Quantitative evaluation of regional endocardial visualisation with second harmonic imaging and contrast left ventricular opacification in heart failure patients

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Abstract Aims Wall motion score index (WMSI) is an important prognostic indicator in heart failure (HF) patients but requires endocardial visualisation. This study evaluated the role tissue harmonic imaging (THI) and contrast opacification (LVO) for improving endocardial visualisation and the determination of WMSI in HF patients.

Methods and results Thirty-one HF patients and 30 controls underwent apical echocardiography with fundamental imaging (FUND), THI and THI with contrast agent (Leovist®). Visualisation and motion were graded in the six segments from each of the apical two and four chamber views. Both THI and LVO reduced the percentage of non-visualised segments (FUND 13.6%, THI 5.6%, LVO 2.8%, p < 0.01) in the controls, but in HF patients, only THI improved visualisation (% segments not visualised FUND 9.7%, THI 3.5%, LVO 4.8%, p = 0.06). The anterior and lateral walls were the least well visualised with FUND, but improved with LVO (anterior p = 0.0026, lateral p = 0.0003). No improvement was seen in the inferior wall (p = 0.30) or septum (p = 0.2). WMSI was similar by all methods and negatively correlated with ejection fraction (FUND r = −0.69, THI r = −0.74, LVO r = −0.77, all p < 0.001).

Conclusion THI improved endocardial visualisation in all subjects and LVO offered additional benefit in the controls, but not in HF patients. Regional endocardial
Introduction

Echocardiography is widely recommended and integrated into routine clinical management of patients with heart failure (HF) to assist diagnosis, determine aetiology, and to assess left ventricular (LV) size and function.\(^1,2\) Echocardiography also provides important prognostic information, for example LV end-systolic volume (LVESV)\(^3\) and ejection fraction (EF)\(^4-6\) are important prognostic indicators in HF, as is the echo-derived wall motion score index (WMSI), which correlates with EF\(^7-9\) and is similarly predictive of long-term outcome.\(^8,10,11\) However, current echo techniques for measuring EF and WMSI are hampered by poor endocardial definition. In addition, patients with HF often have dilated ventricles with displaced apices, making visualisation of all wall segments even more difficult.

Second harmonic imaging\(^12-21\) and LV opacification using transpulmonary echo contrast (LVO)\(^22-27\) improve endocardial definition when compared to fundamental gray scale imaging. Both techniques have been shown to improve the diagnostic capability of echo\(^24,28\) by increasing the number of segments seen and also enhancing the overall quality of the endocardial visualisation and are now widely advocated for use in patients with suboptimal images. These methods may also increase the number of patients in whom quantitative echocardiography may be performed. However, most of these studies have investigated the role of LVO in patients with ischemic heart disease and it remains unclear whether these benefits are the same in patients with HF, who may have reduced cardiac output and markedly dilated chambers. It has been suggested that LVO may not be as efficacious in patients with low cardiac output.\(^29\) Additionally, endocardial definition varies throughout the LV chamber and there may be regional differences in both visualisation with fundamental imaging, as well as with harmonic imaging and contrast LVO.\(^19,30\)

We have previously investigated the effects of harmonic imaging and contrast LVO upon biplane echocardiographic measurements of EF in HF patients and control subjects. In both groups, harmonic imaging improved endocardial definition, but the addition of a contrast agent (Levovist\(^6\)) further improved endocardial visualisation in the control subjects only and not in the HF patients. In addition, neither harmonic imaging nor contrast LVO improved either the intra-observer, inter-observer or test–retest reproducibility of EF measurements.\(^31\) This may have been related to inferior contrast opacification of the LV in HF patients compared with control subjects, due to excessive bubble destruction as a result of longer ultrasound exposure, or attenuation at depth in the dilated ventricles. This may also have been related to a delay in passage of contrast through the pulmonary circulation and indirectly to clinical status.

The aim of the current study was to determine whether the improvement in endocardial visualisation observed with both second harmonic imaging and contrast LVO was uniformly distributed throughout the LV wall segments in patients with HF and a group of healthy controls and to evaluate how these techniques affected the semi-quantitative assessment of regional wall motion, in particular the agreement of wall motion score index with ejection fraction using these methods.

Methods

Subjects and echocardiography

The effects of the different echo techniques upon the reproducibility of ejection fraction measurements in heart failure patients and control subjects have been reported.\(^31\) Briefly, we studied 31 outpatients with chronic stable heart failure (all patients had at least one prior hospital admission requiring diuresis) and 30 healthy volunteers. Subjects were not selected on the basis of echo quality. The study complied with the Declaration of Helsinki and all subjects provided written informed consent and the study was approved by the Auckland District Health Board Human Subjects Ethics Committee. All subjects underwent the same echo protocol on two different days (at least 1 day apart: mean 14 days (sd 24.5), median 7 days). Paired image sets were obtained on the same ultrasound machine (ATL HDI-3000 or HDI-5000, ATL Ultrasound, Bothell, WA). Standard diagnostic echo views were obtained in five thoracic windows and recorded onto super-VHS videotape and digitally acquired. All analyses were performed off-line (Nova Microsonics, Kodak Eastman, NJ).
Study imaging protocol

The sector depth of the apical four and two chamber views was optimized to maximize the LV chamber on the screen, eliminating most of the left atrial chamber from view, and the focus placed at the junction of the mid and basal segments of the LV wall. Six to ten beats for each view were obtained under each condition and in the same order for each subject: (1) fundamental imaging; (2) harmonic imaging (factory tissue harmonics settings); and (3) harmonic imaging with Levovist®.

Contrast protocol

The machine was set to the factory settings for Levovist® and modified for individual patients. Images were obtained using contrast specific harmonics machine settings (mechanical index 1.2, frame rate medium) and recorded in real-time. Intravenous access was obtained via a canula in the subjects’ right arm. A three-way tap was put in place and the line flushed with saline. Levovist® (Schering NZ Ltd) is an air based contrast agent composed of galactose (99.9%) and palmitic acid (0.01%). Contrast was prepared according to the manufacturer’s instructions to obtain the best opacification for patients with heart failure (4 g, in solution 400 mg/ml) and given as a bolus followed by a 0.9% saline flush. Six to ten cardiac cycles of the four and two chamber views were recorded onto videotape.

Endocardial visualisation

The 12 segments seen in the apical four and two chamber views were graded for quality of visualisation: 0 = not visible, 1 = barely visible, 2 = well visualised and a mean endocardial border delineation score calculated (EBD). The grading was performed by reviewing the videotapes, in random order by one observer without knowledge of the results of the other methods or any clinical details. LV opacification was consistently lower quality in the HF patients and pulmonary transit time was prolonged in the HF patients and was related to LV size and function.31

Left ventricular wall motion scoring

Only segments visible in the apical four and two chamber views were scored. One observer scored each of the 12 segments in random order according to ASE guidelines (1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic, 5 = aneurysmal).33 Wall motion was scored under three different imaging modalities: fundamental, second harmonic imaging and contrast + harmonic imaging. It was not possible to blind the observer to the imaging modality or LV function, although the observer was unaware of the subjects’ identity and group allocation, clinical details and other echo measurements of all subjects. We have previously demonstrated excellent inter-observer agreement (coefficient of variation 6.8%, n = 100) and intra-observer agreement (coefficient of variation 5.2%, n = 30) in our laboratory for wall motion score index assessment.34

Left ventricular volume measurements

LV volume was calculated according to the modified Simpson’s biplane method using the apical four and two chamber views. The endocardial border was manually traced at end-diastole (the largest LV area just prior to the QRS wave) and end-systole (the smallest LV area close to the end of the T wave) for three different cardiac cycles. The papillary muscles were included in the blood volume.33 One observer measured all volumes in random order without knowledge of the clinical status. Analyses of the effects of the different echo methods upon the variability of EF measurements have previously been published33 and EF measurements were used in this study for reference only.

Statistics

Student’s t-test, or the Chi-square test were used to determine significance of pairwise comparisons. Two way analysis of variance (ANOVA), with Tukey’s post hoc analysis used to compare the proportions of segments visualised (not visualised, barely visualised and well visualised) by each method and the differences between HF patients and control subjects and the interaction between method and subject type. Segments were grouped according to anatomical position (anterior, inferior, posterior, septal, basal, mid and apical walls) and a further two way ANOVA performed. Wilcoxon non-parametric analysis of variance was used to compare the relationship between EF and WMSI by each echo method. Significance was maintained at p = 0.05 throughout the analyses.
Results

Subjects

The two subject groups have been described elsewhere. Briefly, the HF patients were clinically stable (87% in NYHA class I or II, and 25% were in atrial fibrillation) and all were receiving standard treatment, including ACE-inhibitors (94%) and diuretics (97%). Fourteen (44%) patients had a history of ischemic heart disease, 2 (6%) hypertensive heart disease, 2 idiopathic dilated cardiomyopathy, 1 alcoholic cardiomyopathy and the remaining 13 (40%) were considered of mixed aetiology and a single cause could not be determined. Compared with the control subjects, the HF patients had similar body size, but had larger hearts, similar stroke volumes, but lower ejection fraction and comparable body size, but had larger hearts, similar stroke volumes, but lower ejection fraction and similar body size, but had larger hearts, similar stroke volumes, but lower ejection fraction and similar body size, but had larger hearts, similar stroke volumes, but lower ejection fraction.

Endocardial visualisation

When comparing the two groups there were no differences in the quality of endocardial visualisation with fundamental or harmonic imaging, but contrast LVO produced significantly better endocardial visualisation in the healthy control subjects compared with the HF patients (Fig. 1). There was a significant difference in wall visualisation between the three methods (p = 0.0021) and between HF patients and control subjects (p = 0.03) but no interaction between the methods and subject category (p = 0.76). In the healthy control group, wall definition was subjectively improved with both harmonic and contrast LVO imaging. The number of segments not visualised dropped from 49 (13.6%) with fundamental imaging to 20 (5.6%) with harmonic imaging and further reduced to 10 (2.8%) with contrast LVO (overall, Tukey’s post hoc p = 0.01). In the HF patients, endocardial visualisation improved with harmonic imaging, but no further improvement was seen with contrast LVO. In the HF patients, 36 (9.7%) segments were not visualised with fundamental imaging, this was reduced to 13 (3.5%) segments with harmonic imaging, but when contrast LVO was used, the number of non-visualised segments increased to 18 (4.8%) (p = 0.06) (Fig. 1).

Regional differences in endocardial visualisation

There were regional differences in endocardial visualisation in both groups: the anterior and lateral walls were the least well visualised with fundamental imaging but improved with harmonic and contrast LVO (anterior: p = 0.0026, lateral: p = 0.0003) (Fig. 2). There was no effect upon endocardial visualisation associated with the different echo methods in either the inferior or septal walls (inferior: p = 0.30, septal: p = 0.20). There was also a depth-related decline in endocardial definition, with progressive deterioration from the apex to the base of the heart. Endocardial definition was improved by the different echo methods in all three regions: base (p = 0.0007), mid (p < 0.0001) and apex (p = 0.04). Comparing the HF patients with the control subjects, endocardial definition was improved in the anterior (p = 0.04) and lateral walls (p = 0.03), but not in the inferior (p = 0.40) and septal walls (p = 0.50). HF patients had worse basal visualisation by any method (p = 0.001) but similar mid (p = 0.50) and apical (p = 0.80) visualisation as the control subjects (Table 2).

Wall motion score index

Despite significant changes in subjective visualisation, WMSI was similar by all three methods — HF: fundamental WMSI 1.85 ± 0.63, harmonics WMSI 1.77 ± 0.59, contrast WMSI 1.78 ± 0.59; controls: fundamental WMSI 1.05 ± 0.14, harmonics WMSI 1.06 ± 0.14, contrast WMSI 1.04 ± 0.12. For each method, there was a significant difference in WMSI between HF patients and controls.
subjects with all three methods (fundamental \( p < 0.001 \), harmonics \( p < 0.0001 \), contrast \( p < 0.0001 \)). In the HF patients, WMSI was significantly correlated with ejection fraction (EF) and the correlation coefficient for echo imaging modality was similar \(( p = 0.294)\) (Fig. 3). Correlation of WMSI with EF in the healthy controls was not performed because the WMSI values were clustered around a value of 1, consistent with normal systolic function.

**Discussion**

This study investigated the role of tissue harmonic imaging and contrast LVO for enhancement of endocardial wall visualisation in patients with heart failure and a comparison group of healthy controls. Whilst harmonic imaging improved endocardial visualisation in both groups, contrast LVO resulted in improved endocardial definition in the control group only. No additional benefit was observed with contrast LVO when compared with second harmonic imaging in HF patients. There were regional differences in endocardial definition observed with all echo methods — the anterior and lateral walls were consistently the least well defined of all the apical wall segments. Visualisation was also affected by distance from the transducer — the basal segments were poorly visualised compared to the apical segments. Just as baseline visualisation was not uniform, neither was the improvement with contrast. Thus, if one were to follow the ASE guidelines recommending the use of contrast for LVO when two or more segments are not visualised, one needs to consider which segments are not seen and whether they are likely to improve. Lastly, wall motion score index was similar when assessed with any method and therefore no additional prognostic information would be available.

**Contrast performance in heart failure**

Contrast opacification of the LV in HF patients may be inferior due to excessive bubble destruction due to longer ultrasound exposure at high mechanical index, or attenuation at depth in the dilated ventricular chambers. In a previous study, we found that the quality of opacification was generally worse in the HF patients. There was also a delay in the passage of contrast through the pulmonary circulation, which correlated with clinical status. The more advanced the HF, the worse the contrast performance.
Regional differences in endocardial visualisation

The reason for the lack of improvement in the basal segments may arise for several reasons. Firstly, the HF patients were selected on the basis of a clinical diagnosis of HF, and as a result, many had significantly dilated hearts. This dilatation meant that the basal segments were located far from the transducer face and the walls were close to the edge of the ultrasound sector. There are physical differences in the ultrasound beam at the base of the heart compared with the apex. In particular, the beam width is wider and the slice thickness increased at depth. Both of these factors may contribute to poor resolution, which may not have been improved with either harmonic imaging or contrast LVO. This may explain why the basal segments were, in general, the least well imaged of all 12 segments. The proximity of some walls with the edge of the ultrasound sector also poses resolution problems. The effect of side-lobe artifacts might be significantly worse in these walls and may explain why the visualisation of the anterior and lateral walls was inferior compared with either the septum or inferior wall. The combination of these depth-related and sector edge artifacts resulted in poor imaging of the basal anterior and inferior walls. However, even with harmonic imaging and contrast LVO some segments in these areas remained non-visualised.

Harmonic imaging has been previously shown to be particularly useful for improving visualisation of the lateral and anterior walls through reduction of side-lobe artifacts and also in the basal segments of the heart, whereas contrast has shown little benefit for visualising the basal segments of the heart. Although these benefits were observed in the current study for healthy controls, the lack of consistency in HF may have resulted because the HF patients have larger
hearts with different geometrical shape resulting in more pronounced beam width and side-lobe artifacts.

Overall wall motion score versus individual segment motion

This study demonstrated excellent correlation between WMSI and EF in HF patients by all methods, but without significant benefit of either harmonic imaging or contrast. This correlation was of a similar magnitude to that observed in another study comparing WMSI obtained with fundamental and harmonic imaging to EF measured by nuclear methods \(^{37}\) and demonstrates that the different methods are reliably assessing systolic function. Importantly, no significant differences were seen between the mean WMSI obtained by the different methods, which is not the case for EF measurements. \(^{31}\) This probably reflects the way that WMSI is calculated — if a segment is not visualised, it is not included in the calculation of WMSI and thus has no effect on the overall value. Thus, when one or two segments are not visualised the overall effect upon WMSI may be minimal. In isolated cases, such as a small localised infarction or aneurysm, this might lead to underestimation of global dysfunction. However, the improvement of endocardial visualisation with harmonics will minimize such errors, as well as increase diagnostic confidence.

Whilst WMSI is an important global measure of LV function and provides important prognostic information it does not provide any specific diagnostic information or provide aetiologic explanations for the compromised LV function. In this situation, the resolution of a single wall segment may change clinical management. Thus, any method which has the potential to convert even one non-visualised wall segment to a visible one has significant clinical potential.

Limitations

Blinding of the interpreter to the different imaging methods was impossible, given the nature of the study. However, the measurements were made in random order and the measurer was unaware of any clinical details at the time of analysis and each set of images was analysed without reference to the other methods or measurement. Wall motion was only assessed by a single observer and thus may be subject to observer bias. However, we have previously demonstrated excellent intra-observer and inter-observer variability for this person. Importantly, if bias for one method over another was present, it would be likely to affect both subject groups and since the main finding from the study is a different effect in each group, this is likely to be minimal.

This study was limited to the 12 segments seen in the apical four and two chamber views collectively. To include all 16 segments, would have necessitated including short axis images of the LV. Imaging and interpretation of the posterior and inferior walls would have been very poor because of attenuation through the LV cavity during contrast LVO. Thus, in order to make a fair comparison, we chose to only use the apical views.

This study was not restricted to patients with sub-optimal echocardiograms. Many other studies have done so, and whilst this may identify the patients with the potential for the most

<table>
<thead>
<tr>
<th>Echocardiography methods</th>
<th>Healthy controls (n = 30)</th>
<th>HF patients (n = 31)</th>
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<tbody>
<tr>
<td></td>
<td>Anterior</td>
<td>Lateral</td>
</tr>
<tr>
<td><strong>Fundamental imaging</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not-visualised</td>
<td>27 (30.0%)</td>
<td>20 (22.2%)</td>
</tr>
<tr>
<td>Barely visualised</td>
<td>28 (31.1%)</td>
<td>39 (43.3%)</td>
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<tr>
<td>Well visualised</td>
<td>35 (38.8%)</td>
<td>31 (34.4%)</td>
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<tr>
<td><strong>Harmonic imaging</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not-visualised</td>
<td>10 (11.1%)</td>
<td>7 (7.8%)</td>
</tr>
<tr>
<td>Barely visualised</td>
<td>24 (26.7%)</td>
<td>31 (34.4%)</td>
</tr>
<tr>
<td>Well visualised</td>
<td>56 (62.2%)</td>
<td>52 (57.8%)</td>
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<tr>
<td><strong>Contrast + harmonics</strong></td>
<td></td>
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</tr>
<tr>
<td>Not-visualised</td>
<td>4 (4.4%)</td>
<td>4 (4.4%)</td>
</tr>
<tr>
<td>Barely visualised</td>
<td>9 (10.0%)</td>
<td>14 (15.6%)</td>
</tr>
<tr>
<td>Well visualised</td>
<td>77 (85.5%)</td>
<td>72 (80%)</td>
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</table>
improvement, the objective of the current study was to determine the general applicability of the method in patients with HF. The different methods are not interchangeable for LV volume or EF measurements and thus for longitudinal evaluation, it is possible that laboratories will adopt a policy of routinely using contrast for assessment of systolic function, it is likely that contrast may be used in subjects without a clear need for contrast according to the ASE guidelines.

The results of this study need to be considered carefully given that the contrast agent used, Levovist, is a first generation agent and newer agents, used with low mechanical index imaging may result in quite different results, especially in the heart failure patients. In such patients, with low cardiac output, excessive destruction of microbubbles may occur and thus lead to poor cavity opacification.

Conclusion

On a segment by segment basis, harmonic imaging and contrast LVO improves endocardial visualisation, but is wall segment specific. In particular, segments which lie at the extremes of the ultrasound sector are not as well visualised with fundamental imaging and thus may have the most room for improvement with the use of contrast LVO. All of the methods performed differently in patients with heart failure compared to control subjects with normal sized and functioning hearts. Importantly, WMSI was not affected by these different methods. This study has important and clinically relevant implications for the initial assessment and serial follow-up of systolic function in patients with HF. Harmonic imaging should be used routinely for regional wall motion analysis in HF patients, but contrast LVO should be carefully considered in light of the specific location of non-visualised segments and heart size.

Acknowledgements

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