Background—The sequence of left ventricular (LV) systolic emptying is not completely understood. Using real-time 3-dimensional echocardiography, we investigated this sequence and LV synchronicity in physiological and pathological conditions.

Methods and Results—The study population consisted of 116 healthy volunteers, 20 top-level athletes, 35 patients with LV dysfunction, and 84 patients with LV dysfunction and left bundle-branch block (LBBB). We subdivided the LV into 16 volumetric segments for regional analysis and into apical, middle, and basal regions to calculate the mean of end-systolic times and the time to minimum systolic volume of each region. In healthy volunteers and in top-level athletes, the emptying systolic times increased smoothly from apex to base. These differences determined an apex-to-base time gradient in the LV emptying sequence. In patients with LV dysfunction and without LBBB, this gradient was maintained with a relatively higher LV dyssynchrony. However, in patients with LV dysfunction and LBBB, there was no clear sequence in LV emptying volumes, and this group had the highest LV dyssynchrony.

Conclusions—Real-time 3-dimensional echocardiography tomographic slicing of the LV enables accurate analysis of LV emptying in physiological conditions and in conditions of LV dysfunction with and without electrical dyssynchrony. Progressive dilation of LV produces deterioration in LV synchronicity. However, it is the presence of LV dysfunction in combination with LBBB that determines the loss of the apex-to-base time gradient in LV emptying. (Circ Cardiovasc Imaging. 2008;1:41-49.)

Key Words: arrhythmia ■ echocardiography ■ heart failure ■ remodeling
Clinical Perspective see p 49

The introduction of real-time 3-dimensional (3D) echocardiography has allowed evaluation of the magnitude of spatial and temporal changes in global and regional volumetric LV function.18–21

In this study, we investigated (1) the sequence of LV systolic emptying in normal individuals and in top-level athletes; (2) the effect of LV dysfunction on LV systolic emptying; (3) the effect of LV dysfunction and electrical dysynchrony in LV systolic emptying; and (4) the distribution of dysynchrony, in regional volumetric terms, in all sample subjects. To do so, we divided the LV into 3 major annular tomographic regions (apical, middle, and basal) using a real-time 3D echocardiography machine equipped with commercially available software.

Methods

The study was performed at 2 centers: La Sapienza University Hospital, Rome, Italy, and the Cardiocentro Ticino, Lugano, Switzerland. All subjects gave written informed consent for the study. The research ethics committees of the centers approved the study. The authors had full access to the data and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Study Population and Patient Selection

The study population consisted of 267 selected subjects: 116 healthy volunteers; 22 top-level athletes; 39 patients affected by LV dysfunction and narrow QRS; and 90 patients affected by LV dysfunction and LBBB. Selection criteria and classification were based on clinical history, blood pressure, clinical examination, ECG, and 2D/Doppler echocardiographic studies.

The 116 healthy volunteers (75 men) satisfied the following criteria: normal physical examination, normal blood pressure (<135 mm Hg and <80 mm Hg), normal ECG findings, no history of chest pain and dyspnea, no diabetes, and normal 2D echocardiographic and Doppler examination. None of the subjects was on medication. Subjects with evidence of heart disease, hypertension, or other systemic disorders were excluded. The 22 top-level athletes were professional soccer players in the Italian first division (who train at least 20 h/wk). Within the LV dysfunction and narrow QRS group, 40% of the patients had been diagnosed with ischemic dilated cardiomyopathy and 15% with idiopathic dilated cardiomyopathy. Within the LV dysfunction and LBBB group, 71% patients were diagnosed with ischemic dilated cardiomyopathy and 19% with idiopathic dilated cardiomyopathy. Twenty-nine of 129 LV dysfunctional patients with and without LBBB had a history of myocardial infarction. All patients had undergone coronary angiography and/or multislice CT scan within the previous 6 months. The diagnosis of dilated cardiomyopathy was based on M-mode and 2D/Doppler echocardiographic examination demonstrating an end-diastolic diameter >3.2 cm/m² and LV ejection fraction (LVEF) <40%.22 Idiopathic dilated cardiomyopathy patients had normal coronary arteries, whereas ischemic patients had had a documented abnormal coronary angiography and/or multislice computed tomographic scan. General exclusion criteria were any of the following: atrial fibrillation, poor echocardiographic acoustic window, or significant mitral or aortic regurgitation (>2+/4+).

Two-Dimensional Echocardiography

Two-dimensional echocardiography was performed by 2 expert cardiologists using commercial ultrasound machines (Sonos 7500 or i.E33, Philips Medical Systems, Andover, Mass) with an S5 probe (2 to 4 MHz). A complete examination of each subject included 2D and Doppler analysis. The LVEF was estimated in 4- and 2-chamber windows by the modified Simpson’s method.33

Three-Dimensional Echocardiography

Real-time 3D echocardiography was performed by 2 expert cardiologists using an i.E33 Live 3D echo (Philips Medical Systems) equipped with the X44 transducer. The acquisition time was recorded from the apical 4-chamber view. To encompass the entire LV cavity within the pyramidal scan volume, data sets were acquired by the wide-angled mode, whereby 4 or 7 wedge-shaped subvolumes (93°×21°) were acquired during a single breath hold. Acquisition of each subvolume was triggered by the ECG R wave of every heart beat. LV end-diastolic volume and end-systolic volume were evaluated with the use of semiautomatic frame-by-frame LV endocardial contours. These were corrected manually when necessary with 4-dimensional (4D) LV analysis 2.0 software (TomTec, Unterschleissheim, Germany). The papillary muscles were included in the LV cavity evaluation. The time taken for the offline quantitative analysis of the 3D data sets was also recorded.

Regional Volumetric Emptying and Synchronicity Analysis

All measurements were performed by 2 investigators experienced in the interpretation of cardiac images, who were blinded to each other’s results. Three-dimensional data were analyzed offline with the use of a contour-tracing algorithm over a complete cardiac cycle. Graphs displaying volumetric changes in the whole cardiac cycle were assessed on the basis of 3D data. Three-dimensional models of the LV were generated and subdivided into 16 volumetric segments for regional analysis so that the volume curves could be analyzed for the complete LV and for each segment individually. The surface patches of the LV cavity reconstruction were linked to the center of gravity of the 3D shell to create pyramidal-shaped regional volumes. A center of gravity was used that represented the average of the centers of gravity of all phases (Figure 1a).

After classification in a 16-segment model, displayed in a segmental bull’s eye map, each regional time-volume curve was analyzed throughout the cardiac cycle. Then the time to minimum systolic volume was measured from the onset of the cardiac cycle (Q wave of ECG signal) to the minimum volume for each segment. Subsequently, the LV segments were grouped into 3 major annular tomographic regions: basal (n=6), middle (n=6), and apical (n=4) (Figure 2). This was done to derive the following values for each of the selected segments: mean end-systolic time (MEST%) and time to minimum systolic volume and the standard deviation.

The systolic dyssynchrony index (SDI%) is a global parameter describing dyssynchrony of the whole ventricle. In our study, we used, in both global and in regional volumetric terms, a definition of SDI% as the standard deviation of the time taken to reach minimum systolic volume for each annular tomographic region. The differentiation between LV synchrony or dys synchrony was done on the basis of a cutoff value of 5%, as previously reported.24 All data were expressed as a percentage of the cardiac cycle length.

Three-Dimensional Echocardiography Validation Protocol

In 20 of 116 healthy volunteers, real-time 3D echocardiography and cardiac magnetic resonance (CMR) were performed, on the same day, to validate LV emptying analysis. CMR was performed with a commercially available 1.5-T scanner with highly performing gradients (Siemens Avanto; Siemens Medical Solutions, Erlangen, Germany) with the use of a phased-array cardiac coil and a vectorcardiographic gating system. ECG-gated turbo spin-echo images were initially acquired as anatomic reference during a 14-second breath hold to identify the horizontal long axis of the LV and to obtain...
images in 8 rotated planes around the long axis at 22.5° steps. Steady-state free-progression gradient-echo cine mode (repetition time 2 × RR interval, echo time 64, matrix 138 × 256, flip angle 60°) was then used to acquire dynamic cine loops (≈20 frames per cardiac cycle) of radial long-axis views of the LV (10-mm slice thickness; 1.4- to 1.8-mm in-slice resolution) and short-axis images covering the entire LV from the mitral valve plane to the apex (10-mm slice thickness, no gaps). All images were acquired during a 10- to 15-second breath hold and digitally archived to a picture archiving and computerized system and a DVD for offline analysis of LV function. The offline analysis was performed in 6 of the 8 acquired long-axis planes with the same algorithm and same software as for the 3D echo images with 4D LV analysis 2.0 (TomTec). The surface patches of the LV cavity reconstruction were linked to the center of gravity of the 3D shell to create pyramidal-shaped regional volumes. A center of gravity was used that represented the center of gravity of the 3D data set for performing LV analysis. The acquisition time was ≈8 seconds for each volume scan, and the LV global and segmental quantitative evaluation time was 10 to 20 minutes. Semiautomatic endocardial border LV detection was, in most cases, corrected manually. Offline tomographic regional analysis (basal, middle, and apical) of the LV required a prolonged evaluation time compared with a simple global LV functional evaluation, as previously reported.

Validation of 3D LV Emptying Analysis
Comparisons between 3D echo and MRI performed in 20 healthy volunteers showed very high agreement. The absolute difference for global LV MES% on the total 16 segments was −2.3 (95% CI, −7.5 to 2.8), and for global LV SDI% it was −0.08 (95% CI, −0.75 to 0.60). For tomographic LV emptying, regional MES% analysis was −1.7 (95% CI, −7.2 to 3.9), −1.3 (95% CI, −7.0 to 4.4), and −1.2 (95% CI, −7.0 to 4.7) for the apical, middle, and basal regions, respectively. For LV emptying, regional SDI% analysis was 0.48 (95% CI, −0.29 to 1.25), −0.13 (95% CI, −1.04 to 0.77), and 0.37 (95% CI, −0.78 to 1.54) for apical, middle, and basal regions, respectively.

Interobserver and Intraobserver Variability
Fifty healthy volunteers, with adequate acoustic windows, were selected for reliability analysis for SDI% and MES% measures. As Figure 3 shows, the Bland-Altman analyses yielded an excellent agreement with a mean ± SD difference for intraobserver SDI and MES of 0.02 ± 0.44 and 0.34 ± 0.92, respectively, and with a mean ± SD difference for interobserver SDI and MES of −0.04 ± 0.52 and −0.11 ± 0.97.

Global LV Function
As expected, healthy volunteers and the top-level athletes were younger than LV dysfunctional patients with and without LBBB (Table 1). Compared with healthy volunteers, the global end-diastolic volume and end-systolic volume rose gradually from top-level athletes to LV dysfunctional patients without LBBB (P < 0.001) and with LBBB (P < 0.001). With regard to the value of global LVEF, there was no significant difference between healthy volunteers and top-level athletes, whereas there was, as expected, a significant difference in LV dysfunctional patients with and without LBBB (P < 0.001). In
Figure 2. LV regional volume-time curves (right) showing time to minimum systolic volume for the 3 major annular tomographic regions.
terms of stroke volume, there was an increase in the value for top-level athletes in comparison with healthy volunteers, and there was a significant decrease in that of the other groups. The comparison between LV dysfunctional patients with and without LBBB did not show any difference in terms of end-diastolic volume, end-systolic volume, and stroke volume except for a mild reduction in EF in those with LBBB.

The MES% of 16 segments was lower, but not significantly so, in top-level athletes than in healthy volunteers (Table 2). Compared with the latter, the value for LV dysfunctional patients without LBBB was higher but not significantly so, whereas the value for the LV dysfunctional patients with LBBB was significantly higher ($P<0.001$).

The SDI% value of 16 segments was similar between healthy volunteers and top-level athletes, whereas it was significantly higher for both groups of LV dysfunctional patients (with the highest value for those with LBBB; $P<0.001$).

There was a highly significant negative correlation between SDI% and EF% ($r=-0.79; P<0.001$) even after adjustment for age and sex (age- and sex-adjusted $t$ statistics, $-9.48$). On regression analysis, 72% of the SDI% variability was explained by LBBB, history of myocardial infarction, and EF. In particular, the presence of LBBB, myocardial infarction, and a 10% decrease in EF were associated with a 4.3-fold (95% CI, 3.35 to 5.22), 1.78-fold (95% CI, 0.64 to 2.72), and 1.14-fold increase in SDI%, respectively.

### Table 1. Summary Data

<table>
<thead>
<tr>
<th></th>
<th>(1) Healthy Volunteers $(n=116)$</th>
<th>(2) Athletes $(n=20)$</th>
<th>(3) Without LBBB $(n=35)$</th>
<th>(4) With LBBB $(n=84)$</th>
<th>(2) vs (1)</th>
<th>(3) vs (1)</th>
<th>(4) vs (1)</th>
<th>(4) vs (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>45.3±16.2</td>
<td>23.5±6.8</td>
<td>52.9±17.7</td>
<td>67.8±9.8</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (male), n(%)</td>
<td>75 (64.7)</td>
<td>20 (100)</td>
<td>25 (71.4)</td>
<td>66 (78.6)</td>
<td>&lt;0.001</td>
<td>0.543</td>
<td>0.041</td>
<td>0.478</td>
</tr>
<tr>
<td>End-diastolic volume, mean ± SD, mL</td>
<td>98.4±27.3</td>
<td>127.6±30.1</td>
<td>162.2±39.6</td>
<td>173.1±61.4</td>
<td>0.055</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.732</td>
</tr>
<tr>
<td>End-systolic volume, mean ± SD, mL</td>
<td>40.0±12.7</td>
<td>52.2±13.8</td>
<td>110.8±34.7</td>
<td>118.6±47.0</td>
<td>0.453</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.674</td>
</tr>
<tr>
<td>Stroke volume, mean ± SD, mL</td>
<td>58.8±15.8</td>
<td>75.8±19.0</td>
<td>51.4±11.8</td>
<td>47.0±15.8</td>
<td>0.001</td>
<td>0.158</td>
<td>0.002</td>
<td>0.678</td>
</tr>
<tr>
<td>EF, mean ± SD, %</td>
<td>59.2±4.5</td>
<td>59.4±4.3</td>
<td>32.7±7.9</td>
<td>29.1±7.5</td>
<td>0.999</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.035</td>
</tr>
</tbody>
</table>
tolic volume, the mean end-systolic time, and the standard
available software to extrapolate the time to minimum sys-
tolic volume, the mean end-systolic time, and the standard
device of each LV regional volumetric region. Nesser et al.\textsuperscript{26} confirmed the validity of using such software through their analysis of regional volumetric assessment of the LV by real-time 3D echocardiography and CMR.

Our study is the first on the human heart using regional volumetric analysis by real-time 3D echocardiography that demonstrates that, in healthy volunteers and in top-level athletes, there is a peristaltic emptying of the LV from the apex to the base. These data confirm what logic would suggest, ie, there is a proper sequence with a regular time gradient that determines the correct and efficacious emptying of the LV, moving the blood from the apex to the aortic valve.

We also evaluated the influence of LV global function in all groups. The expected progressive increment in mean end-systolic time, to time to minimum systolic volume, and standard deviation from top-level athletes to LV dysfunctional patients with LBBB confirms the usefulness of this technique in evaluation of LV function. Although the normal ventricle works in an efficient manner to distribute stress and strain uniformly, an altered ventricle resulting from cardiac remodeling, regional myocardial dysfunction, or asynchronous conduction determines wall motion abnormalities, which are responsible for the degradation of the synchronicity of LV emptying.

Although LV dysfunctional patients without LBBB maintain the apex-to-base time gradient, in the presence of an increased SDI\%, the extended emptying time for the basal compared with the apical and middle regions may indicate a progressive deterioration in LV systolic performance. This may reasonably lead us to suppose that, in altered LVs, the basal regions require more time to empty their already major volume of blood than do the other regions. We found the same basal/middle region extended emptying time in LV dysfunctional patients with LBBB. It is precisely the presence of the electrical dyssynchrony that is responsible for the delay in the activation of the apical segments, as shown by the higher value of SDI\% for patients with LBBB than for those without LBBB. The information pertaining to LV dysfunction and LBBB patients confirms that, in the presence of electrical dyssynchrony, some LV regions delay their contracting motion, resulting in an uncoordinated and irregular LV emptying. They produce an increased ejection time, a reduced stroke volume, and an inefficient expulsion dynamic. As regression analysis of our data shows, LBBB is the main factor in determining an increased dyssynchrony index (SDI\%) and the loss of LV emptying sequence, followed by the presence of myocardial infarction and a reduced EF.

Furthermore, our study highlights another aspect that is the subject of much current research. It shows that, in the presence of electrical dyssynchrony, although all 3 tomo-
graphic regions are affected by mechanical dyssynchrony, the region most severely affected is the apical one. This finding is particularly important because no widely available/used techniques for assessing dyssynchrony can analyze the apical region. Doppler imaging has methodological limitations relating to its longitudinal velocity, and its strain and strain rate are prone to angle-related errors. Helm et al. using 3D MRI, demonstrated that longitudinal strains were less sensitive than circumferential strains as an indicator of dyssynchrony. Again, apical regions cannot be assessed by TDI because of the limited movement of the apex and unfavorable angle of incidence of apical myocardial motion with respect to the transducer position. Consequently, most investigators use a 2-, 6-, or 12-segment model for assessing intraventricular dyssynchrony.

Our study analyzed the regional volume-time curves of the LV but did not evaluate the whole myocardial motion in time sequence. This relatively easy 3D method provides informa-
tion for the timely and accurate assessment of LV emptying. This concrete result adds a simple technique to the range of procedures that analyze myocardial motion rather than LV volume emptying.

Assessment of mechanical activation and contraction by conventional imaging methods is complex. Although they provide high temporal resolution, TDI, strain, and strain rate present limitations because of the complex architecture of the myocardium. Sengupta et al. showed that differences in timing of contraction exist between segments and also between longitudinal and circumferential shortening within the same segment. Recently, 2D strain by speckle tracking has been used to overcome the limitations of Doppler-derived data. This new technique provides angle-independent information on motion and deformation in any direction of a cardiac coordinate system. It can analyze longitudinal and transverse strains by apical views and circumferential and radial strains in the parasternal short-axis plane. It can also evaluate LV torsion. Several studies have demonstrated its validity with sonomicrometry and tagged MRI.

The 2 most common MRI methods used by researchers for measuring myocardial motion are tagging and phase-contrast velocity mapping. The latter quantifies wall motion with a sensitivity comparable to implanted ultrasonic crystals and displays high correlation for myocardial velocities with TDI measurements in healthy volunteers. However, this technique is time consuming, is not widely available, and does not provide information on the LV emptying sequence.

The advantage of LV regional volumetric analysis using real-time 3D echocardiography consists of a reliable, straightforward, and reproducible assessment of the temporal sequence of LV emptying. This strengthens the case for using real-time 3D echocardiography because it enables volumetric assessment rather than resorting to parameters influenced by distortion and translation of LV wall motion. Indeed, a recent study, performed in healthy volunteers using different TDI procedures, demonstrated that systolic LV motion seemed to be significantly more synchronous in the radial direction than in the long axis. This confirms that assessment of mechanical synchronicity by conventional imaging methods is complex, considering the particular 3D pattern of ventricular contraction. For this reason, real-time 3D echocardiography has been used to quantify global LV mechanical dysynchrony in congestive heart failure patients with moderate to severe symptoms and substantial LV dysfunction.

Our study has some technical limitations. First, in 7 patients, we were unable to encompass the entire LV because of the extremely enlarged chamber. Second, there is the issue of a low frame rate, which is 16 to 20 Hz. However, the frame rate is the same as that accepted with CMR studies. To conduct offline 3D analysis, it is necessary to have optimal acoustic windows that guarantee clear definition of the LV endocardial borders. For this reason, we chose to select the study population because, in a daily clinical scenario, 20% of consecutive patients cannot be evaluated in a reproducible manner.

Despite a low temporal resolution, we consistently found a time gradient from the apical to the middle and basal regions in the healthy volunteers and top-level athletes.

With regard to apex-to-base LV emptying analysis, our research is still ongoing. This first stage has shown that it is a feasible and validated technique that provides information on physiopathological changes in LV function. In the current stage of our research, we are applying this analysis in end-stage heart failure patients who can benefit from resynchronization therapy.

Conclusions

Three-dimensional tomographic analysis of the LV enables accurate analysis of LV emptying in physiological conditions and in those of LV dysfunction with and without electrical dys synchrony. Progressive dilation of LV produces deterioration in LV synchronicity. However, it is the presence of LV dysfunction in combination with LBBB that determines the loss of the apex-to-base time gradient in LV emptying. Determination of whether this gradient could be utilized as an index for optimizing selection of candidates or whether patients can recover the normal temporal sequence of LV emptying after cardiac resynchronization therapy is a long process that requires considerable effort in terms of patient selection, data collection and analysis, and proper follow-up. Real-time 3D echocardiography is a relatively simple procedure and a robust method for investigating global and regional LV dynamics.

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Disclosures

None.

References

Detailed understanding of left ventricular (LV) functional dynamics has become more important as new options to treat LV dysfunction become available. We performed a study, using real-time 3-dimensional echocardiography, investigating the time gradient of LV emptying in the axial direction during systole in a large sample of normal individuals and in LV dysfunctional patients with and without left bundle-branch block. We demonstrated that, in physiological conditions, there is a proper sequence with a regular time gradient that determines the correct and efficacious emptying of the LV, moving the blood from the apex to the aortic valve. Conversely, progressive LV dilatation and the presence of LV electrical dys synchrony produce delay, resulting in uncoordinated and irregular LV emptying. These conditions determine an increase in the ejection time, a reduction in stroke volume, and an inefficient expulsion dynamic. The presence of left bundle-branch block is the main factor in determining an increased dys synchrony index and the loss of LV emptying sequence. This study demonstrates that real-time 3-dimensional echocardiography is a feasible and validated technique that can provide new and clinically relevant information on physiopathological changes in LV function. We believe that this type of analysis may be useful in evaluating patients in end-stage heart failure who might benefit from resynchronization therapy or in assessing the effects of different therapeutic strategies on LV performance.
Tomographic Left Ventricular Volumetric Emptying Analysis by Real-Time 3-Dimensional Echocardiography: Influence of Left Ventricular Dysfunction With and Without Electrical Dyssynchrony

Stefano De Castro, Francesco Faletra, Emanuele Di Angelantonio, Cristina Conca, Andrea Marcantonio, Marco Francone, Domenico Cartoni, Francesca Mirabelli, Carlo Gaudio, Stefano Caselli, Iacopo Carbone, Angelo Auricchio and Natesa G. Pandian

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