# Incremental value of advanced cardiac imaging modalities for diagnosis and patient management : focus on real-time three-dimensional echocardiography and magnetic resonance imaging

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# CHAPTER 5

## Usefulness of multimodality imaging for detecting differences in temporal occurrence of left ventricular systolic mechanical events in healthy young adults

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## ABSTRACT

**Objectives:** Detailed information about the absolute temporal occurrence of myocardial motion and deformation events during the cardiac cycle is still lacking. However, the normal time-range of these parameters may be of great importance as a reference for detecting and interpreting mechanical dyssynchrony and for identifying a delayed contraction in case of left ventricular (LV) dysfunction. The aim of this study was to determine in young healthy subjects and for different LV segments the value of: 1) time to peak systolic longitudinal velocity, displacement, strain rate and strain, using tissue Doppler imaging (TDI); 2) time to minimum systolic volume, using real-time three-dimensional echocardiography (RT3DE) and 3) time to maximum thickness, using cardiac magnetic resonance imaging (MRI).

**Methods:** A total of 20 young healthy volunteers (13 men, mean age 32±4 years) underwent both cardiac MRI and echocardiografic examination, including TDI and RT3DE. To define LV ejection time and isovolumic relaxation time (IVRT), aortic valve closure and opening and mitral valve opening were identified.

**Results:** For all LV segments, longitudinal peak systolic velocity and strain rate were early-systolic events. Peak systolic longitudinal displacement and strain, in turn, occurred in the late systole or, in 20-30% of LV segments, during IVRT, similarly to minimum systolic volume and maximum myocardial thickness.

**Conclusions:** The current study provides a systematic report of the normal time-range of the measurements obtained by TDI, RT3DE and cardiac MRI. Peak systolic longitudinal velocity and strain rate significantly precede peak longitudinal displacement, strain, minimum systolic volume and maximum thickness.

## INTRODUCTION

Tissue Doppler imaging (TDI) has been extensively applied for the assessment of left ventricular (LV) dyssynchrony [1] and systolic function [2–4]. Measurements were mainly based on myocardial velocities [4–7] (expression of myocardial motion), but also on strain and strain rate imaging (which evaluate myocardial deformation) [3,8,9]. A systematic description of the normal temporal occurrence of myocardial motion and deformation events has not been reported. However, this information would be of great interest to better interpret LV dyssynchrony and to define when a segment has a delayed contraction [10–12]. Real-time 3-dimensional echocardiography (RT3DE) has also been proposed as a novel technique for the assessment of LV dyssynchrony and systolic function, based on the analysis of regional volumetric changes [13]. Also for this technique, the normal values of the time taken to reach the minimum systolic volume are not known. This may be of clinical importance for comparison with other imaging techniques. Similarly, cardiac magnetic resonance imaging (MRI) provides accurate information on myocardial deformation (as myocardial thickness) [14], but the normal time-values of this measure have not been extensively explored [15]. Accordingly, the aim of this study was to determine the value of time to peak systolic velocity, strain rate, displacement, strain, minimum systolic volume and maximum thickness for different LV segments, in young healthy subjects using the various techniques.

## METHODS

A total of 20 young healthy volunteers (13 men, mean age 32±4 years) underwent, on the same day, both cardiac MRI and an echocardiografic examination, including TDI and RT3DE. All subjects gave informed consent and the protocol was approved by the institutional review board. No subject had a history of cardiac disease or cardiac symptoms and all of them were

**Table 1.** Baseline characteristics of the study population (n = 20).

| | |
|---|---|
| Age (years) | 32±4 |
| Gender (male/female) | 13/7 |
| Body surface area (m2) | 1.86±0.14 |
| Heart rate (bpm) | 63±10 |
| Diastolic function | |
| E/A | 1.7±0.2 |
| Deceleration time (ms) | 163±20 |
| Left ventricular ejection fraction (%) | 63±2 |
| Left ventricular end-diastolic volume (ml) | 102±18 |
| Left ventricular end-systolic volume (ml) | 38±8 |

normotensive and in sinus rhythm. The resting electrocardiogram (ECG) and the standard 2-dimensional echocardiographic examination were normal (Table 1).

Studies were performed using a commercially available system (Vingmed Vivid Seven, General Electric Healthcare, Horten, Norway) and a 3.5-Mhz transducer. Left ventricular end-diastolic and end-systolic volumes and LV ejection fraction were calculated from the conventional apical 2- and 4-chamber views using the biplane Simpson's technique. Peak velocity in early (E wave) and late (A wave) diastole of the transmitral flow was derived from conventional pulsed-wave Doppler imaging and the ratio was E/A calculated. To define LV ejection time and isovolumic relaxation time (IVRT), aortic valve closure (AVC) and opening (AVO) and mitral valve opening (MVO) were identified on pulsed-wave Doppler traces obtained from LV inflow and outflow tract and expressed as a percentage of the cardiac cycle.

Color Doppler TDI was superimposed on the underlying 2-dimensional grey-scale images (2-, 4- and 3-chamber apical views) to assess longitudinal myocardial regional function. Gain settings, filters and pulse repetition frequency were adjusted to optimize color saturation and to avoid any aliasing within the image. Sector size and depth were optimized for the highest possible frame rate (>150/s). At least 3 consecutive beats were recorded and the

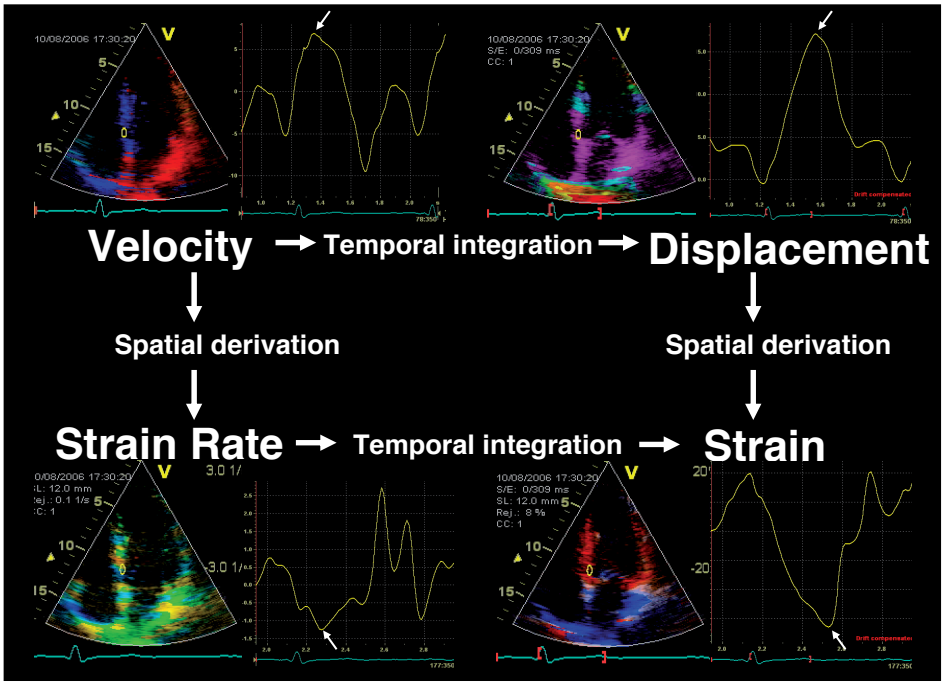


**Figure 1.** Examples of normal myocardial velocity, displacement, strain rate and strain curves obtained from the basal septum. The small arrows indicate the systolic peak of each curve. Myocardial displacement is obtained integrating velocity over time. Myocardial strain rate is the spatial derivative of velocity and can be integrated throughout systole to obtain strain [3].

images were digitally stored for off-line analysis (EchoPac, GE Vingmed Ultrasound, Horten, Norway). During post-processing, sample areas (8 x 5 mm) were placed at the level of 12 LV segments (basal and mid segments of the septum, lateral, inferior, anterior, posterior and anteroseptal walls) and a semi-automated tissue tracking was used to maintain the sample area in the region of interest throughout the cardiac cycle. For each segment, assessment of regional myocardial velocity, displacement, strain and strain rate were performed. Time from R wave (from the ECG signal) to peak systolic longitudinal velocity (Ts), displacement (Td), strain rate (Tsr) and strain (Tϵ) were calculated (Figure 1) and expressed as a percentage of the cardiac cycle to take the possible difference in heart rate during the echocardiographic and MRI studies into account. In particular, whether peak systolic longitudinal velocity, displacement, strain rate and strain occur after the AVC was noted, and the time from AVC was measured.

Apical full-volume data sets were obtained in all subjects using the iE33 system (Philips Medical Systems, N.A., Bothell, Washington, USA) equipped with X3, fully sampled matrix transducer. Gain and compression were optimized to obtain a good image quality and scan line density was adjusted to ensure a complete capture of the LV (sector width = 90 x 90 degrees). Real-time sub-volumes were acquired from alternate cardiac cycles and combined to provide the larger pyramidal volume during 1 breath-hold. Frame rate was optimized (32 frames/sec) reducing the depth and acquiring a full-volume data set of 7 sub-volumes. RT3DE data sets were stored digitally and quantitative analysis was performed off-line using a semi-automated contour tracing algorithm (Q-Lab, version 5.0, Philips Medical Systems) over a complete heart cycle. After first identifying, with 5 reference points, the apex and mitral annulus on end-diastolic and end-systolic slices, a preconfigured ellipse is fitted to the endocardial border for each frame and manually adjusted as required. Three-dimensional (3D) model of the LV is generated and subdivided in 17 wedge shaped (apart from the apex) sub-volumes. For 12 volumetric segments (6 basal and 6 mid) the time taken to reach the minimum systolic

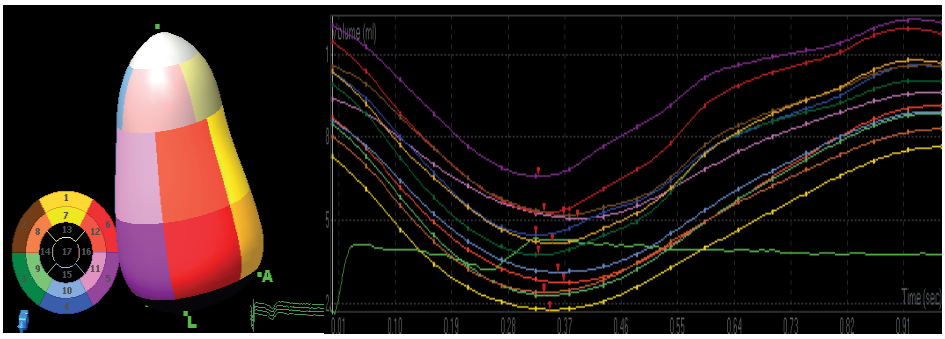


**Figure 2.** Three-dimensional model of a normal left ventricle (left panel) and time-volume curves derived from the 6 basal and 6 mid segments (right panel). The red dots identify the minimum systolic volume for each segment.

volume (Tmsv) from the R wave of the ECG was calculated (Figure 2). Furthermore, the time from AVC to the minimum systolic volume was assessed. To be comparable with the other imaging techniques, these timings were expressed as a percentage of the cardiac cycle.

MRI data acquisition was performed on a 1.5 T scanner (ACS-NT15 Intera, software release 11, Philips Medical Systems, Best, The Netherlands), using the body coil for transmission and a five element phased array cardiac-coil placed on the chest for signal reception. First, scout images and 2- and 4-chamber acquisitions were performed, needed for planning. A cine-set of 10-12 multi-slice images were acquired in short-axis orientation, covering the complete left ventricle from apex to base. Each slice was acquired in one single breath-hold. Steady-state free-precession was used for optimal image contrast. The following imaging parameters were used: slice thickness of the imaging planes = 10 mm, with no gap; Field-of-View = 350 mm (80% rectangular); scan matrix = 192 × 154, with reconstructed voxels of 1.37 × 1.37 × 8.0 mm; flip angle α = 50°; TR/TE = 3.3/1.7. One signal average was used. Gated cardiac synchronization was applied and 40 phases per cardiac cycle were reconstructed, yielding a temporal resolution of around 20 ms. From the complete short-axis dataset, 2 slices were selected representing the basal and mid-ventricular level and divided into 6 standard segments [16]. In these slices, epicardial and endocardial contours were manually drawn for all phases, using the QMass software package (Medis, Leiden, The Netherlands). For each segment, a radial wall thickness curve was plotted and the time from the R wave (and, in case of post-systolic peak thickness, from the AVC) to maximum wall thickness (Tt) was determined and expressed as a percentage of cardiac cycle (Figure 3).

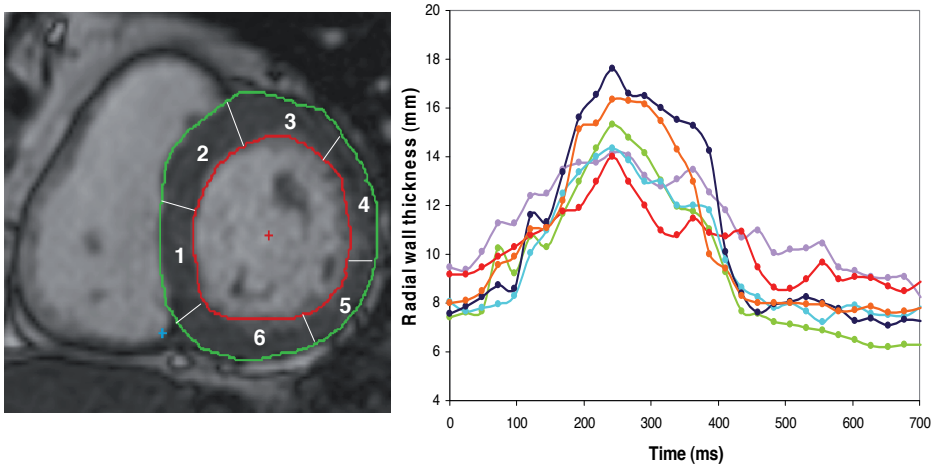


**Figure 3.** Example of the assessment of myocardial thickness using magnetic resonance imaging in a normal subject. In the slice representing the basal left ventricular level (left panel), epicardial and endocardial contours are drawn for all phases and the radial wall thickness curves for the 6 segments are plotted (right panel) to derive the time to maximum thickness.

Continuous data are presented as mean±SD; dichotomous data are presented as numbers and percentages. For multiple comparison between different LV segments and different timing parameters, parametric analysis of variance (ANOVA) was performed with Scheffe's post hoc analysis, after testing for normal data distribution (Kolmogorov-Smirnov test). The reproducibility of the TDI, RT3DE and MRI measurements was assessed by Bland-Altman analysis using the image dataset of 10 randomly selected subjects (120 segments): mean differences ±2SD are reported. Statistical significance was set at two tailed $p < 0.05$. A statistical software program SPSS 12.0 (SPSS Inc, Chicago, II, USA) was used for statistical analysis.

## RESULTS

### Tissue Doppler imaging

The mean Ts values for each LV segment are displayed in Table 2. The myocardial peak systolic velocity occurred for all the segments immediately after the AVO (= 7.5±6%, expressed as percentage of cardiac cycle) (Figure 4A) and no significant differences were found between the segments, although a trend toward an earlier Ts for the mid segments compared to the

**Table 2.** Mean segmental (12-segment model) values of time to peak systolic velocity (Ts), peak displacement (Td), peak systolic strain rate (Tsr) and peak strain (Tε) as derived from TDI. Also summarized are the mean segmental (12-segment model) values of time to minimum systolic volume (Tmsv) as measured by RT3DE and time to maximum thickness (Tt) as measured by MRI. The timings are expressed as a percentage of the cardiac cycle.

| | Ts (%) | Td (%) | Tsr (%) | Tε (%) | Tmsv (%) | Tt (%) | p-value (ANOVA) |
|---|---|---|---|---|---|---|---|
| Septal | | | | | | | |
| Basal | 11.3±2.3 | 34.0±5.9 | 11.3±2.4 | 35.4±7.1 | 35.4±4.8 | 33.2±7.2 | <0.001 |
| Mid | 10.9±2.1 | 34.3±6.0 | 10.5±2.5 | 35.1±6.2 | 34.5±5.4 | 31.8±5.1 | <0.001 |
| Lateral | | | | | | | |
| Basal | 10.9±1.8 | 33.1±4.5 | 11.3±2.1 | 33.9±5.7 | 35.6±5.1 | 32.2±4.4 | <0.001 |
| Mid | 10.7±1.9 | 33.0±4.2 | 10.5±1.9 | 33.3±4.9 | 34.5±5.6 | 32.0±5.2 | <0.001 |
| Inferior | | | | | | | |
| Basal | 10.7±1.7 | 33.6±5.3 | 11.0±1.7 | 33.8±6.7 | 35.5±4.8 | 34.6±4.9 | <0.001 |
| Mid | 10.4±1.5 | 33.9±5.1 | 10.3±1.8 | 33.7±6.0 | 34.1±5.1 | 33.1±4.6 | <0.001 |
| Anterior | | | | | | | |
| Basal | 10.4±2.2 | 33.1±4.9 | 10.4±2.2 | 32.9±6.0 | 34.3±5.6 | 31.4±3.6 | <0.001 |
| Mid | 10.1±1.8 | 33.3±4.3 | 10.0±1.7 | 33.6±4.4 | 34.3±4.0 | 31.3±4.5 | <0.001 |
| Posterior | | | | | | | |
| Basal | 10.9±1.9 | 33.7±5.5 | 11.0±2.2 | 35.0±6.2 | 35.8±5.0 | 35.5±5.0 | <0.001 |
| Mid | 10.4±1.6 | 33.5±5.4 | 10.5±1.6 | 34.4±5.7 | 34.7±5.7 | 33.5±4.5 | <0.001 |
| Anteroseptal | | | | | | | |
| Basal | 10.6±2.0 | 33.2±4.7 | 10.5±2.1 | 34.2±5.0 | 35.1±5.7 | 32.0±4.3 | <0.001 |
| Mid | 10.7±2.2 | 33.6±4.2 | 10.4±2.3 | 34.1±5.3 | 34.8±4.9 | 31.6±4.6 | <0.001 |

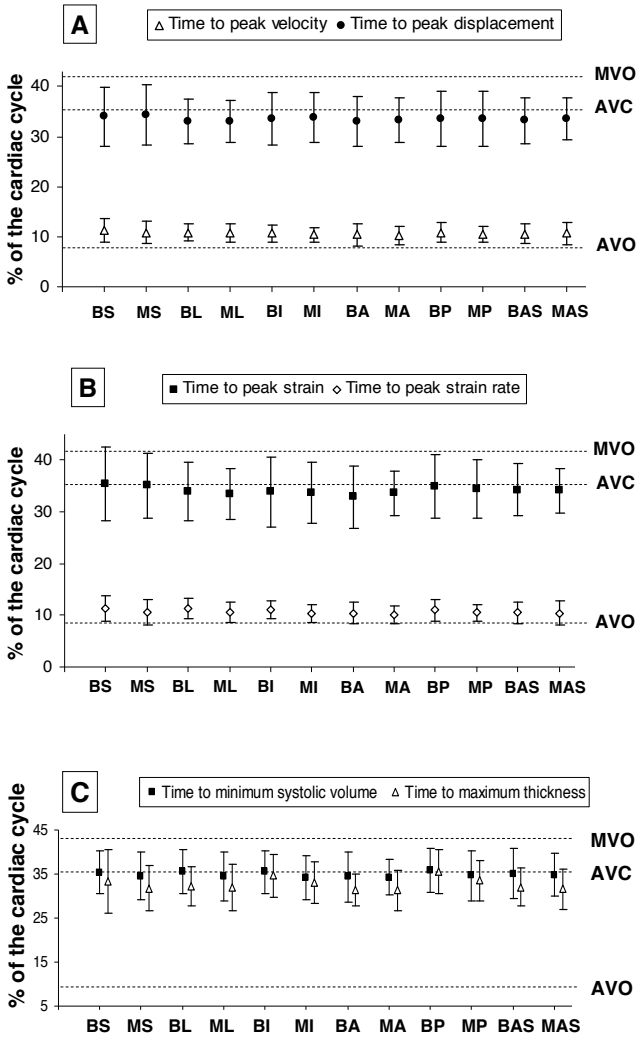


**Figure 4.** Distribution of time to peak systolic velocity and displacement (panel A) and time to peak systolic strain rate and strain (panel B), all measured with TDI, in relation to the aortic valve opening (AVO) or closing (AVC). Of note, MVO = mitral valve opening. In panel C, distribution of time to minimum systolic volume, measured with RT3DE, and time to maximum wall thickness, measured with MRI. Peak systolic velocity and strain rate are early systolic events, whereas peak displacement and strain occur late in systole. Likewise, minimum systolic volume and maximum myocardial thickness occur late in systole.

On the Y-axis, each of the 12 LV segments analyzed: BA = basal anterior; BAS = basal anteroseptal; BI = basal inferior; BL = basal lateral; BP = basal posterior; BS = basal septum; MA = mid anterior; MAS = mid anteroseptal; MI = mid inferior; ML = mid lateral; MP = mid posterior; MS = mid septum.

basal segments was noted. The intra- and inter-observer agreement for the Ts measurement, calculated on 120 segments, were good: 3±16 ms and 7±28 ms (p = NS), respectively.

The mean Td values for each LV segment are shown in Table 2 and were significantly different from the Ts values (p <0.001, post hoc analysis of ANOVA). Of interest, peak displacement occurred immediately before AVC (= 36.7±5.3%) or during the IVRT (before MVO = 41.2±5.9%) (Figure 4A). Out of 240 segments, 31 (13%) showed a peak displacement 9±6 ms (= 0.9±0.6% of the cardiac cycle) after the AVC. No significant differences for Td values were found between the LV segments (Table 2). The intra- and inter-observer agreement for the Td measurement (120 segments) were good: 2±18 ms and 1±46 ms (p = NS), respectively.

Table 2 shows the mean values of Tsr for each LV segment. Peak systolic strain rate occurred immediately after the AVO (Figure 4B). Subsequently, Tsr was similar to Ts (p = NS) and significantly different from Td (p <0.001, post hoc analysis of ANOVA). The intra- and inter-observer agreement for the Tsr measurement (120 segments) were good: 2±12 ms and 3±34 ms (p = NS), respectively.

Peak strain, in turn, occurred just before AVC or during the IVRT (Figure 4B). In particular, 43 (18%) out of 240 segments showed a peak displacement 16±10 ms (= 16±11% of the cardiac cycle) after AVC. The post hoc analysis of ANOVA revealed that Tε was similar to Td (p = NS) and significantly different (p <0.001) from Ts and Tsr (Table 2). The intra- and inter-observer agreement for the Tε measurement (120 segments) were good: 2±29 ms and 4±56 ms (p = NS), respectively.

No significant differences both for Tsr and Tε were found between the LV segments. However, Tsr and Tε tended to occur earlier in the mid compared to the basal segments (Table 2).

## Real-time three-dimensional echocardiography

Table 2 shows the Tmsv values for each LV segment. The minimum systolic volume has been reached before the AVC or during the IVRT (Figure 4C) and therefore Tmsv was similar to Td and Tε (p = NS) and significantly different from Ts and Tsr (p <0.001). Of interest, 75 (31%) out of 240 segments showed a minimum systolic volume 33±27 ms (34±27% of the cardiac cycle) after AVC. No significant differences were found between the LV segments for Tmsv, although Tmsv tended to occur earlier in the mid compared to the basal segments (Table 2). The intra- and inter-observer agreement for the Tmsv measurement (120 segments) were good: 1±11 ms and 1±42 ms (p = NS), respectively.

### Magnetic resonance imaging

The maximum myocardial radial thickness was reached before the AVC or during the IVRT (Figure 4C) and therefore Tt was similar (p = NS) to Td, Tε and Tmsv and significantly different (p <0.001) form Ts and Tsr. A total of 49 (20%) segments showed a maximum thickness 23±18 ms (24±18% of the cardiac cycle) after AVC. No significant differences were found between the LV segments, although a trend toward an earlier Ts for the mid segments compared to the basal segments was noted (Table 2). The intra- and inter-observer agreement for the Tt measurement (120 segments) were good: 1±10 ms and 2±33 ms (p = NS), respectively.

## DISCUSSION

The present study provides insight into the temporal occurrence of cardiac mechanical events in normal subjects using different imaging techniques. The main findings can be summarized as follows: 1) peak systolic velocity and strain rate are early systolic events; 2) peak displacement and strain occur in the late systole, similarly to minimum systolic volume, measured with RT3DE, and maximum myocardial thickness, measured with MRI.

Different imaging techniques, using either myocardial motion or myocardial deformation measurements, have been applied to evaluate LV function and more recently, to detect the time difference in mechanical events among different LV segments (in order to assess LV dyssynchrony for patients considered for cardiac resynchronization therapy) [4–9]. However, beyond the relative comparison between segments, the absolute temporal occurrence of myocardial motion and deformation events during the cardiac cycle has been reported only occasionally [17] and detailed information on the normal range of these timings is still lacking. Nevertheless, these values may be of great importance and are needed as a reference for detecting and interpreting mechanical LV dyssynchrony. Furthermore, these values may be helpful for identifying a delayed contraction in case of (subclinical) cardiac dysfunction.

The current study provides normal reference values for timing of the different phenomena occurring in cardiac systole. No significant differences in the time-occurrence of these phenomena were found among different LV segments, probably because of the limited temporal-resolution of these imaging techniques. However, the results highlight the difference between these different phenomena, namely that peak velocity and strain rate occur early in systole whereas the resultant action (displacement, strain, minimal LV volume, maximum wall thickness) occur late in systole.

Tissue Doppler imaging, because of the high temporal resolution, is one of the most suitable techniques to detect small differences in myocardial timings [4] and is currently one of the frequently used techniques to assess LV dyssynchrony. In particular, TDI can measure myocardial velocity and displacement (obtained by integration of velocity over time) that both

reflect myocardial motion, but also myocardial strain rate (as the spatial derivative of velocity) and strain (obtained by integration of strain rate over time), both reflecting myocardial deformation [3]. Other echocardiographic modalities, such as RT3DE [13], and non-echocardiographic imaging modalities, such as MRI [18;19], provide further possibilities to evaluate LV dyssynchrony in different manners. RT3DE measures LV regional volumetric changes during the cardiac cycle, reflecting myocardial motion. MRI provides accurate information on changes of regional myocardial thickness, reflecting myocardial deformation. Based on temporal delays in any of these parameters between different regions in the LV, dyssynchrony can be derived. Since these imaging modalities do not assess the same mechanical phenomena, these different echocardiographic and MRI approaches may not be entirely comparable. Only few studies performed a direct comparison between these different techniques. Burgess et al. [20] compared TDI and RT3DE for the assessment of LV dyssynchrony in heart failure patients and reported a poor agreement between the 2 techniques ($r = 0.11$). The different mechanical events and, more important, the different ventricular timings measured by these techniques may be potential explanations for these findings [20]. In normal subjects, as demonstrated in the current study, peak velocity and peak strain rate are reached in early systole, while peak strain, displacement, minimum systolic volume and maximum thickness are end-systolic events. The early-systolic phase of the cardiac cycle corresponds to the peak systolic ventricular pressure, while at the end of the systole and during IVRT, ventricular pressure rapidly declines. Furthermore, these phases of the cardiac cycle may be differently influenced by alterations of myocardial contractility and loading conditions [21]. LV dyssynchrony may therefore affect the abovementioned systolic measurements in a different way and a systematic report of the normal range of these timings for each modality would be of great importance as a reference. For example, Breithardt et al. [10] described in heart failure patients a significant delay between myocardial motion and deformation using TDI. The authors found that peak myocardial velocities significantly preceded (~ 90 ms) peak myocardial strain and suggested that this dissociation might be dependent on the degree of asynchrony and on the underlying disease (ischemic vs. non-ischemic cardiomyopathy). However, no references to normal values were reported to further interpret these findings. The present study provides these values and showed that, also in normal subjects, Ts consistently preceded Tε, although with greater difference (~ 200 ms). Furthermore, Tsr was also found to be significantly earlier than the measurements of total amount of deformation or motion (peak displacement, peak strain, miminum systolic volume and maximum thickness). Consequently, these measurements will not correlate well in direct comparisons, since they represent different parameters, occurring at different timings in systole; in contrast, these parameters may be combined to provide more solid information on LV dyssynchrony [22]. However, further studies, including normal subjects with older age and heart failure patients, are needed to confirm these results.

Cardiac MRI and TDI have been applied to obtain quantitative information on global and regional LV systolic function [2,3,14], avoiding the disadvantages of observer-dependent inter-

pretation. RT3DE has recently become available with the potential of similar application [23]. Beyond the absolute measure of the maximum motion and/or deformation of a LV segment, the time-analysis of these events might be helpful to further interpret myocardial (subclinical) dysfunction. The presence of myocardial dysfunction and/or conduction disturbances may in fact lead to an absolute delay of LV contraction with or without any intra-ventricular relative delay or significant reduction of the global contraction. Several studies proposed the presence of post-systolic (after AVC) shortening as a marker of myocardial dysfunction, mainly during acute/chronic ischemia or in case of myocardial scar [11,12]. In fact, this phenomenon may occur in dyskinetic segments as a passive mechanism, but can also occur in hypokinetic segments as a result of prolonged contraction (active process) or delayed relaxation, and therefore may be related to residual myocardial viability [11,12]. However, post-systolic shortening has also been described as a normal finding in healthy subjects in approximately 20-30% of LV segments [12]. In particular, Kowalski et al. [17] found in 40 normal subjects that both peak radial and longitudinal strain occur either during IVRT (20 to 60 ms after AVC) or shortly before AVC. Zwanenburg et al. [24] obtained similar results for peak circumferential strain. The present study further confirms these findings for peak longitudinal strain and broadened the analysis including measurements of other imaging modalities. Peak displacement, minimum systolic volume and maximum thickness were found to occur during IVRT in 20-30% of LV segments, as well. The precise physiologic basis of this phenomenon is not known but can be related to a reshaping of the LV cavity during IVRT that should facilitate LV filling phase [25]. The presence of post-systolic shortening, besides the technique used to detect it, can therefore not be considered pathognomonic for disease. Further studies are needed to confirm these findings in subjects with older age, in which this phenomenon might be even accentuated, and to compare normal individuals with different type of patients.

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