Effect of harmonic imaging on the measurement of ultrasonic integrated backscatter and its interpretation in patients following myocardial infarction

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Abstract Background Recently, we have demonstrated that cyclic variation in ultrasonic integrated backscatter (IBS) can be used to predict patency of the infarct related artery (IRA) post-acute myocardial infarction (AMI). Second harmonic imaging has become widely available on ultrasound machines and enhances endocardial definition. The effect of harmonic imaging on the measurement and interpretation of cyclic IBS is unknown.

Methods and results Twenty-eight patients were studied post-AMI. Cyclic IBS was measured in myocardial segments supplied by the IRA as well as in remote segments with normal myocardial function in both fundamental and second harmonic modes. Harmonic imaging increased the measurement of cyclic IBS in IRA as well as normal myocardial territories. However, the difference in cyclic IBS between IRA and normal myocardial territories remained unchanged.

Conclusion Second harmonic imaging increases the measurement of cyclic IBS. However, the interpretation of these data is unchanged in the setting of AMI. It is important that repeated studies in the same patient are performed in the same mode (fundamental or harmonic) as the values are not interchangeable.

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KEYWORDS
Harmonic imaging; Integrated backscatter; Myocardial infarction.

Introduction

Ultrasonic integrated backscatter (IBS) represents the total reflected ultrasound energy from a selected region of the myocardium. In normal myocardium, IBS is known to vary in a cyclical fashion throughout the cardiac cycle, generally rising to a peak at end diastole and falling to a
nadir at end systole, though this does vary with fibre orientation relative to the ultrasound transducer.1–5 Furthermore, myocardial fibre orientation and depth of field significantly affect the magnitude of the IBS.1,2,6,7 Following acute myocardial infarction (AMI) the cyclic variation in IBS is blunted in the myocardial territory supplied by the infarct related artery (IRA).8–11 Cyclic IBS can be measured in myocardial territories supplied by the IRA and in remote myocardial territories with normal function. Changes in the level of cyclic IBS within the IRA territory, as well as differences in the level of cyclic IBS between IRA and normal myocardial territories, may help determine the success of thrombolytic therapy following AMI and may predict restoration of microvascular perfusion and subsequent recovery of left ventricular function.8,9,12,13

New ultrasound technology has become available which has been shown to improve endocardial definition (second harmonic imaging).14–19,27 This was a coincidental finding, since second harmonic imaging was developed to enhance the detection of contrast microspheres. In this imaging mode, the tissue signal should be minimal, but the difference between the tissue and contrast signal should be optimised.20–22 Although this is the case, harmonics can be generated within the tissue, which also enhance the tissue image, even in the absence of contrast.

It has been proposed that harmonic imaging improves endocardial definition by reducing image clutter through suppression of beam sidelobes and rib reverberation artifacts.23,24 Now, this technique is used routinely in transthoracic imaging, especially when image quality is sub-optimal in fundamental mode. However, there is little information on its effect on myocardial texture, appearance or definition.15,18,24 Little work has been done describing the use of harmonic imaging with IBS. Pislaru et al. calculated the cyclic variation in IBS in fundamental and second harmonic modes in five closed chest dogs and nine healthy volunteers.25 This found no significant difference in IBS in fundamental and second harmonic modes. However, it is unknown whether IBS measurements and analysis can be legitimately made from second harmonic images, in patients with cardiac pathology.

In the present study we have measured cyclic IBS in patients who have had an AMI in both fundamental and second harmonic imaging modes in order to determine the effect of harmonic imaging on this parameter in normal and abnormal myocardial segments. In addition, we expect to gain information on whether harmonic imaging affects the interpretation of IBS data in this setting.

Methods

An unselected group of 28 patients (23 male; mean age, 61.6 years) admitted with AMI were admitted into the study. All patients were treated with thrombolysis or primary angioplasty. Patients who were thrombolysed subsequently had coronary angiography so that the coronary anatomy and, in particular, information on the patency of the IRA was known for all patients. The study had local ethical approval.

Data acquisition

Cyclic IBS was measured in the territory of the IRA as well as in a remote territory with a normal blood supply and normal function in both fundamental and second harmonic modes. All four, standard, echocardiographic views (parasternal long axis [PLAX], parasternal short axis [PSAX], apical four chamber [AP4C] and apical two chamber [AP2C]) were imaged using a Philips (Andover, MA) Sonos 5500 ultrasound system. Acoustic densitometry (AD) with IBS software was available on the system. With the ultrasound machine operating in the AD acquisition mode, real time IBS images were acquired for 60 consecutive frames at a rate of 30 frames per second (two to three cardiac cycles), displayed, stored to magneto-optical disc and subsequently analysed. System settings were optimised in fundamental mode by adjusting the depth, total gain and time gain compensators (TGCs) so that all segments of myocardium were clearly visualised. These settings were kept constant throughout the study so that any difference in cyclic IBS measured within an individual region of interest (ROI) should be due to differences between the two imaging modes. Fundamental imaging was performed using an S4 transducer (2–4 MHz). Harmonic imaging was performed transmitting at 1.8 MHz and receiving at 3.6 MHz. In total, 56 studies were performed in both imaging modes.

Data analysis

IBS data were analysed off line for each myocardial region for each subject in each view using the AD analysis package available on the SONOS 5500 imaging system. An elliptical ROI of 31×31 or 41×41 pixels was placed in the mid-myocardial region in each segment, positioned to avoid endocardium and epicardium, and tracked manually on a frame by frame basis for the entire loop of 60 frames. For each segment the analysis package provides a mean IBS value in decibels (dB) for the
entire loop as well as a mean value for each frame. This allows assessment of the magnitude of the cyclic variation, which we have taken as the difference between the average peak and average nadir values of IBS.\textsuperscript{1,8} When using the parasternal views for analysis, ROIs were placed in the anterior septum and posterior, or inferior, wall as perpendicular as possible to the ultrasound beam and directly opposite each other whenever possible, to reduce the effect of anisotropy. In the apical views ROIs were positioned in the mid-septum and mid-lateral wall for the AP4C view, and in the mid-inferior wall and mid-anterior wall for the AP2C view. In all cases one ROI represented the IRA territory and the other the normal myocardial territory.

The number of segments visible in each echocardiographic view for both the imaging modes was assessed. This was done using the standard 16-segment model as defined by the American Society of Echocardiography.\textsuperscript{26} Because several segments appear in more than one view, a total of 22 visible segments is possible.

Statistics

Difference in mean values between fundamental and harmonic imaging and between infarcted and normal myocardial segments in each imaging mode were analysed using a paired Student’s t test. Inter-observer reliability was compared using an analysis of variance.

Results

Among the 28 patients studied, coronary angiography showed that the IRA was occluded in 18 patients and patent in 10. In 16 patients the IRA was the left anterior descending coronary artery (LAD), the right coronary artery (RCA) in 10 and the left circumflex (Cx) in two.

In fundamental mode cyclic IBS measurements in the PLAX view were 4.0 ± 1.2 dB in the myocardial territory supplied by the IRA and 5.3 ± 1.5 dB in harmonic mode ($P < 0.0001$). In a normal myocardial segment these measurements were 5.3 ± 1.5 and 6.4 ± 1.6 dB for fundamental and harmonic modes, respectively ($P < 0.0002$) (Fig. 1 and Table 1). The mean difference between cyclic IBS in an IRA segment and a normal segment was 1.3 ± 1.9 dB in fundamental mode and 1.2 ± 2.1 dB in harmonic mode (NS) (Fig. 2 and Table 2). In the PSAX view, cyclic IBS was 3.9 ± 1.2 dB and 4.7 ± 1.5 dB in the IRA territory in fundamental and harmonic modes, respectively ($P < 0.006$) and 5.1 ± 1.5 vs 5.9 ± 1.7 dB in normal segments ($P < 0.002$) (Fig. 3 and Table 1). Once more, the mean difference between cyclic IBS in normal and IRA segments was similar in both imaging modes, being 1.1 ± 2 dB in fundamental mode and 1.3 ± 2.2 dB in harmonic mode (NS) (Table 2). In the AP4C view, cyclic IBS IRA was 3.8 ± 1.5 vs 4.7 ± 1.5 dB ($P < 0.007$) and in a normal segment 4.1 ± 1.5 vs 5.5 ± 1.4 dB ($P < 0.0001$) in fundamental and harmonic modes (Fig. 3 and Table 1). The mean difference between normal and IRA territories in the AP4C view was 1.0 ± 1.4 dB in fundamental and 1.1 ± 1.6 dB in harmonic mode (NS) (Table 2). The AP2C view had similar results, cyclic IBS being 3.4 ± 1.7 vs 4.6 ± 1.5 dB in IRA territory ($P < 0.02$) and 4.5 ± 1.5 vs 5.7 ± 1.7 dB ($P < 0.004$) in normal myocardium for fundamental and harmonic modes, respectively (Fig. 3 and Table 1). The mean difference in this view was 1.2 ± 2.3 dB in fundamental mode and 1.2 ± 2.5 dB in harmonic mode (NS) (Table 2).

Wall motion analysis was possible in 547 of 636 segments (86%) in fundamental mode and in 592 of 624 segments (95%) in harmonic mode ($P < 0.002$).

Inter-observer reliability improved with harmonic imaging from 0.55 to 0.62 for the IRA territory and from 0.61 to 0.8 for normal myocardial segments.

Discussion

IBS represents the total reflected ultrasound energy from a selected region of the myocardium. IBS varies in a cyclical fashion with the cardiac cycle. This cyclic variation in IBS is reduced following myocardial infarction in myocardial segments supplied by the IRA.\textsuperscript{8,9,11,12} The effect of harmonic imaging on the measurement of IBS is unclear. In this study we have studied the effect of harmonic imaging on the measurement of cyclic and total IBS in infarcted and normal myocardial segments, as well as the effect this imaging mode has on the interpretation of these data. The amplitude of cyclic IBS was greater in both infarcted and remote normal myocardial segments in all views in harmonic mode compared with fundamental mode. However, the difference in cyclic IBS between infarcted and normal myocardial segments appears to be the same for all views for both fundamental and harmonic imaging modes. Therefore, it appears that whilst harmonic imaging increases the measured cyclic IBS, all segments seem to be affected equally so that any difference in measurements between normal and abnormal myocardium is maintained and interpretation of the IBS data is
the same. However, because the measurements of cyclic IBS are greater in harmonic than in fundamental mode, the two cannot be used interchangeably, such that, within any IBS study, only fundamental or harmonic imaging mode should be used. Additionally it will be necessary to define a new ‘normal range’ of IBS measurements for harmonic imaging mode. This ‘normal range’ could be system dependent as IBS intrinsically includes the resolution of the scanner. In this assessment no adjustment has been made for the phase of the cardiac cycle when the cyclic IBS is at its peak, but rather the raw average peak to average nadir values of IBS. This may make comparison with other papers which generally present the phase corrected average cyclic IBS somewhat difficult, though different methods to extract the IBS measurements have been proposed and compared by van der Steen et al.\textsuperscript{28} However, the phase correction is generally around 1 for parasternal views when the segments being analysed are perpendicular to the ultrasound beam, as the peak of the cyclic IBS is at end diastole.\textsuperscript{1} The parasternal measurements will, therefore, be reasonably comparable with phase-adjusted measurements. Comparison is more difficult for the apical views, where the peak and nadir of the cyclic IBS are often at a different phase of the cardiac cycle compared with the parasternal view, so that phase-adjusted measurements may be quite different to the pure peak to peak cyclic IBS measurement. This is termed the anisotropic effect and is thought to be due to the orientation of the myocardial elements reflecting the ultrasound beam relative to the angle of insonation. However, even though we have not made phase-adjusted measurements, we did observe that the phase of the peak and nadir level of cyclic IBS was not affected by harmonic imaging, so that the overall effect of harmonic imaging on cyclic IBS measurements will be the same even if phase correction were applied.

A further limitation of the study is that the ultrasound system used samples IBS at a rate of 30

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![Figure 1](https://academic.oup.com/ehjcimaging/article-abstract/5/3/189/2367116)
frames per second which is insufficient to resolve the IBS curve completely.\textsuperscript{29}

The reason harmonic imaging should have this effect on IBS measurements is unclear. One possibility is that harmonic imaging increases the signal to noise ratio, facilitating the detection of this parameter. When using harmonic imaging the mechanical index (MI) is higher than with fundamental imaging, usually 1.6 as opposed to 0.8–1. Thus the output power is almost doubled, although the received harmonic signal is relatively weak. This might explain the difference in IBS measurements. Certainly, the fact that harmonic imaging uses a lower frequency to insonate enabling better penetration, but a higher frequency to receive, enabling better resolution may be responsible in part for the increased IBS measurements. The fact that the beam is kept narrower than for fundamental imaging and that harmonics are only generated after the ultrasound has travelled some distance in the tissue (reducing rib reverberation artefacts) may enhance this effect.\textsuperscript{28} This means that almost all harmonics will be formed before the ultrasound reaches the ROI where the IBS is studied. This means, effectively, the IBS is calculated in harmonic mode for a 3.6 MHz field, whereas in fundamental mode it is <3 MHz. Since ultrasound backscatter is highly related to the ratio between the wavelength and the scatterer size, this may explain the difference between harmonic and fundamental measurements of IBS.

It is possible that this may also explain the difference between our results and those of Pislaru et al. who found no difference between IBS in fundamental and harmonic modes. However, they acquired all their data in second harmonic mode and then retrospectively filtered it to extract fundamental or second harmonic IBS, therefore using narrow band pulsing throughout. In our study IBS was acquired with different transmit band widths as described above. Undoubtedly more myocardial segments could be seen with harmonic imaging (1003 vs 920 [\(P < 0.0002\)]) and the borders of the myocardial segments were more easily visualised, possibly leading to a higher analysis success rate and more accurate placement and maintenance of an area of interest within a myocardial segment on a frame by frame basis during analysis. This is reflected in the improved inter-observer reliability in harmonic imaging mode. This may mean that IBS measurements can be made more accurately during harmonic imaging and therefore will be more useful clinically.

**Table 2** The difference in cyclic IBS between myocardial segments supplied by the IRA and normal myocardial segments for each view in fundamental and harmonic imaging modes

<table>
<thead>
<tr>
<th>View</th>
<th>Difference IBS IRA/normal fundamental (dB)</th>
<th>Difference IBS IRA/normal harmonic (dB)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLAX</td>
<td>1.27</td>
<td>1.16</td>
<td>0.38</td>
</tr>
<tr>
<td>PSAX</td>
<td>1.13</td>
<td>1.27</td>
<td>0.37</td>
</tr>
<tr>
<td>AP4C</td>
<td>0.96</td>
<td>1.1</td>
<td>0.49</td>
</tr>
<tr>
<td>AP2C</td>
<td>1.18</td>
<td>1.23</td>
<td>0.46</td>
</tr>
</tbody>
</table>

IBS, integrated backscatter; IRA, infarct related artery; 2HI, second harmonic imaging; PLAX, parasternal long axis; PSAX, parasternal short axis; AP4C, apical four chamber; AP2C, apical two chamber.
Conclusions

Second harmonic imaging increases the average peak to average nadir measurement of IBS in both infarcted and normal myocardial segments when compared with fundamental imaging. However, the interpretation of these data appears to be unaffected by the imaging mode as there is no change in the measured difference between normal and infarcted segments for fundamental and harmonic modes. Therefore, the advantage of using harmonic IBS relates to the standard advantages of using harmonic imaging.

References


