Novel wall motion score-based method for estimating global left ventricular ejection fraction: validation by real-time 3D echocardiography and global longitudinal strain

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Aims
To evaluate the reliability of a regional wall motion score index (WMSI)-based method for assessment of left ventricular (LV) ejection fraction (EF).

Methods and results
Two-dimensional (2D) echocardiography was used to assess a LV 16-segment-based regional wall motion. Each segment received a score based on contractility status: 4, normal kinesis; 3, mild; 2.5, moderate; and 1.5, severe hypo-kinesis; 0, akinesis; −1, dyskinesis; 3.5 and 4.5 were used for low-normal and high-normal kinesis; 5 for hyper-kinesis. Hence, WMSI-based EF was derived by summing the score assigned to each segment. Contextually, EF was evaluated by real-time three-dimensional (3D) echocardiography and by traditional Simpson’s method (2D). Global longitudinal strain (GLS) by speckle-tracking method was derived as a volume-independent indicator of LV chamber contractility sensitive to regional wall motion abnormalities. In 40 subjects with 3D-EF ranging from 14 to 80%, including clinically healthy hypertensive and patients with Stage B–D congestive heart failure with global or segmental wall motion abnormalities, on average, WMSI-EF did not differ from EF measured by 3D or 2D (all \( P > 0.5 \)). By intraclass correlation coefficients, reliability of WMSI-EF vs. 3D method was as good as the reliability of 2D method vs. 3D method. GLS correlated with WMSI-EF as strongly as with 3D-EF (both \( r^2 \approx 0.90 \)). Moderate–severe mitral regurgitation was associated with increased difference between WMSI-EF and 3D-EF, independent to potential confounders. Intra-observer and inter-observer reproducibility of WMSI-EF was comparable to the reproducibility of EF estimated by 3D echocardiography. Feasibility (WMSI, 3D, 2D, and GLS all available) was 78%; however, feasibility of WMSI per se was \( \sim 92\% \) in clinical series.

Conclusion
Trained readers may rapidly estimate EF by a novel WMSI system, which was found to be accurate compared with 3D method and GLS.

Keywords
Echocardiography • Wall motion • Ejection fraction • Reliability • Strain

Introduction
Echocardiography is the first-choice technique for estimation of left ventricular (LV) ejection fraction (EF), a widely used and prognostically important indicator of LV systolic function. Common echocardiographically-based method used for EF calculation requires the estimation of LV volumes, either derived from LV cavity linear measurements or by two-dimensional (2D) LV planimetry or using real-time three-dimensional (3D) echocardiography. All those methods may have limitations. EF from LV linear measurements relies on geometrical assumptions and may be misleading in patients with wall motion abnormalities; 2D LV

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planimetry may be time-consuming and its reliability may be suboptimal;\textsuperscript{3,5} 3D is not diffused widely, requires advanced echocardiographic machines, is affected by relatively low-frame rates, requires some processing and highly trained personnel.

In a previous report, we demonstrated that LV EF derived from wall motion score index (WMSI), from simple 2D echocardiography, is prognostically informative as much as LV EF estimated from LV linear measurements.\textsuperscript{1} WMSI requires neither advanced echocardiographic machines nor assessment of LV volumes, and may be used in a very wide clinical scenarios. In fact, previous studies have demonstrated that the estimation of EF from WMSI may be feasible and accurate.\textsuperscript{6,7} However, in those previous studies, EF was estimated from WMSI by applying regression equations.\textsuperscript{6,7} Our method is significantly different because it is based on the contribution of each LV segment to global EF.\textsuperscript{8} Nevertheless, while tested in clinical epidemiology context,\textsuperscript{8} such an approach has not been validated in clinical setting. Thus, we explored the reliability of LV WMSI-derived EF (WMSI-EF) against real-time 3D echocardiography\textsuperscript{4} and against 2D biplane EF (2D-EF);\textsuperscript{9} furthermore, we compared WMSI-EF with global longitudinal strain (GLS) by speckle tracking\textsuperscript{8} as a surrogate measure of LV systolic function independent of the estimation of LV volumes and sensitive to segmental wall motion abnormalities.\textsuperscript{9}

**Methods**

**Patients**

We selected randomly patients with a variety of clinical conditions to obtain a large range of LV EF. For this purpose, we enrolled patients from the Unit of Cardiology of the ‘Ospedale dei Pellegrini—ASL Napoli 1’. All patients had stable clinical conditions. Outpatients were selected from those with stable coronary heart disease, or chronic congestive heart failure, or those clinically normal but with arterial hypertension and referred for echocardiography. In-hospital patients were selected among those admitted for acute coronary syndrome or acute congestive heart failure. Although patients’ screening was consecutive, recruitment was random according to the need for comprising a wide span of possible EF values and including patients with a variety of regional wall motion abnormalities (apical, inferior, anterior, with LV aneurysm). Feasibility was computed as the ratio between rejected/accepted cases based on quality of echo-views and confidence of operator to provide appropriate imaging.

**Echocardiography**

Methods used for LV chamber quantification have been published previously\textsuperscript{1,10–12} following current recommendations.\textsuperscript{2,13} An index of LV sphericity was derived by the ratio between LV long axis (from LV apex to the mitral annular plane in apical views) and LV internal diastolic diameter, with higher values indicative of more spherical ventricles in diastole. Mitral and aortic regurgitations were classified as mild, moderate, and severe according to the vena contracta width method\textsuperscript{14} in addition to the methods described previously.\textsuperscript{15,16}

Assessment of WMSI was performed using a 16-segment model of the left ventricle. Regional wall motion was evaluated using orthogonal views from apical and parasternal long and short axis and based on effective segmental radial thickening. An initial testing population of 10 subjects (not comprised in the present sample, Simpson’s method based EF 18–78%) was used for training purpose (4 weeks) to standardize judgment of wall motion score measuring relative %

<table>
<thead>
<tr>
<th>Segment contractility status</th>
<th>Score assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal kinesis</td>
<td>4</td>
</tr>
<tr>
<td>High-normal kinesis</td>
<td>4.5</td>
</tr>
<tr>
<td>Hyperkinetic</td>
<td>5</td>
</tr>
<tr>
<td>Low-normal kinesis</td>
<td>3.5</td>
</tr>
<tr>
<td>Mildly hypokinet ic</td>
<td>3</td>
</tr>
<tr>
<td>Moderately hypokinetic</td>
<td>2.5</td>
</tr>
<tr>
<td>Severely hypokinetic</td>
<td>1.5</td>
</tr>
<tr>
<td>Akinetic</td>
<td>0</td>
</tr>
<tr>
<td>Dyskinetic</td>
<td>−1</td>
</tr>
</tbody>
</table>

See Methods section for details.
and from the postero-lateral to the antero-lateral mitral annular corners in apical long-axis views, passing through the apex in all cases (TomTec 4D LV analysis V 2.0). An automated border detection followed the endocardium throughout the whole cardiac cycle; subsequently a frame-by-frame point-and-click correction was manually performed by the operator to adjust the tracking of the endocardium for all segments. EF was derived from the quantification of the EDV and end-systolic volume (ESV) automatically identified as the largest and the smallest LV volumes. For 3D-EF, biplane LV planimetry at end-systole and end-diastole was obtained from apical four- and two-chamber views; LV EDV and ESV were calculated by modified Simpson’s rule, and EF was derived as 100 × (EDV – ESV)/EDV. End-diastole was identified by the onset of the QRS complex, whereas the end-systole was identified by playing cine-loops 1–2 frames backward from the first frame of the anterior movement of the mitral annular plane, resolving the matter of the identification of the smallest LV volume in the context of patients with dysynchrony/dyssnergy.

GLS was assessed by speckle-tracking analysis based on gray-scale view from apical four-, two-, and long-axis chamber views (GE Echopac workstation version 7.0.1) by the methods reported previously in detail.8,12,26

Statistical analysis
Data in table are mean ± standard deviation or percent when indicated. Statistical analyses were performed using SPSS® (release 15.0). Intraclass correlation coefficients (ICC) and their 95% confidence intervals (CI) were estimated using a two-way random effect and absolute agreement method for continuous variables. Kappa statistic was used for categorical variables. Regression analysis was used to estimate the unstandardized residuals of the regression of WMSI over 3D-EF, to be subsequently correlated with age, sphericity index and LV volumes to investigate conditions able to affect the reliability of WMSI method for the estimation of EF. A P < 0.05 was considered for statistical significance.

Results
Clinical characteristics and main echocardiographic data of the study population are reported in Table 2. Feasibility was 78%; most frequent causes for case rejection were: full WMSI not assessable lack of identification of clear endocardial border in apical and/or in anterior segments. Severe chronic obstructive pulmonary disease and body mass index > 30 kg/m² were the two clinical conditions more often associated with case rejection. ICC showed that agreement between EF estimated by WMSI and by 3D was high and substantially equivalent to the reliability of the more popular 2D vs. 3D methods (Table 3).

In Bland–Altman plots, 3D-EF vs. WMSI-EF showed a between-method difference of approximately −0.3% (Figure 1) and 95% CI of the difference was comprised between ±10%. 2D method tended to yield EF values slightly higher than those obtained by WMSI method (mean difference between the two methods 2%, 95% CI −10 to 13%). For reference, 2D method tended to yield EF values higher than those obtained by 3D-EF, with mean between-method difference of 2%, 95% CI −9 to 14%.

No cases of normal EF by WMSI were re-coded as having EF > 35% by 3D method (k = 0.84, P < 0.01).

WMSI-EF showed a significant correlation with GLS (Figure 2A), with a coefficient of determination (r²) comparable to that observed between 3D-EF vs. GLS (Figure 2B). Mean GLS and its 95% CI were −20.2% (−18.8%−21.7%) in patients with normal WMSI-EF, whereas it was −6.9% (−5.3%−8.4%) in those with WMSI-EF ≤ 35% (P < 0.001); similar results were found for GLS by 3D EF categories (3D-EF ≥ 50%: mean GLS = −20.1 (95% CI −18.4%−21.6%); 3D-EF ≤ 35%: mean GLS = −6.1% (−4.4%−7.7%) (both P > 0.1 for paired comparisons).

Intra-observer reproducibility data (V,P, on 10 cases selected randomly) were consistent with previous experience11: 3D-EF: ICC 0.95, 95% CI 0.87–0.97, mean EF 45% at reading 1 and mean EF 43% at re-reading 1, between reading difference 2% with 95% CI −10/+8%; 2D-EF: ICC 0.96, 95% CI 0.86–0.98, between reading difference 1% with 95% CI −12/+10%; WMSI derived EF: ICC 0.93, 95% CI 0.86–0.97, mean EF 45% at reading 1 and mean EF 43% at re-reading 1, between reading difference 1% with 95% CI −11/+10%. Inter-observer reproducibility data (V,P, on C.S., on 10 cases selected randomly) were also consistent with previous experience:11 3D-EF: ICC 0.90, 95% CI 0.82−0.95, mean EF 45% by reader 1 and mean EF 42% by reader 2; WMSI derived EF: ICC 0.88, 95% CI 0.78–0.94, mean EF 44% by reader 1 and mean EF 43% by reader 2.

Unstandardized residuals of the regression of 3D-EF on WMSI-EF were not related to mean EF, LVIDD, LV sphericity...
Discussion

In the present study, we validated a novel method for rapid assessment of LV EF using WMSI. Our method is based on the concept that each segment of the LV contributes to systolic LV cavity reduction, and therefore to global EF, and does not rely on LV volumes estimation. Accuracy of WMSI method was satisfactory when compared with real-time 3D method (i.e. reliability of WMSI method). In addition, WMSI and real-time 3D showed comparable correlations vs. GLS, a method of estimation of LV chamber contractility independent to LV volumes and sensitive to wall motion abnormalities.\(^{27}\) This information further validates independently the WMSI score system. Since WMSI-EF appears to be accurate, it has the potential to provide prognostic information as much as EF estimated by more traditional (Simpson’s rule) or new technology (real-time 3D).\(^{1}\)

Our results are in line with the previous reports which validated the concept of estimating LV EF by WMSI.\(^{6,7,28}\) However, all previous studies relied on the method of regressing traditional WMSI on reference EF values derived by nuclear medicine to develop equations to predict EF from computed WMSI.\(^{6,7,28}\) We added a novel, simpler approach, validated the segmental score system using three distinct reference methods, and avoided statistical issues associated with the regression method such as assumption of linear relationship between reference and testing variables.

Our method has intrinsic advantages. In fact, it does not require LV area planimetry to estimate EF, uses live wall motion evaluation as opposed to still frames, and it takes therefore advantage of the full range of obtained frame rate. Moreover, for WMSI, each segment is evaluated in several orthogonal views (parasternal long and short, apical views), whereas by LV planimetry, endocardium of each segment is visualized only in one view. Commonly, especially in relatively old echocardiographic machines, frame-stop determines some image quality degradation with inevitable problems for endocardial border identification. Those factors may help explaining relatively high reproducibility of the WMSI method. On a different matter, while in the present study feasibility was \(\sim 80\%\), in line with data reported by others,\(^{4}\) because recruitment process required WMSI, 3D and Simpson’s derived EF, and GLS to be all available, in our clinical practice, WMSI is reported in 92% of the studies, and Simpson’s EF was performed in \(\sim 84\%\) of the echocardiographic studies in the laboratory. Feasibility of real-time 3D echocardiography was 87%.

The difference between 3D and WMSI methods for the assessment of EF increased with severity of mitral regurgitation. The result was independent to age, body size, LV volume, and EF itself. More severe mitral regurgitation was associated with lower EF independent of the method used for estimating LV chamber function (3D, Simpson’s rule, WMSI, data not shown). Thus, because the difference between WMSI-EF and 3D-EF was in the negative territory with more severe mitral regurgitation, it
of confidence of readers was increased by assessing LV volumes on resonance imaging. We cannot exclude completely that the level of GLS. 3D method has been validated against magnetic nuclear resonance, but validated WMSI-EF vs. 3D echocardiography and We did not use a non-echocardiographic method for EF estimation during the training period to standardize WMSI and reduce inter- and intra-observer variability may be considered arbitrary. However, the % of wall thickening has been used in a variety of previous studies and was reported to be inversely related to diastolic wall thickness in subjects without coronary heart disease. In a populations of hypertensive and normotensive healthy subjects without coronary heart disease from our laboratory, the % thickening was related inversely to diastolic wall thickness (IVS: $r = -0.25$, PWT $r = -0.39$, both $P < 0.01$; V. Palmieri, personal communication).

Study limitations

We did not use a non-echocardiographic method for EF estimation, but validated WMSI-EF vs. 3D echocardiography and GLS. 3D method has been validated against magnetic nuclear resonance imaging. We cannot exclude completely that the level of confidence of readers was increased by assessing LV volumes using 3D and GLS, influencing therefore the performance of regional wall motion score assessment. The random sequence of readings was implemented to avoid such a potential bias. Nevertheless, the training period, used to cross-check the capability of readers to be consistent in judging segmental contractility, and set the standard for WMSI, may have determined at least in part our results. If this is the case, it may actually demonstrate that new technologies may improve reliability of traditional procedures with a wide clinical impact. GLS by speckle-tracking analysis provides a more objective method of LV function assessment, because independent of in-plane translation and recording angle. However, GLS by speckle tracking also has a number of limitations associated with noisy images; in addition, intra-myocardial echocardiograms (speckles) being tracked may be affected significantly by random phenomena and their consistency between frames may be not consistent. Our data are based on single reader (V.P.), who was the final arbiter. However, even considering data from the first reader (C.R.), reliability performance of WMSI-EF did not deteriorate significantly (ICC of WMSI-EF vs. 3D-EF 0.90, 95% CI 0.82–0.95). Thus, further studies are needed to assess the extent to which inter-observer variability may impact on reliability of WMSI for the assessment of EF. Use of % wall thickening during the training period to standardize WMSI and reduce inter- and intra-observer variability may be considered arbitrary. However, the % wall thickening has been used in a variety of clinical conditions.

Conclusions

Well-trained operators may use WMSI for rapid assessment of global LV EF without the need for the assessment of LV volumes and complex processing. After a well-structured learning phase using different modalities for a standardized evaluation of LV regional wall motion contractility, this method may contribute to a reliable bedside assessment of LV systolic performance in a variety of clinical conditions.

Conflict of interest: none declared.

References

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