

How to Define End-Diastole and End-Systole?



Impact of Timing on Strain Measurements

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ABSTRACT

OBJECTIVES This study aimed to investigate to what extent timing definitions influence strain measurements and which surrogates are reliable and feasible to define end-diastole (ED) and end-systole (ES) during speckle-tracking (STI) analysis.

BACKGROUND Current STI-based strain measurements are highly automated. It remains unclear when a particular analysis software defines the zero baseline and the systolic strain measurement position.

METHODS A total of 60 subjects (20 healthy volunteers, 20 patients with coronary artery disease, and 20 patients with typical left bundle-branch block) underwent a complete echocardiographic examination. In one-half of them, a real M-mode through the mitral valve was acquired for each electrocardiographic (ECG) lead of the echo machine. Timing of peak R and automatic ECG trigger were compared with mitral valve closure for every electrode. Mitral and aortic valve closure, as observed in the apical 3-chamber view, served as reference for ED and ES. With the use of these references, end-systolic global longitudinal strain (ES-GLS) and end-systolic segmental longitudinal strain (ES-SLS) longitudinal end-systolic strain were measured at baseline and after changing the definition of either ED or ES by ± 4 frames. Furthermore, strain and volume curves derived from the same tracking, as well as the Doppler interrogation of the valves, were compared with the references.

RESULTS Depending on the selected lead, timing of the ECG-derived time markers changed considerably compared with mitral valve closure. Changing the definition of ED and ES resulted in significantly different ES-GLS and ES-SLS values in all subjects. ES-SLS in dyssynchronous hearts showed the highest sensitivity to timing definition. From all methods, spectral Doppler was the most reliable time marker in all subjects ($p > 0.05$).

CONCLUSIONS Exact temporal definition of ED and ES has a major impact on the accuracy of strain measurements. After direct observation of the valves, Doppler evaluation is the best means for characterizing ED and ES for STI analysis. (J Am Coll Cardiol Img 2015;8:148-57) © 2015 by the American College of Cardiology Foundation.

Cardiac function is a cyclic process, commonly sub-divided into time intervals describing ventricular diastolic filling, isovolumetric contraction, ejection, and isovolumetric relaxation. The frame after end-diastole (ED), marked by mitral valve closure (MVC), is often considered as the beginning of a new cardiac cycle, and aortic valve

closure (AVC) is used to describe the end of systole (ES). Although this phenomenological partition of the cardiac cycle does not necessarily reflect the functional state of the individual underlying myocardial fiber (1), it has become a commonly accepted concept in physiology and clinical cardiology (2). Therefore, echocardiographic measurements describing

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myocardial function do usually relate to time points such as ED and ES (2,3).

Echocardiographic deformation imaging is increasingly used for the quantitative assessment of myocardial function. Both tissue Doppler imaging (TDI) and speckle-tracking Imaging (STI) have proven feasibility and added value in physiologic investigations in healthy subjects as well as in patients with different pathologies (4-8). Its user-friendliness makes STI often the first choice for the assessment of the myocardial deformation (7-9). In STI, timing information is needed at 2 levels of the data analysis.

First, timing information is required for image processing. After speckle tracking, the noisy raw data need intensive regularization and—in the case of motion and deformation data—drift compensation. The latter is achieved by influencing the frame-by-frame motion of the tracking points to return to their initial position after 1 cardiac cycle. Software algorithms do repetitively detect and use particular time points derived from auto-correlation or from the easy available electrocardiographic (ECG) dataset (10,11).

Second, timing definitions are needed for data interpretation. MVC should indicate ED and, with this, should be the time point when the curves of motion and deformation are zero. Accordingly, AVC should indicate ES and should be the time point when the “end-systolic” motion or deformation value is measured (11). Furthermore, parameters such as post-systolic shortening require the knowledge of ES for their correct assessment (7).

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Most of the software solutions approximate ED by detecting the QRS in the ECG, which is commonly an intrinsic part of the echocardiographic datasets. For the definition of ES, a variety of solutions has been found, ranging from the detection of the end of T-wave in the ECG, over algorithms that process segmental or global tracking data or Doppler-based velocity traces, to manual inclusion of AVC timing derived from observation in the gray-scale image loop or blood-Doppler data from the aortic valve (12-15).

Most of the automatic approaches of approximating ED and ES are not documented or communicated with the user and can only be deduced from the behavior of the software or enquiries with the software vendor. Furthermore, it remains completely unclear which of the different approaches are valid and if they allow reproducible results under different clinical conditions.

Therefore, we have set up this study to investigate potential surrogate time markers that can be used to define ED and ES, to characterize how they behave

under different conditions, and to explore which are most feasible and can be recommended for clinical use.

METHODS

STUDY POPULATION. Sixty subjects were enrolled in this study, 20 of whom were healthy volunteers without a history of cardiovascular disease and with normal ECG and normal resting echocardiogram. Furthermore, we included 20 patients with a history of myocardial infarction, confirmed by coronary angiography, who had apparent residual resting wall motion abnormalities of more than 2 segments on rest echocardiography.

The third group consisted of 20 patients with left bundle-branch block (LBBB) on ECG and a typical LBBB-like mechanical dyssynchrony, characterized by the presence of apical rocking and septal flash in the echocardiogram. All subjects were in sinus rhythm, had no more than mild valve disease, or more than mild pulmonary hypertension. Written informed consent was obtained from all study participants before inclusion. The study was approved by the Ethics Committee of the University Hospital Leuven.

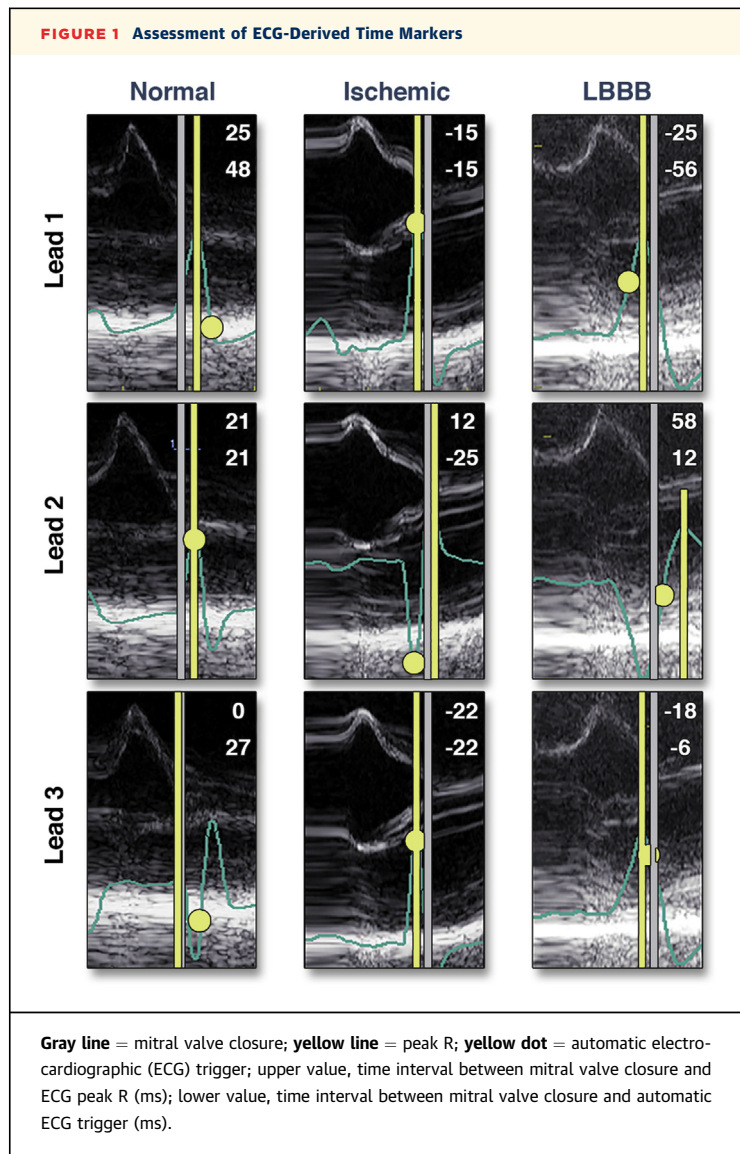
ECHOCARDIOGRAPHY. A standard echocardiographic examination was performed in each subject, with the use of a commercially available Vivid E9 ultrasound system with a M5S probe (GE Vingmed Ultrasound, Horten, Norway). From each view, 3 consecutive cardiac cycles were digitally stored for later offline analysis. All images were acquired in the left lateral decubitus position at a frame rate of at least 50 frames/s, by use of the second lead of the ECG. In 30 subjects (10 per group) a real M-mode through the mitral valve was repetitively acquired in the parasternal long-axis view by use of each of the 3 ECG leads of the echo machine (resembling Einthoven leads I, II, and III).

All echocardiographic data were analyzed offline with the use of EchoPac BT13 software with and without a specific research option (GE Vingmed Ultrasound). The research option allowed the simultaneous extraction of both strain and volume curves from the same tracking. All reported results are averaged from 3 cardiac cycles, except for the tracking-based parameters, in which only the default cycle of the software was assessed.

DEFINITION OF THE ED AND ES REFERENCE. Visual assessment of 2D images in apical 3-chamber view was used to define the reference for ED and ES. The reference ED was considered as the first frame when the mitral valve was closed. The reference ES was

ABBREVIATIONS AND ACRONYMS

AVC	= aortic valve closure
CAD	= coronary artery disease
ED	= end-diastole/diastolic
ES	= end-systole/systolic
ES-GLS	= end-systolic global longitudinal strain
ES-SLS	= end-systolic segmental longitudinal strain
ICC	= intraclass correlation coefficient
MVC	= mitral valve closure
STI	= speckle-tracking imaging
TDI	= tissue Doppler imaging



defined as the first frame when the aortic valve was closed. These definitions of ED and ES were repeated by a second investigator, and the average results were used for data analysis.

ECG-DERIVED TIME MARKERS. Peak R was defined as the first positive peak within the QRS. With the use of parasternal M-mode acquisitions of the MVC, the time from peak R to the automatic ECG trigger, as well as to MVC, was measured for all 3 ECG leads (Figure 1). For each subject, the maximum time between the automatic ECG trigger points in the different leads was calculated. The same evaluation was performed for peak R.

INFLUENCE OF THE TIMING OF ED AND ES ON STRAIN MEASUREMENTS. Two-dimensional strain images derived from STI in the apical 4-chamber view

were analyzed by a single experienced investigator. End-systolic global longitudinal strain (ES-GLS) and end-systolic segmental longitudinal strain (ES-SLS) were first measured with the use of our reference ED and ES. Measurements were then repeated with changing the definition of either ED or ES by ± 4 frames (Figure 2). The resulting strain changes were expressed as absolute strain differences and relative change of the strain value at reference timing. Intraobserver variability of ES strain measurements was assessed in 10 randomly selected cases (with subjects from all groups) and its standard deviation used as threshold to define relevant strain changes.

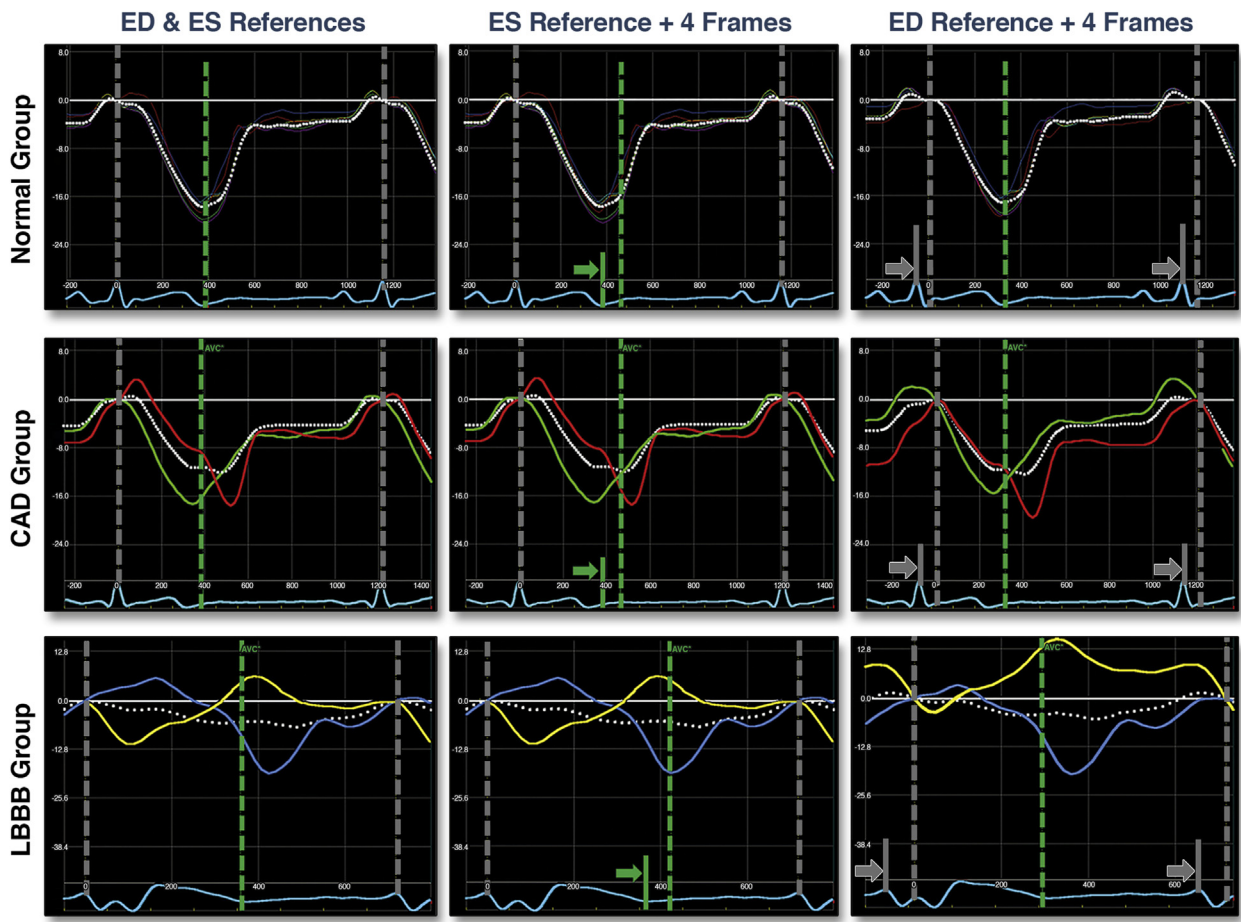
ECHOCARDIOGRAPHIC SURROGATE PARAMETERS FOR ED AND ES. In images from all 3 apical views, global longitudinal strain curves were generated by speckle tracking. A dedicated research version of EchoPac software allowed us to extract automatically a complete left ventricular (LV) volume curve from the endocardial border of exactly the same tracking by applying the Simpson method. Subsequently, the curves from all 3 apical views were averaged after normalizing their R-R intervals to the related apical 3-chamber view. In both curves per image plane and averaged curves, the time differences between the reference ED and ES and the volume and strain peak and nadir, respectively, were measured with the use of a Matlab-based (MathWorks Inc., Natick, Massachusetts), custom-made program (AVS, J-U Voigt, Leuven, Belgium) (Figure 3). Besides that, the automatic AVC detection algorithm of the EchoPac software (2D-Strain tool, single-view mode) was evaluated.

In the spectral Doppler data from the LV inflow (mitral spectral Doppler) and outflow (aortic spectral Doppler), we measured the end of the A wave and the end of the AVC artifact relative to the reference ED and ES, respectively.

The intraobserver and interobserver reproducibility of the proposed surrogate parameters for ED and ES was assessed in 30 randomly selected subjects (10 per group).

STATISTICAL ANALYSIS. Analysis was performed with the use of SPSS Statistics 22 (IBM, Chicago, Illinois). All continuous variables are expressed as mean \pm SD, if normally distributed, or otherwise by median \pm interquartile range. Normality was assessed with the use of the Shapiro-Wilk test. Repeated-measures analysis of variance for pairwise comparisons were used to analyze within-groups data and 1-way analysis of variance for between-groups results. A Bonferroni correction was applied to compensate for multiple comparisons. Statistical significance was set at a 2-tailed probability level of $p < 0.05$. Intraclass

FIGURE 2 Methodology Used to Assess End-Systolic Strain Variability While Changing Timing Definition



Gray dashed line = current end-diastolic (ED) time; gray solid line = reference ED time; green dashed line = current end-systolic (ES) time; green solid line = reference ES time; arrows = direction of the tested time shift. The dashed white strain curve indicates the mean segmental strain. The solid strain curves show selected segments: green = remote segment, red = infarcted segment, yellow = early activated (septal) segment, blue = late activated (lateral) segment.

correlation coefficient (ICC) was used to test the reproducibility of the analyzed methods.

RESULTS

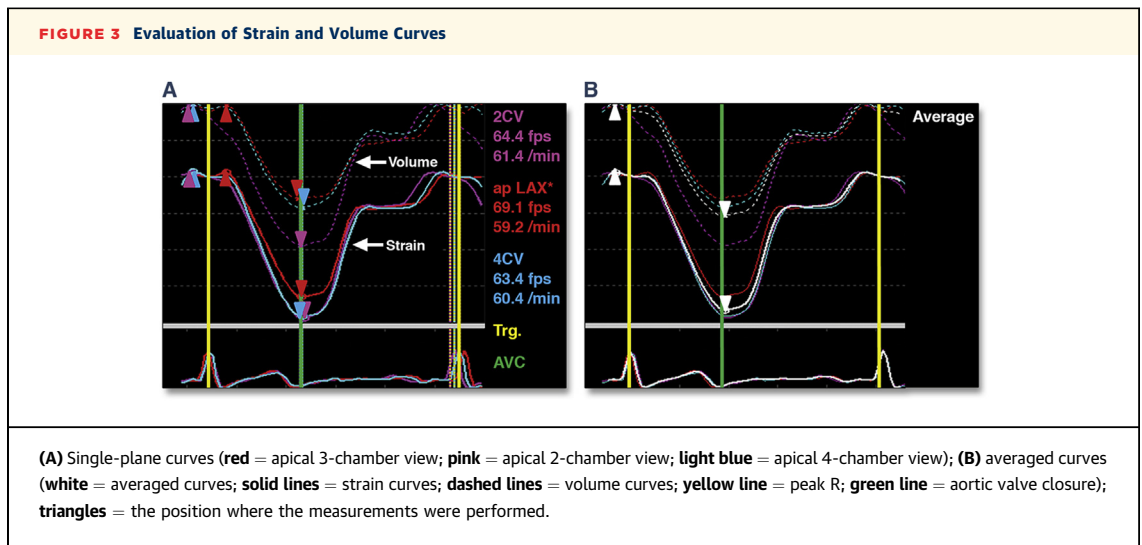
STUDY POPULATION. Characteristics of the study population are summarized in Table 1. The average frame rate of our acquisitions was 61 frames per second, corresponding to a temporal resolution of 16.2 ms.

TIMING REFERENCES. The agreement between the 2 readers regarding the definition of the reference ED and ES was 95% (57 of 60 cases) and 96.6% (58 of 60 cases), respectively. In all other cases, the difference between the readers was only 1 frame, and the average results were used for data analysis.

ECG-DERIVED TIME MARKERS. Depending on the QRS morphology, the timing of the manually defined

peak R changed considerably between the 3 ECG leads. Compared with normal subjects, the variability between leads was larger in the coronary artery disease (CAD) group and highest in the LBBB group (Figure 1, Table 2). The automatic trigger algorithm of the analysis software did not necessarily detect peak R but also steep slopes within the QRS. The variability of the automatic trigger point between ECG leads was higher than for the manual peak R definition but showed the same tendency among the 3 groups.

INFLUENCE OF THE TIMING OF ED AND ES ON STRAIN MEASUREMENTS. ES-GLS and ES-SLS were significantly altered by the variation of ED or ES in all subjects (Figure 4). Changing the definition of ED by ± 4 frames resulted in ES-GLS relative changes of up to 40% and ES-SLS relative changes of up to 85%



compared with reference ED timing. The observed changes were smallest in the normal group and highest in the LBBB group. Changing the definition of the ES trigger by ± 4 frames resulted in ES-GLS relative changes of up to 20% and ES-SLS relative changes of up to 75% compared with reference ES timing. Similarly, strain values in the normal group were the least affected, whereas they changed most in the LBBB group.

ECHOCARDIOGRAPHIC SURROGATE PARAMETERS FOR ED AND ES. Candidate parameters to define ED. The mean errors (considering the sign of the deviation) and mean absolute errors (without the sign) of the echocardiographic and ECG candidate parameters used to characterize ED are shown in [Figure 5](#).

Mitral spectral Doppler assessment of ED was very close to the reference ED. It differed only by -4 ± 10 ms in the normal group, 0 ± 12 ms in the CAD group, and -2 ± 14 ms in the LBBB group ($p > 0.05$).

Strain curves were not accurate enough in characterizing ED. Strain peaks in single apical planes differed from the ED reference in the LBBB group

(47 ± 46 ms; $p < 0.05$). Moreover, peaks of both single-plane and averaged strain curves differed significantly from MVC in the normal group (-19 ± 26 ms and -24 ± 19 ms, respectively; $p < 0.05$).

Volume peaks in single-plane curves differed significantly from ED reference in the normal and LBBB groups (13 ± 49 ms and 44 ± 50 ms, respectively; $p < 0.05$). Peaks of the averaged volume curves differed significantly from MVC in the CAD group (-14 ± 33 ms; $p < 0.05$).

Analysis of the absolute errors from the reference ED showed that mitral spectral Doppler is significantly better compared with the other methods in all cases ($p < 0.05$).

Candidate parameters to define ES. The mean errors (considering the sign of the deviation) and mean absolute errors (without the sign) of the candidate surrogate parameters used to define ES are presented in [Figure 6](#).

AVC derived from the spectral Doppler data was the most accurate parameter in defining the ES reference. It had an error of 3 ± 10 ms in the normal

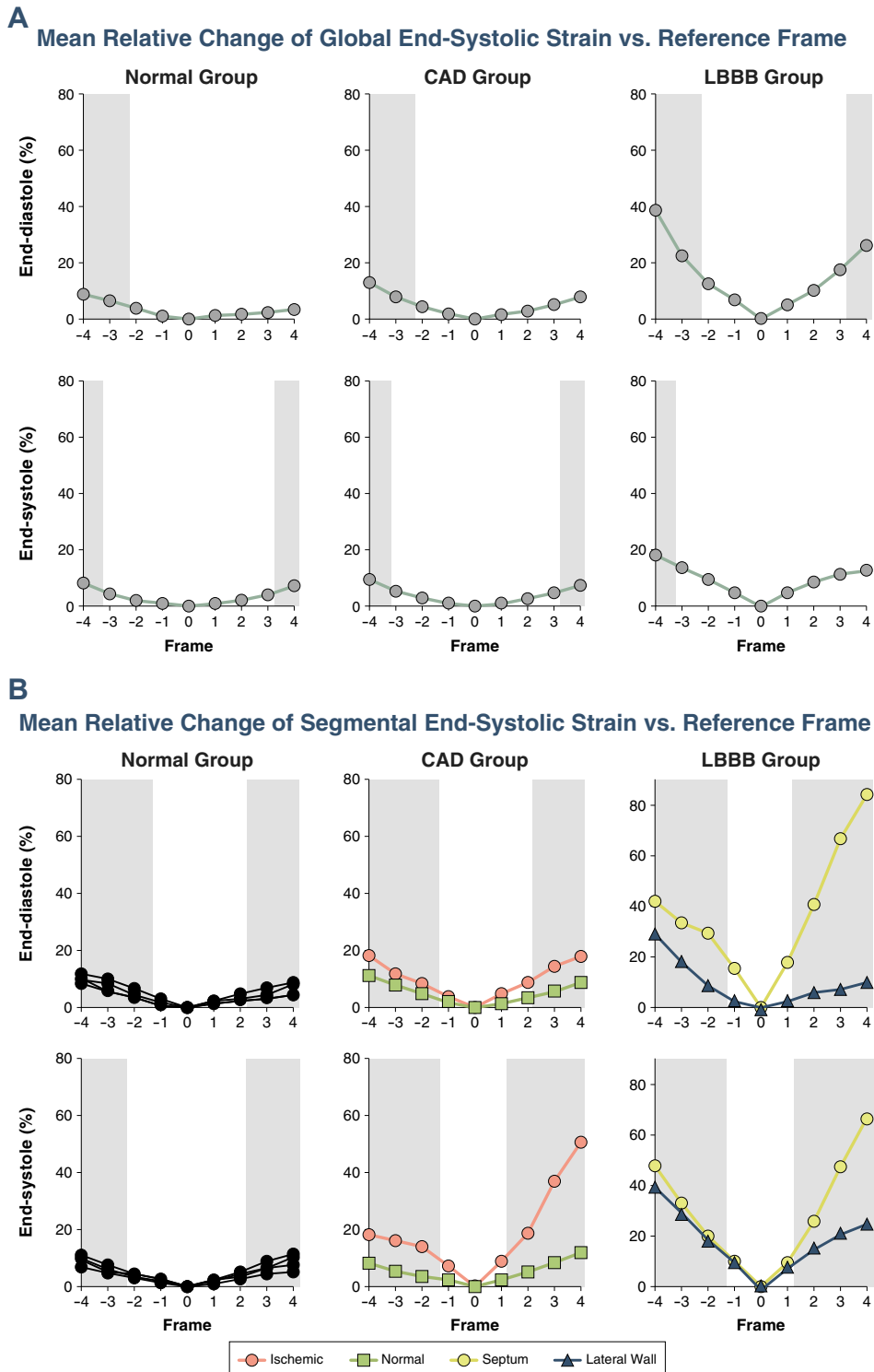
	Normal Group (n = 20)	CAD Group (n = 20)	LBBB Group (n = 20)
Age (yrs)	28 \pm 3	61 \pm 13	63 \pm 10
Male	14	16	12
Heart failure	0	13	20
Heart rate (beats/min)	59 \pm 9	63 \pm 10	75 \pm 14
QRS width (ms)	92 \pm 11	110 \pm 16	169 \pm 15
Ejection fraction (%)	61 \pm 4	43 \pm 6	23 \pm 7
Wall motion score index	1 \pm 0	1.65 \pm 0.28	2 \pm 0

Values are mean \pm SD or n.
CAD = coronary artery disease; LBBB = left bundle-branch block.

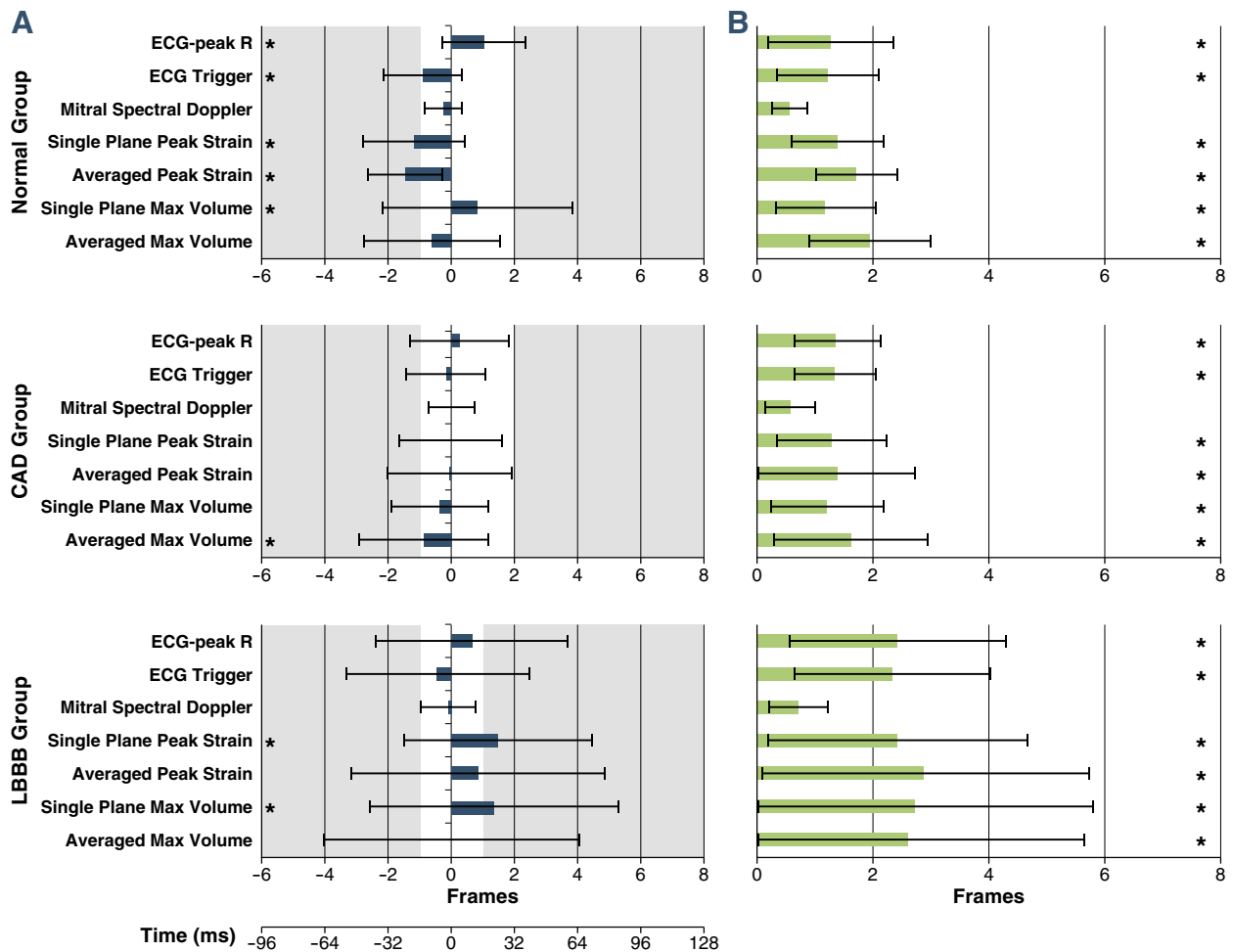
	Normal Group	CAD Group	LBBB Group
Variability of peak R (ms)	23 \pm 12	25 \pm 10	52 \pm 27
Difference between peak R and MVC (ms)*	20 \pm 13	23 \pm 13	42 \pm 36
Variability of automatic ECG trigger (ms)	24 \pm 8	29 \pm 10	57 \pm 26
Difference between automatic ECG trigger and MVC (ms)*	25 \pm 16	27 \pm 15	48 \pm 35

Values are mean \pm SD. *Average value of the 3 ECG leads.
CAD = coronary artery disease; ECG = electrocardiography; LBBB = left bundle-branch block; MVC = mitral valve closure.

FIGURE 4 Mean Relative Change of End-Systolic Strain Measurements Versus Reference Frame While Changing the Definition of Either End-Diastole or End-Systole in Different Clinical Conditions



(A) Global longitudinal strain. (B) Selected segmental longitudinal strain curves. **Gray shaded areas** = difference from the reference strain value above the intraobserver variability.

FIGURE 5 Surrogate Parameters Used to Define Timing of End-Diastole

(A) Mean error (considering the sign) \pm SD; (B) mean absolute error (without the sign) \pm SD; max indicates maximum. Gray shaded areas = time at which the difference of the segmental strain value from the reference exceeds the intraobserver variability. *Analysis of variance post-test, $p < 0.05$; ECG-derived time markers are from lead 2. Abbreviation as in Figure 1.

group, 2 ± 10 ms in the CAD group, and -1 ± 11 ms in the LBBB group ($p > 0.05$).

The automatic AVC detection algorithm of the analysis software was reasonably accurate in the normal and CAD groups, with a difference from the ES reference of 13 ± 20 ms and -4 ± 21 ms, respectively ($p > 0.05$). However, it failed in the LBBB group (difference, -54 ± 75 ms; $p < 0.05$).

Strain curves were not accurate in defining ES in the pathological groups. The nadir of both single-plane and averaged strain curves differed significantly from the AVC (31 ± 43 ms and 24 ± 50 ms in the CAD group; 63 ± 70 ms and 83 ± 95 ms in the LBBB group; $p < 0.05$).

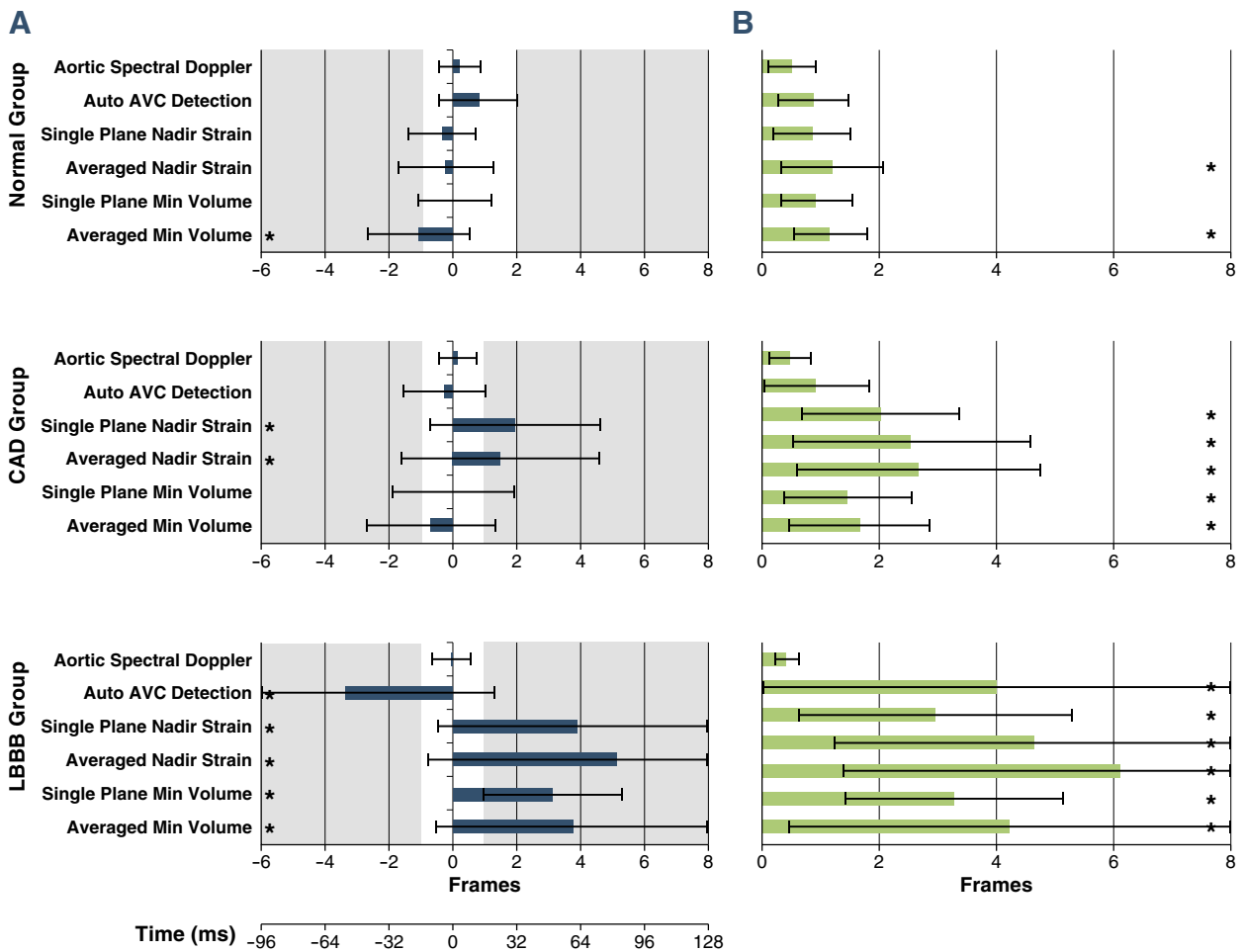
The nadir of the averaged volume curves was inaccurate in defining ES in the normal and LBBB

groups (difference, -17 ± 26 ms and 61 ± 69 ms, respectively; $p < 0.05$). Volume nadirs in single apical planes failed only in the LBBB group (difference, 50 ± 35 ms; $p < 0.05$).

Analysis of the absolute errors from the reference ES revealed that aortic spectral Doppler is significantly better compared with almost all other methods in the pathological groups and more accurate than the nadirs of the averaged strain/volume curves in the normal group ($p < 0.05$).

Reproducibility. Analysis of the intraobserver and interobserver variability of the evaluated methods showed a good correlation for the speckle-tracking-derived parameters (ICC = 0.846 to 0.877 and ICC = 0.811 to 0.842, respectively) and a strong

FIGURE 6 Surrogate Parameters Used to Define End-Systole



(A) Mean error (considering the sign) ± SD; (B) mean absolute error (without the sign) ± SD; min indicates minimum. Gray shaded areas = time at which the difference of the segmental strain value from the reference exceeds the intraobserver variability. *Analysis of variance post-test, $p < 0.05$; electrocardiogram-derived time markers are from lead 2.

correlation for all other techniques (ICC = [0.926 to 0.995] and ICC = [0.906 to 0.942], respectively).

DISCUSSION

Timing of cardiac events is a frequently neglected problem in the quantitative analysis of myocardial function as definitions of ED and ES directly influence the measurement results. However, the commonly used references for these time points—MVC and AVC—are not always directly available in the image datasets under analysis and must be replaced by surrogates. The aim of the current study was to investigate to which extent timing definitions influence the accuracy of strain measurements and which surrogates are reliable and feasible in the daily

routine for the definition of ED and ES during STI analysis.

Our main findings were that changing the definition of ED and ES by only 4 frames can influence strain measurement results significantly and in a clinically relevant magnitude. Frequently used surrogate parameters for ED and ES, such as the ECG peak R or the LV global strain curve nadir are sufficiently accurate only in hearts without regional dysfunction and should be replaced by the observation of mitral and aortic valve closure in case of pathology.

TIMING REFERENCES. Cardiac time intervals are arbitrary partitions of a cyclic process, but MVC and AVC are commonly used to define ED and ES (2,15,16). In this study, we therefore decided to derive timing

information from observation of the aortic valve and the mitral valve in the long-axis view because this is the only echocardiographic data source that combines both myocardial function and timing information in 1 image. If all 3 apical views are acquired with the use of the same image settings, the timing information achieved can safely be extrapolated to the other views because a potential ECG off-set would be similar in all.

ECG-DERIVED TIME MARKERS. Most vendors report the use the ECG peak R as the time reference in their software solutions. Our results illustrate that both the manual detection of peak R and the automatic ECG trigger algorithms of the echo machines are influenced by the QRS morphology, which may be considerably different in different leads (Table 2).

INFLUENCE OF THE TIMING OF ED AND ES ON STRAIN MEASUREMENTS. Changing the definition of ED and ES resulted in significantly different ES-GLS and ES-SLS values in all subjects. ES-GLS was less affected than was the individual ES-SLS. Measurements in the normal group were least sensitive to changes in the definition of ED and ES because curves are almost horizontal at these 2 time points. In the CAD group, particularly the presence of post-systolic shortening in ischemic segments leads to considerable changes in ES strain measurements when the definition of ES is altered (red curves, Figure 2, Figure 4B). This effect is not seen in ES-GLS curves because post-systolic shortening is less dominant in those (Figure 4A). In the LBBB group, strain curves show steep slopes around ED and ES, which results in considerable changes in strain measurements when the definition of either time point is altered (yellow and blue curves, Figure 2, Figure 4B). In this patient population, the higher percentage changes in ES-GLS are mainly due to the lower absolute values of ES-GLS.

The lack of available data makes it very difficult to determine the clinical relevance of a certain measurement error in regional strain measurements. We assume, however, that deviations in the range of up to 80% of the correct value must be considered relevant in any case. For global longitudinal strain, several studies report standard deviations of normal values in the range of 1.5% to 2% absolute (i.e., 7% to 10% relative), which coincides approximately with the cut-offs used in our study (16,17). It can be assumed that deviations exceeding this range must be considered relevant because they could convert a normal value into a pathologic one.

ECHOCARDIOGRAPHIC SURROGATE PARAMETERS FOR ED AND ES. Candidate parameters to define ED. Comparing different methods to assess ED (Figure 5)

revealed that mitral spectral Doppler was the most reliable surrogate for the direct observation of MVC, independent of the underlying myocardial dysfunction. All other parameters may introduce ES-GLS or ES-SLS measurement errors beyond the intra-observer variability of the respective measurements.

Candidate parameters to define ES. The accuracy of the different tested methods to define ES depended strongly on the underlying pathology (Figure 6). In hearts without regional dysfunction, most surrogates for ES were sufficiently accurate. In ischemic patients, regional dysfunction may particularly influence strain curves in a way that the strain nadir becomes unreliable. Volume curves follow the same trend. In patients with LBBB, none of the tracking-based surrogate parameters was sufficiently accurate, and only AVC derived from Doppler can replace the direct observation of AVC.

Previous studies illustrated that ES can be approximated by particular time points on the velocity and strain curves in the cardiac cycle under analysis. Aase et al. (12,13) validated a method in normal and ischemic subjects that analyzed high frame rate velocity traces of the basal segment of the antero-septal wall. It remains to be proven whether this method can be extended to the other apical views and other pathology. We did not include the method in our tests because the temporal resolution of current clinical speckle-tracking datasets is mostly insufficient to derive the proposed parameter. Lyseggen et al. (14) proposed a surrogate parameter for the identification of ES in subjects with acute myocardial infarction that is based on the occurrence of post-systolic shortening. Because this approach is probably not directly applicable in other pathology, it was also not tested in our study.

ES VERSUS PEAK-SYSTOLIC MEASUREMENTS. In our study, we tested the influence of the temporal definitions of ED and ES on the ES strain measurement result, which is the recommended parameter according to the consensus document of the EACVI/ASE/Industry Task Force to Standardize Deformation Imaging (15). Their impact on peak systolic strain measurements was not assessed. We can conclude, however, that changes in the temporal definition of ED have identical effects on peak systolic strain measurements because the entire strain curve is shifted. In contrast, peak strain measurements should not be affected by changes in the definition of ES because this information is not considered. This does not imply, however, that peak strain measurements are a preferable alternative because they are not defined in time and may not necessarily

reflect the true systolic deformation of the myocardium (15).

CLINICAL IMPLICATIONS. Our study demonstrated that the definition of ED and ES directly influences measurement results in a clinically relevant way. It appears therefore important to carefully consider timing definitions when quantifying myocardial function. Our data suggest that the commonly used peak R is a sufficiently reliable approximation for ED as long as the ECG morphology is normal. With altered QRS morphology or regional myocardial dysfunction, such as in ischemic or dyssynchronous hearts, mitral valve closure should be used. Similarly, a global strain or volume nadir may serve as approximation for end-systole in hearts without regional dysfunction. In all other cases, only the use of aortic valve closure allows correct and well-defined measurements.

Given the limited temporal resolution of speckle-tracking data, the direct observation of the valve closures in the gray-scale images is sufficient. Events can be measured relative to the ECG and in this way applied to all acquisitions from the same examination as long as the ECG leads remain unchanged and the heart rate of the different recordings is similar. Measuring the valve closure artifacts in aortic and mitral valve Doppler traces can replace the direct observation if needed.

STUDY LIMITATIONS. In our tests, we used the ECG to time-align different image acquisitions from the same patient but did not test for a potential off-set between ECG and image data. This is irrelevant for the comparison of data derived from different views that are acquired with the same image settings. For other comparisons, current literature suggests that errors are minor in contemporary machines (18).

CONCLUSIONS

The correct definition of ED and ES is relevant for accurate measurements of the myocardial function parameters. If direct observation of the valves closure is not used, spectral Doppler, acquired at a similar heart rate, is recommended for defining ED and ES. The use of ECG peak R to define ED is a feasible alternative as long as the QRS morphology is normal. ES STI-derived parameters may be used in hearts without relevant regional dysfunction or dyssynchrony but should be always checked versus direct observation.

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KEY WORDS cardiac timing, echocardiography, end-diastole, end-systole, strain measurements