improve image quality in obese patients as long as tissue attenuation effects do not dominate (3,23,25,27–29).

Disadvantages of THI

Axial resolution is decreased by THI because of the narrowed bandwidth (29). Fundamental frequency imaging may be clinically more efficacious than harmonic imaging in other situations, such as diffuse fatty liver, because of compromise of axial resolution from filtration-related bandwidth reduction, and higher attenuation of the higher frequency harmonic component. As noted in this article, the pulse inversion method is more sensitive to motion than fundamental frequency imaging and also has lower temporal

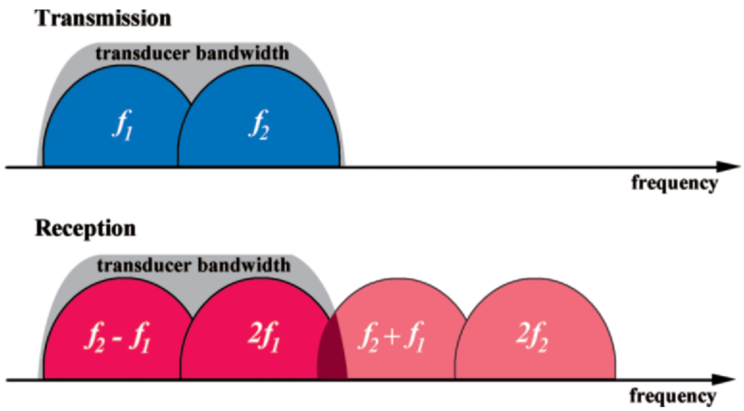


Figure 10. Diagram shows transmission and reception of DTHI. Two frequencies are contained within each pulse. The returning echoes contain frequencies at the sum and difference of the emitted frequencies as well as their harmonics. The two lower-frequency components of the echo are used for image generation.

resolution because of image formation that requires two pulses per line.

THI Safety

Both the thermal and mechanical indexes remain the same for THI as for conventional B-mode US, and therefore THI is considered safe for routine clinical use (30).

Differential Tissue Harmonic Imaging

THI uses only half of the available transducer bandwidth for image formation: The lower half is used for transmission and the upper half is used during reception. DTHI, also known as multitone nonlinear THI, uses the entire transducer bandwidth, which combines the advantages of conventional gray-scale US with those of THI. This is particularly useful at greater depths (>8 cm) (4,9,31). In addition to broadband transducers, fast signal processing is essential for DTHI (9).

In DTHI, two pulses are transmitted simultaneously at different frequencies, referred to as f_1 and f_2. In addition to their second harmonic frequencies ($2f_1$ and $2f_2$), among others, the sum and the difference of the transmitted frequencies ($f_2 + f_1$ and $f_2 - f_1$, respectively) are generated within the tissue. The second harmonic signal of the lower frequency ($2f_1$), and the difference frequency ($f_2 - f_1$), are detected by the transducer; other generated frequency components do not fall within the bandwidth of the transducer. Both fundamental frequencies are cancelled by the subtraction technique (a technique similar to pulse inversion) and are therefore not detected in the signal. By receiving the second harmonic $2f_1$ and the difference of the frequencies ($f_2 - f_1$), the effective bandwidth of the tissue harmonic signals is expanded to between $f_2 - f_1$ and $2f_1$ (32) (Fig 10). By using DTHI, higher resolution, better penetration, and fewer artifacts can be achieved.

Comparison of DTHI with THI

DTHI and THI are substantially better than fundamental US imaging for noise reduction, detail resolution, image quality, focal abnormality margin sharpness, and penetration for hepatic imaging (31). DTHI also performed better than THI regarding detail resolution, image quality, and contrast-to-noise ratio in evaluation of focal hepatic abnormalities (31,33) (Fig 11).

Clinical Applications of THI and DTHI

THI and DTHI are advantageous in the following common clinical settings: breast and axillary lymph node, thyroid, hepatobiliary and pancreatic, genitourinary, and pediatric.

Breast and Axillary Lymph Node

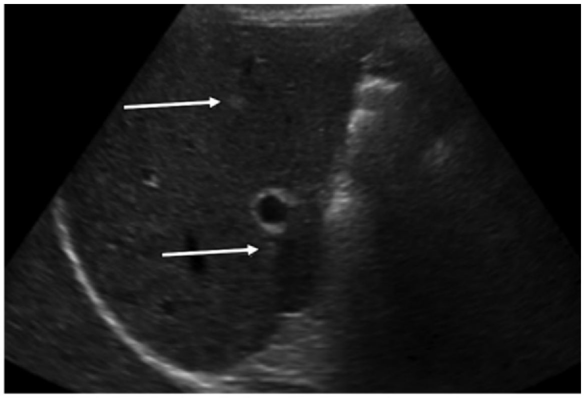
THI has been shown to improve detection and characterization of focal breast abnormalities, especially in fatty breasts, but it has limited value for needle visualization in interventional breast US (4,34,35). It has better diagnostic accuracy in axillary lymph node lesions than does gray-scale US, due to improved contrast and resolution (36).

Thyroid

THI improves the image quality of thyroid US. A limitation that has been reported is increased shadowing from the overlying sternocleidomastoid muscle in transverse imaging planes, but this is easily overcome by moving the transducer (37,38).

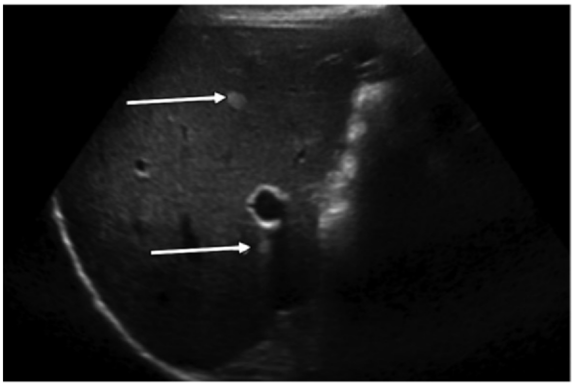
Hepatobiliary and Pancreas

THI and DTHI can improve image quality in hepatobiliary US (Fig 12) through a variety of mechanisms: *(a)* reduced reverberation and side lobe artifacts from the body wall, especially in



a.

Figure 11. Images of two small hepatic focal abnormalities (arrows), thought to be hemangiomas, obtained by using fundamental imaging **(a)**, THI **(b)**, and DTHI **(c)**. Note the superior definition of the liver parenchyma and focal liver abnormalities in **b** and **c** in comparison with **a**.



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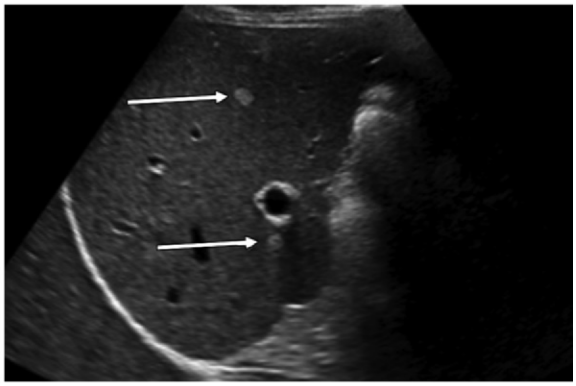

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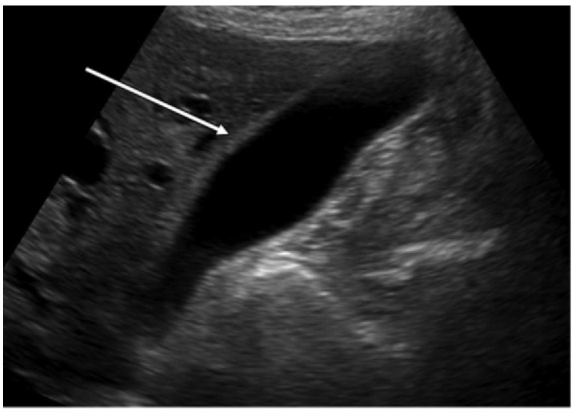

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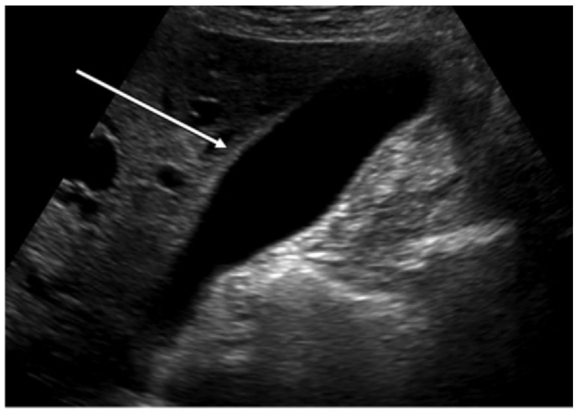
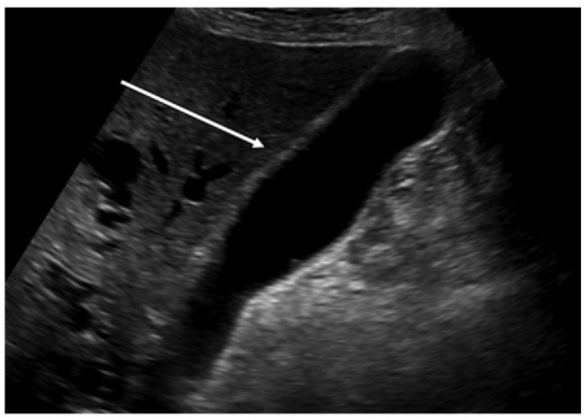


b.

Figure 12. Images of the gallbladder obtained by using fundamental imaging **(a)**, pulse-subtraction imaging **(b)**, and DTHI **(c)**. Note the marked reduction in reverberation artifact from the anterior gallbladder wall in **b** and **c**. The scan in **c** demonstrates improved delineation of the gallbladder neck (arrow).



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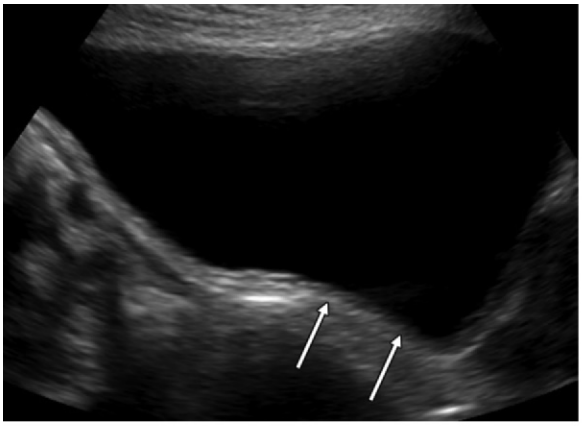

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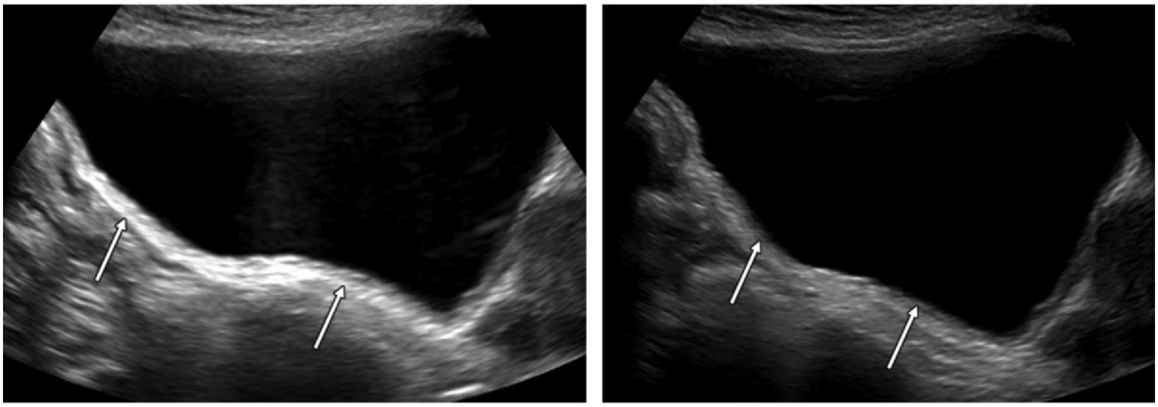

b. c.

Figure 13. Fundamental **(a)**, pulse subtraction **(b)**, and DTHI **(c)** images of the bladder. Note the reduced reverberation artifact, especially in **c**, and improved delineation of the layers of the posterior bladder wall (arrows).

obese patients and with narrow intercostal acoustic windows, which can improve visualization of small anatomic structures such as peripheral portal veins and smaller biliary branches; *(b)* improved visualization of focal abnormalities because of reduced artifacts and improved contrast between abnormalities and tissue; *(c)* improved characterization of focal abnormalities that contain fluid, which include cysts and fluid collections, because of a reduction in reverberation artifact, which is particularly useful to distinguish hypoechoic solid abnormalities, such as lymphomatous lymph nodes, from cysts; *(d)* increased conspicuity of posterior acoustic shadowing from gallstones, especially in obese patients; and *(e)* improved conspicuity of the comet-tail artifact that is diagnostic of adenomyomatosis of the gallbladder (23,39–41). THI techniques improve detection of pancreatic focal abnormalities, especially of abnormalities smaller than 1 cm, and improve fluid-solid differentiation (13).

Genitourinary

THI and DTHI are useful in renal imaging (Fig 13). Clinically, substantial improvements include improved capability to distinguish between cysts and solid renal focal abnormalities, improved detection of shadowing from urinary calculi, improved renal cell carcinoma and renal parenchymal tissue contrast enhancement (23), and improved transrectal delineation with US of the prostatic urethra and rectal wall (42–44). Transabdominal THI has been shown to have better image quality than transabdominal gray-scale US for ovarian follicle detection in patients with a high body mass index (45).

Pediatric

Harmonic imaging may be helpful for newborns and toddlers, but because of their smaller size, fundamental frequency imaging with higher-frequency transducers may be more clinically efficacious (13,46–49).

Conclusion

THI and DTHI are technologies that improve US image quality. An understanding of the essential concepts and techniques discussed in this article can help radiologists select US technologies suitable for specific clinical problems.

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