Tissue harmonic imaging for standard left ventricular measurements: Fundamentally flawed?

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Abstract
Tissue harmonic imaging (THI) is a B mode imaging technique that improves echocardiographic image quality by reducing superficial artefact. The modality increases image signal-to-noise ratio at the expense of reduced axial resolution.

While the qualitative improvements of harmonic echocardiographic imaging are widely accepted, the degree to which this is translated into improved quantitative measurements and whether THI-derived measurements result in systematic bias continue to be areas of uncertainty. This review examines differences between THI and fundamental imaging-derived measurements from a theoretical, tissue phantom and clinical perspective.

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Introduction

Tissue harmonic imaging (THI) has been in clinical use for over half a decade following its serendipitous discovery in the course of bubble contrast research. It has produced a substantial improvement in two dimensional and M mode image quality such that fundamental frequency scanning is now rarely used. Despite the widespread adoption of THI technology for routine echocardiography on qualitative grounds, its validity for the derivation of LV dimensions remains an area of uncertainty.

This review sets out to briefly revisit the physics underpinning THI and then to summarise the principle validation studies that followed its introduction. From this vantage point issues regarding the quantitative accuracy of THI will be examined.
The theory of THI

Physics

Ultrasound is a mechanical energy propagated through tissue (or other elastic media) as longitudinal waves with alternating zones of compression and rarefaction. This disturbance can be displayed graphically as pressure versus time. A pure (fundamental) frequency of vibration traces a sine wave on the pressure time graph. Harmonics are additional vibrations that distort the fundamental sine wave pattern. They are disturbances of lower amplitude but higher frequency than the original vibration and when isolated, have frequencies of exact multiples of the fundamental frequency, such that the first harmonic has twice the frequency and the second harmonic three times the frequency of the original.

THI utilises the phenomenon of propagation harmonics. These occur when a high amplitude ultrasound disturbance passes through an elastic medium. It travels faster during the higher density compression phase than the lower density rarefaction phase (Fig. 1). This causes harmonic distortions in the, originally pure, fundamental frequency. This is a cumulative process, which produces a progressively stronger harmonic component with distance travelled. Attenuation of the harmonic component is, however, greater due to its higher frequency, resulting in the highest harmonic signal at a set distance from the transducer rather than at the greatest depth (Fig. 2).

THI makes use of the second harmonic (twice the fundamental frequency) to minimise artefactual echoes. These cause indistinct tissue—tissue and tissue—blood interfaces and are the main reason for uninterpretable or ‘technically difficult’ studies. Echo artefacts have two features in common: (a) they are generally low in amplitude, (b) they predominantly occur in the superficial tissue layers (reverberation between ribs and transducer and scattering within large fat layers are particularly rich sources of artefact).

THI should be particularly suited to the reduction of this form of artefact for two principle reasons:

1. **Depth dependence**: unlike the fundamental, the harmonic component of the ultrasound beam becomes progressively stronger with depth of tissue penetration. In practical terms harmonics only begin to be produced after the ultrasound pulse has passed through the superficial tissue layers. Hence they should not be subject to the artefacts that arise within these layers (Fig. 2).

2. **Non-linearity between fundamental amplitude and harmonic production**: harmonic amplitude is proportional to the fundamental amplitude squared. Stated another way, halving the fundamental amplitude will reduce the harmonic amplitude fourfold. Hence low amplitude components of the fundamental ultrasound beam should develop little harmonic component and produce essentially no harmonic containing echoes (Fig. 3).

Instrumentation principles

THI places great demands on the transducer. It must be able to transmit low frequency, narrow band, (i.e. little frequency spread) but high amplitude ultrasound pulses and receive high frequency, low amplitude echoes (i.e. broadband with high dynamic range). Any overlap between the fundamental and harmonic frequencies either during the transmit (harmonic leakage) or receive (inadequate filtering) phases will degrade the image.

Given these demands compromises are inevitable. Firstly a low frequency transmit pulse must be used as detailed above. This will increase the spatial pulse length (SPL). Furthermore, to create a narrow band transmit pulse with little 2nd
harmonic component the transducer must have less dampening or be driven for longer. Both strategies entail an increase in the number of cycles per pulse which increases the SPL.

\[ \text{SPL} = \text{wavelength} \times \text{cycle number} \]

SPL is the main determinant of axial resolution. A longer SPL produces longer echoes at each acoustic interface resulting in degraded axial resolution. Reducing the cycle number will shorten the SPL but this occurs at the expense of higher ‘harmonic leakage’ (fundamental frequencies overlapping harmonic frequencies), with a consequent reduction in the signal-to-noise ratio (SNR) and image quality. Hence a trade off exists between axial resolution and SNR with this set at different levels depending on the imaging platform.

Secondly, because the amplitude of the second harmonic is closer to the electrical noise of the system the lower amplitude echoes are lost. These contribute to the fine echo texture of the tissue, resulting in reduced dynamic range of the image.

**Summary – theoretical considerations of THI**

**Benefits:** THI should reduce spurious echoes resulting in a cleaner echo signal and an increased SNR. This effect should be most pronounced in the most degraded images with little effect on good images. THI should also produce a small improvement in lateral resolution.

**Costs:** THI should reduce axial resolution and the dynamic range of the image.

**Laboratory testing**

Extensive phantom testing has objectively measured the attributes of THI to determine if the theoretical differences between THI and FI are borne out in reality.

**Signal-to-noise ratio**

SNR is measured by determining the difference in pixel brightness and brightness variation between anechoic ‘cysts’ and the phantom ‘tissue’ itself. The greater the difference in these values between the phantom cysts and tissue, the higher the SNR and clearer the image.

As predicted by theory there is no difference in SNR between the 2 imaging modalities because phantoms do not produce spurious echoes, so no advantage is gained using THI. A different picture emerges when a fat layer is simulated by interposing a layer of ethanol between the phantom and the transducer. This has no effect on THI SNR but reduces FI SNR by up to 50%.

**Spatial resolution**

Spatial resolution is a general term which covers both axial (along the ultrasound image line) resolution, which depends on SPL, and lateral (perpendicular to the image line) resolution, which depends on beam width. Results vary between imaging platforms but follow a common trend when switching between FI and THI. Lateral resolution improves by 20–50% whereas axial resolution is reduced by 40–100% during THI imaging. A trade off exists between axial and lateral resolutions when using harmonic mode such that additional improvements in lateral resolution are accompanied by losses in axial and vice versa. If both resolution components are considered together THI is associated with a slight net loss of spatial resolution.
'Real world' experience

Phantom testing has validated the theory behind THI and quantitated the difference in imaging parameters between THI and FI objectively, under ideal conditions. Much work has also been performed to determine the degree to which the advantages and disadvantages of THI apply in the clinical setting and in the areas of echocardiography most likely to be affected by THI.

**Endocardial visualisation**

THI effects on endocardial visualisation have been assessed both quantitatively by computer analysis of endocardial grey scale (relative to the entire scan plane) and qualitatively by subjective scoring of endocardial visualisation in an unselected patient group referred for assessment of systolic function.

The main findings comparing THI to FI were:

- 90% increase in relative grey scale
- 2 point increase (out of 8) in visual endocardial scoring
- 30% increase in studies suitable for biplanar ejection fraction (EF) calculation
- 40% reduction in inter-observer error for EF calculation

THI significantly increased readable studies and increased the confidence in EF calculations.

**Mitral valve**

Mitral valve thickness, viewed from the 4 chamber plane, has been reported to be 45% thicker when imaged using THI. The practical implications of this were studied in a group of moderate severity, rheumatic mitral stenosis patients referred for echocardiographic assessment prior to intervention. Each patient underwent THI and FI.

THI increased the average score of the group by one point (out of a total 16). If used alone, THI scoring would result in between 30 and 50% more patients being assessed as unsuitable for percutaneous intervention. This is due to THI overscoring primarily affecting those with milder degrees of mitral valve restriction. The other interesting observation was that, of the 4 scored components, only the subvalvar thickening contributed to the higher score. The leaflet thickening and valve calcification scores were identical. Planimetered valve areas were also unaffected by THI and significantly more patients had images suitable for planimetry with THI than FI.

Overall THI seems analogous to transoesophageal rheumatic mitral valve assessment, as it produces better images and hence cannot be confidently used with a scoring system developed utilising the poorer quality FI images.

**Left ventricular measurements**

The most requested indication for echocardiography is the assessment of left ventricular size and systolic function. Determination of wall thickness is also commonly required. The magnitude of these values forms the basis of many cardiac management decisions.

Most echo reports provide quantitative evaluation of these parameters, which continue to be derived from the M mode examination. The normal range and prognostic implications of these values were established with FI using the leading edge (LE) to leading edge measurement technique. The leading edge protocol is the American Society of Echocardiography (ASE) standard and was devised to minimise differences in axial resolution between sonographic platforms. The LE technique is necessary because a component of M mode echo thickness is determined by the axial resolution of the ultrasound pulse in addition to the true thickness of the insonated structure. A system with poor axial resolution will cast a longer trailing edge echo (Fig. 4).

The leading edge will always be positioned correctly irrespective of the axial resolution. This is because the leading edge placement depends on the unchangeable physics of sound velocity within tissue. A good analogy is the sound of thunder from two lightning bolts striking exactly the same distance from an observer. The time taken for the observer to first hear the thunder will be identical even if one thunderclap lasts for longer than the other. Hence the seconds between the flash and when the sound begins, not when it ends, is the method to calculate distance from lightning strikes. Even though THI degrades axial resolution, it does not change the physical principles governing ultrasound propagation. THI measurements taken using the LE/LE protocol will be the same as FI measurements.

Two dimensional measurements (as opposed to M mode) present additional difficulties regarding correction for differences in resolution as they involve images with elements of both axial and lateral resolutions. To ensure that accurate dimensions are recorded in a standardised fashion an outside-to-inside technique should be employed.
This involves tracing the leading edges of the myocardium perpendicular to the scan plane and tracing the inner border of the myocardium parallel to the scan plane (Fig. 5). Lateral resolution should be maximised by optimising focal depth.

**2D**

*Parasternal measurements*: 2 dimensional measurement of the LV in parasternal short axis view using the leading edge to trailing edge method to derive interventricular septum, left ventricular internal diameter and posterior wall dimensions has been conducted in vitro and in vivo (normal population). The ventricular wall measurements were significantly overestimated using THI (by an average of 2.5 mm or 20%) resulting in an underestimation of the LV cavity size (by a mean of 4.7 mm or 15%).\(^9\) M mode derived EF was not different between the methods indicating that the degree of LV cavity underestimation applied equally in systole. Significantly more subjects would have received a diagnosis of LVH with THI. These findings are not unexpected because measurements were taken using the trailing edge technique. What the data really demonstrate is the critical importance of using the LE to LE standard of measurement when imaging in harmonic mode.

*Apical measurements*: biplanar border tracing for LV volumes and EF, using both manual and automated techniques, has been studied for the 2 imaging modalities.\(^{10,11}\) Contrast ventriculography and scintigraphic methods were used as gold standards for EF. For both types of border tracing there was a tendency for THI to result in (non-significantly) smaller LV volumes in comparison to FI. In terms of EF, THI-derived values did not differ from FI. THI measurements demonstrated less test/retest and inter-observer variability and were more strongly correlated with the angiographic and scintigraphic standards.

When endocardial border tracing is performed, THI is more likely to display the true endocardium resulting in smaller but more reproducible LV volumes than FI. Echocardiographic derived volumes are usually underestimated in comparison to

**Figure 4** Graphical representation of measurement error incurred using the trailing edge (TE) to leading (LE) edge technique and how this is magnified when the axial resolution is reduced.

**Figure 5** An example of outside-to-inside tracing in the parasternal short axis plane. This technique minimises measurement error in 2D images.
angiographic/scintigraphic imaging because the endocardium is defined by the outer edge of the intraventricular trabeculations with echo rather than the inner edge as it is with the other techniques. Hence the reason that THI underestimates 2D apical volumes compared to FI is because it more accurately visualises the endocardial border (as shown previously).⁶

**M mode**

Conflicting results have emerged from the three studies that have addressed the accuracy of THI-derived M mode measurements, in the clinical environment.

Graham et al.¹² directly compared measurements of wall thickness, LV internal diameters, aortic root and left atrial dimensions taken from identical imaging planes in both FI and THI modes. Scans were performed prospectively in 58 unselected patients (mean age 58, 50% male) and were analysed by two observers, blinded to patient identity, in random order. A LE to LE technique was used.

No significant difference was found between the cardiac measurements derived from the two imaging modalities with the magnitude of measurement discrepancies no different from those caused by intra-observer error. When plotted, measurement differences clustered uniformly around a mean of zero, indicating the absence of THI-associated systematic bias.

The next two studies compared M mode measurements taken from THI and FI images in the context of LV mass calculation.

Mansencal et al.¹³ prospectively evaluated 46, predominantly hypertensive, patients (mean age 53, 60% male). LE to LE diastolic measurements were made of the septum, posterior wall and left ventricular internal diameter with a LE to LE technique by two observers. They reported that THI produced a significant but trivial overestimation of both septal thickness (by 0.7 mm or 8%) and posterior wall thickness (by 0.5 mm or 7%). They found no difference in internal LV dimensions between the imaging modalities. Inter-observer variation was significantly reduced when readings were made from the THI images.

McGavigan et al.¹⁴ used an identical study methodology as Mansencal but acquired the images using different ultrasound equipment. In his study, data from 30 patients were analysed (mean age 52, 70% male). In contrast to Mansencal they found that harmonic imaging produced a substantial difference in measurements. THI overestimated septal thickness by 2.1 mm or 19% and posterior wall thickness by 1.7 mm or 18%. In addition LV internal diameter by THI was underestimated by 1.7 mm or 3%.

In summary, two studies have shown trivial or no discrepancy in M mode measurements taken from THI or FI images including one that was specifically designed to address this question. The third found that THI significantly and substantially overestimated LV wall thickness. The authors of the third study concluded that THI caused echoes from paraseptal structures and the pericardium to coalesce with the septal and posterior walls, respectively, resulting in artefactual exaggeration of wall thickness. Why this should have occurred in the third and not in the first two studies is not entirely clear but is probably the result of differences in axial resolution which are known to be exist between the various, commercially available ultrasound machines.¹⁵

**LV mass**

LV mass has traditionally been calculated from M mode measurements. This involves cubing M mode dimensions which magnifies measurement differences. This magnification effect was observed in both the above studies. Mansencal found that THI dimensions resulted in LV mass calculations that were 10% greater than those derived from FI images. McGavigan reported a 25% greater mass with THI. These findings are now largely obsolete given the widespread use of alternative, substantially more accurate, methods of LV mass calculation.

No studies have been performed to compare 2D or 3D techniques of LV mass calculation using THI or FI.

**Summary**

In the clinical setting THI produces the same results as FI for:

- M mode and biplane derived EF
- MV area (by planimetry)
- Aortic root and left atrial dimensions

THI is better than FI for:

- Endocardial visualisation (produces more studies suitable for EF calculation)
- Mitral valve visualisation (produces more studies suitable for MV planimetry)
- EF reproducibility
Areas of disagreement between the modalities:

- Subvalvar MV apparatus thickening for MV scoring in rheumatic heart disease.
- Possibly M mode measurement of septal and posterior wall thicknesses.
- Possibly M mode measurements of LV mass.

Overall the majority of clinical studies elegantly show that variations between the THI and FI results are consistently predicted by the theoretical principles of ultrasound. As long as THI is understood to have poorer axial resolution and the appropriate ASE measurement protocols are followed, previously established normal ranges (with the possible exception of rheumatic mitral valve scoring) will apply to harmonic images. The only caveat to the above may occur when THI causes substantial degradation to axial resolution resulting in the inability to distinguish tissue planes. This is becoming less of a problem with the ongoing development of broadband imaging probes which continue to reduce the spatial pulse length (and hence improve axial resolution) during harmonic imaging.

Notwithstanding the disagreements in M mode results, THI has been a major leap forward in ultrasound imaging technology. Few patients now have uninterpretable studies and consistency in results has improved dramatically. To maintain accuracy of echo derived LV dimensions, in this era of THI, the physics of ultrasound and the importance of leading edge measurements should not be overlooked.

References