Impact of Second Harmonic Imaging on the Determination of the Global and Regional Left Ventricular Function by 2D Echocardiography: a Comparison with MIBI Gated SPECT

G. Van Camp*, P. R. Franken, D. Schoors, Y. Hagers, M. Koole, D. Demoor, P. Melis and P. Block

Departments of Cardiology and Nuclear Medicine, Academic Hospital of the Free University of Brussels, AZ VUB, Laarbeeklaan 101, 1090 Brussels, Belgium

Aims: To evaluate the impact of second harmonic (SH) imaging compared to fundamental mode (FM) on the echocardiographic determination of ejection fraction (EF) and wall motion score index (WMSI), using MIBI gated SPECT as an independent reference.

Methods: Sixty-two consecutive patients underwent an echocardiography study and a MIBI gated SPECT over 24 hours. EF was estimated visually (estimated-E) and was calculated with the Simpson biplane method (Tracing-T), for both FM and SH. WMSI was determined by two independent echo-readers blinded to the nuclear imaging results. The same segmentation and scoring system was used for WMSI determined by MIBI gated SPECT.

Results: The percentages of unscored segments because of suboptimal endocardial border detection were 19.5% (FM) and 9.0% (SH). The correlation coefficients ($r$) between SPECT-EF and echo-EF were: FM (E)=0.705, FM (T)=0.705, SH (E)=0.771, SH (T)=0.743. Agreement between SPECT-EF and echo-EF was acceptable for both imaging modalities (mean of the differences $/\pm$ S.D.): $-2.8 \pm 18.5$ (FM) and $-3.5 \pm 16.4$ (SH). Correlation coefficients ($r$) between WMSI calculated by SPECT and by echo were 0.715 (FM) and 0.789 (SH). Agreement between SPECT-WMSI and echo-WMSI was good for all imaging modes but better with SH compared to FM: 0.72 $\pm$ 0.91 (FM), 0.70 $\pm$ 0.77 (SH). The interobserver correlation coefficients ($r$) for the WMSI were 0.939 (FM) and 0.996 (SH). The agreement between the two observers was better for SH compared to FM. The systematic differences (mean differences) were 0.21 (FM) and $-0.01$ (SH), and the random differences between both observers (2 S.D.) decreased from 1.55 (FM) to 0.29 (SH).

Conclusions: The use of SH echocardiography decreases the number of unscored segments. This results in an important gain in correlation and agreement for EF determination between echo and SPECT, and in a considerable decline of the interobserver variability for the echo-determined WMSI. WMSI determined by MIBI gated SPECT correlated closely with the SH WMSI, and agreement between both methods was excellent.

Key Words: LVEF; LVWMSI; MIBI gated SPECT; second harmonic echocardiography.

Introduction

One of the most important issues in the everyday practice of the cardiologist remains the determination of the global (ejection fraction-(EF)) and regional (wall motion score index (WMSI)) left ventricular (LV) performance, both at rest and during exercise or pharmacological stress.

Only echocardiography and nuclear cardiology permit the determination of both parameters on a regular basis. Scintigraphically determined left ventricular EF is considered to be the reference method for the daily measurement of EF. Echocardiography, in contrast, is considered to be the standard for the regional wall motion analysis due to its high spatial and temporal

*Correspondence address: Dr Guy Van Camp, Department of Cardiology, AZ VUB, Laarbeeklaan 101, 1090 Brussels, Belgium.
resolution. Recently, there have been important new developments in both methods.

The accuracy of echocardiography in the determination of EF and WMSI is mainly dependent on the evaluation of endocardial motion and wall thickening, requiring optimal endocardial delineation. Drastic improvements in image quality have been observed when harmonic imaging is used to image both tissue and contrast agents. The non-linear effects of the interaction of ultrasound with matter create frequencies not present in the incident beam. Propagation can generate ultrasound waves containing harmonic frequencies occurring at a multiple of the fundamental frequency. When the ultrasound transducer is set to receive at twice the fundamental frequency, second harmonic imaging (SH) is obtained. In SH, endocardial delineation is superior to fundamental imaging (FM) because most of the artefacts reducing the image quality in FM are cleared. Indeed, reverberations and scattering are generated from the chest wall and contain almost no harmonic frequency energy. Side lobes, which are responsible for much of the clutter present in the LV cavity, are also suppressed in harmonic imaging thanks to a disproportionate reduction in side-lobe energy with respect to the central beam.

The use of ECG gating in conjunction with myocardial perfusion SPECT imaging has increased tremendously over the past 5 years. Gated myocardial perfusion SPECT allows the simultaneous assessment of cardiac perfusion and function. Quantitatively gated SPECT, which was developed by Germano et al., is a widely validated and commonly applied approach to the automatic, 3D quantification of LVEF, LV cavity volumes and segmental myocardial wall motion and thickening.

The aims of this study were to evaluate the incremental value of SH compared to FM echocardiography in the determination of EF and WMSI, taking quantitative MIBI gated SPECT as the independent reference method. Furthermore, we evaluated the impact of SH on the individual segmental endocardial delineation in a group of non-selected patients with myocardial infarction or LV failure. These data enable us to evaluate the importance of both methods in the determination of the global and regional LV function in the everyday clinical practice.

**Methods and Patients**

**Patient Population and Study Design**

We studied 62 consecutive patients hospitalized with an acute myocardial infarction (day 7–10), or for severe left ventricular failure. They were sent to the echolaboratory for the evaluation of left ventricular function. In all these patients, MIBI gated SPECT was obtained within 24 h of the echo-study (mean ± S.D. time of difference (hours) between both methods: 10 ± 9.5). Patients with atrial fibrillation or significant mitral regurgitation (>2/4 defined by colour Doppler) were excluded. Patients without any echocardiographic window were also excluded.

**Methods**

**Imaging modalities**

**Echocardiographic examinations.** All the echocardiographic studies were performed with a Toshiba Powervision, and the images were stored on videotape and on the Toshiba workstation (PC). At least three cardiac cycles were stored from the parasternal long and short axis and from the apical four- and two-chamber view. FM imaging was performed at 2.5 MHz and SH imaging at 1.8–3.6 MHz.

**Gated SPECT imaging.** LVEF was calculated from the gated SPECT images using the full automatic program developed at Cedars-Sinai (GS-Quant, Siemens, Inc.). Myocardial perfusion SPECT gated in eight time bins were acquired 60 min after the injection of 925 MBq technetium-99m labelled sestamibi (MIBI) at rest using a three-head gamma camera (MultiSPECT3, Siemens, Inc., Hoffman Estates, Illinois, U.S.A.) Detailed imaging and data processing have been reported previously.

**LVEF determination**

By echocardiography. LVEF was calculated on-line by one observer with the Simpson biplane method using the Toshiba Powervision software, in first for FM and then for SH (Tracing-T). LVEF was not calculated off-line since no software was available on the workstation. EF was estimated visually (Estimated-E) off-line in both SH and FM. The image characteristics indicate the image modality, and a completely blinded reading of both methods is impossible. We masked the PC and video screens to hide the identity of the patient and the modality of the examination. All echocardiographic examinations and calculations were performed to the results of MIBI gated SPECT and to the clinical context of the patient. All off-line analysis was performed in alphabetical order, some weeks after the initial examinations. For some patients the FM was evaluated first, and for the remainder the SH mode pictures were evaluated first: the reader was blinded to this information. This design closely resembled random measurement.

By gated SPECT imaging. LVEF was calculated as for gated SPECT imaging.

**WMSI determination**

By echocardiography. WMSI was determined by two independent readers, using the 16-segment model as proposed by the American Society of Echocardiography and a 1–5 scale for both echocardiographic and...
both methods were evaluated with a Bland–Altman agreement and the number of unscored segments with FM and SH was noted. The design of the echocardiographic examination interpretation was the same as for off-line LVEF determination, and guaranteed a random measurement.

By gated SPECT imaging. The method used has already been outlined. The same segmentation of the left ventricle (Bull’s eyes representation) as for echocardiography was used for MIBI gated SPECT, and a 45° clockwise rotation of the nuclear images was used to match the echocardiographic data.

**Statistical Analysis**

Correlation between echocardiographic EF and WMSI and those obtained by MIBI gated SPECT was tested with the Pearson correlation test. Mean values were compared using the paired t-test. Agreement between both methods were evaluated with a Bland–Altman analysis. Interobserver variability was described using all three of these methods.

**Results**

**Patient Characteristics**

Of the 62 patients, 15 were evaluated for LV failure and 47 because of a recent myocardial infarction. The majority of the patients were men (45 men and 17 women). Age distribution was similar for men and women (65±7 ± 11.8 and 62.8 ± 11.6), respectively. During the study period, five patients were excluded because of atrial fibrillation and two due to mitral regurgitation ≥2/4. Two patients were excluded because of the absence of any echocardiographic window.

<table>
<thead>
<tr>
<th>Table 1. LVEF (%) determined by echocardiography and MIBI gated SPECT (mean ± S.D.). Comparison between echo data and SPECT (paired t-test (r and p) and Bland–Altman agreement (mean difference and 2 S.D. of the difference).</th>
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<tr>
<td>EF-MIBI</td>
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<td>Mean</td>
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<td>S.D.</td>
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<td>r</td>
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<td>P</td>
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<td>Bland-A</td>
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<td>Mean</td>
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EF-MIBI: EF determined by MIBI gated SPECT.

**LVEF Determination by Echocardiography and MIBI gated SPECT**

LVEF was significantly higher when determined by echocardiography compared to the MIBI gated SPECT (Table 1). The correlation between the echocardiographic measurements and MIBI gated SPECT increased progressively from FM(T)=0.546 to FM(E)=0.705, and SH(T)=0.743 to SH(E)=0.771. Although there was systematic overestimation of EF determined by echo compared to SPECT, a significant difference between the mean values was only seen for FM(T) and SH(T). The agreement (expressed as the systematic differences (mean differences) and the random differences (2 S.D.)) between both methods was comparable for FM and SH (Table 1 and Figures 1–4). Bland–Altman analysis showed that the agreement between the two methods was unaffected for LVEF determination (Figures 1–4).

**LV WMSI Determination by Echocardiography and MIBI gated SPECT**

The correlation between echocardiography and SPECT for the determination of the WMSI increased from FM (r=0.71) to SH (r=0.79) (Table 2). Paired t-test showed no significant difference between echo and MIBI gated SPECT, but the P values again increased from FM to SH. The Bland–Altman agreement test showed a decrease in the mean difference and in the standard deviation (×2) on the difference from FM to SH (Fig. 5).

**Interobserver Variability**

The correlation for WMSI determined by the two independent observers increased from r=0.939 (FM) to r=0.966 (SH). Paired t-test showed no significant difference between both observers for the two imaging modalities. Bland–Altman analysis showed a marked
Figure 1. Regression analysis and Bland–Altman agreement curves between FM (E) and MIBI gated SPECT measurements for LVEF.

Figure 2. Regression analysis and Bland–Altman agreement curves between FM (T) and MIBI gated SPECT measurements for LVEF.

Figure 3. Regression analysis and Bland–Altman agreement curves between SH (E) echocardiographic and MIBI gated SPECT measurements for LVEF.
increase agreement between the two observers from FM to SH (Fig. 6). The mean difference for FM was 0.03, and for SH it was 0.01. The standard deviations (× 2) between the differences were FM=0.43 and SH=0.29.

The Number of Unscored Segments

The percentage of unscored segments declined from 19.5% (observer 1)–18.8% (observer 2) in FM to 9.0% (observer 1)–7.7% (observer 2) in SH.

The Percentage of Unscored Segments for the Different Segments

Changes in image quality between FM and SH are shown in Table 3. The improvements in endocardial border delineation were most clear in the apical, lateral and anterior segments.

Discussion

Left ventricular function (LV) plays an important role in the short- and long-term prognosis of patients with ischaemic and non-ischaemic cardiomyopathy. Because echocardiography is non-invasive, it can be used to monitor LV function. Left ventricular EF (LVEF) can be assessed visually or calculated using the biplane modified Simpson rule[14–16]. LV systolic function can also be estimated by the determination of the WMSI[15].

The accuracy of EF and WMSI measurements by echocardiography depends on the endocardial delineation of the left ventricle, allowing precise judgement of endocardial motion and wall thickening. New techniques, such as automated border detection, 3D echocardiography, new digital instrumentation and tissue Doppler imaging, have been developed to enhance the accuracy of determining the LV systolic function, both at rest and during exercise and pharmacological stress. However, the most practical approach is to develop those techniques which transform a suboptimal echo-image into a LV image with sharp endocardial delineation. Considerable enhancement of suboptimal echo-images has been obtained with harmonic imaging[1,2,8,20–22].

In this paper the EF and WMSI scores determined by standard FM imaging were compared against those obtained by SH. For EF we compared the echo values with those obtained by MIBI gated SPECT. This has two advantages. First, gated SPECT can be considered to be the reference method for EF determination in those patients in sinus rhythm, without significant arrhythmias or mitral regurgitation[9–14]. Second, it allows the echo-methods to be compared against a second independent method. For WMSI we considered echocardiography to be the reference method, and we compared interobserver variability in FM and in SH, evaluating the number of unscored segments. We then compared MIBI gated SPECT against echocardiography for the evaluation of the WMSI.

Our results show that SH improves endocardial delineation considerably, as measured by the number of unscored segments. Not surprisingly, the major gain in endocardial delineation with SH was obtained in the apical segments (reverberations and scattering from the
chest wall are eliminated by SH) and in the anterior and lateral segments (side lobes are eliminated with SH) [8]. For the global systolic function evaluation, we demonstrated that LVEF determined by echo was higher compared to SPECT. Indeed, the normal value for LVEF determined by echo is >60%, and for gated SPECT it is >50%. These criteria are used routinely, and have been validated in most of the echo and nuclear centres, including the authors' own.

The estimated EF agreed better with MIBI gated SPECT than with the traced values. This was also reported by others who used FM only FM [19]. This can be explained by the fact that the echocardiographer can fill in the missing segments by taking into account the motion of the adjacent segments. The final result will be less severely altered than when each segment has to be scored independently.

The better endocardial delineation obtained with SH results in a significant improvement in the interobserver variability for echo-derived WMSI. This may have a major impact on stress echocardiography and can probably decrease the inter- and intra-observer variability of this operator-dependent examination. SH will probably become the standard modality for stress echocardiography [20].

WMSI determined by MIBI gated SPECT correlated closely with echocardiographically determined WMSI, and the agreement between both modalities was best for SH echocardiography.

Economic considerations favour the use of SH echocardiography when the cardiologist wants to
evaluate the global and regional systolic function of the left ventricle. Based on the results of our study, which show close correlation and agreement for both methods (SH-echocardiography and MIBI gated SPECT), we conclude that SH echocardiography should be the examination of first choice. However, patients who are evaluated by MIBI gated SPECT for myocardial perfusion, and for those with suboptimal echocardiographic windows, MIBI gated SPECT is an excellent alternative method.

Table 3. Percentage of unscored segments for the different regions of the left ventricle.

<table>
<thead>
<tr>
<th></th>
<th>FM1</th>
<th>SH1</th>
<th>FM2</th>
<th>SH2</th>
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<td>1.67</td>
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<td>16.67</td>
<td>17.86</td>
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SB=septo-basal; SM=septo-mid; SA=septal-apical; LA=lateral-mid; LM=lateral-basal; LB=lateral-basal; IB=inferior-basal; IM=inferior-mid; IA=inferior-apical; AA=anterior-apical; AM=anterior-mid; AB=anterior-basal; ASM=anterior-septal-mid; ASB=anterior-septal-basal; PM=posterior-mid; PB=posterior-basal; 1=observer 1; 2=observer 2.

References


