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**Comparison of regional quantitative indices of left ventricular
dyssynchrony by three-dimensional echocardiography and
semi-automated border detection prior to and during acute
biventricular pacing**

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Submitted for publication

Abstract

Background: In biventricular pacing most methods to quantify cardiac dyssynchrony rely on assessment of regional timing of contraction. Three-dimensional echocardiography combined with semi-automated endocardial border detection might provide additional information.

Methods and results: Twelve patients in sinus rhythm with a recently implanted biventricular pacemaker underwent transoesophageal rotational three-dimensional echocardiography, before and during acute pacing. Offline, using TomTec 4DLV™ analysis software featuring semi-automatic border detection, segmental time-volume-curves were generated. In a 1440-segment model, standard deviation of times to minimal volumes (SDI), time from earliest to latest moment of minimal volume (L-E) and sum of times between global and segmental minimal volume (SUM) were assessed. Integrating areas under segmental time-volume-curves of segments showing pre-systolic relaxation or post-systolic contraction resulted in a parameter we called systolic time-volume loss (STV). Reproducibility was assessed in a group of 18 patients with and without cardiac abnormalities. Pacing resulted in a significant decrease in SDI (-39%, $p = 0,02$), L-E (-52%, $p = 0,007$), SUM (-30%, ($p = 0,02$) and STV (-40%, $p = 0,001$). Intra-observer variability (bias \pm 2 SD) was $14 \pm 50\%$ for SDI, $18 \pm 78\%$ for L-E, $11 \pm 37\%$ for SUM and $10 \pm 28\%$ for STV.

Conclusions: STV is more sensitive to dynamic changes during acute pacing than other regional indices of dyssynchrony.

Introduction

In patients with advanced heart failure and left ventricular (LV) dyssynchrony, biventricular pacing has emerged as an established therapeutic modality [1,2,3,4].

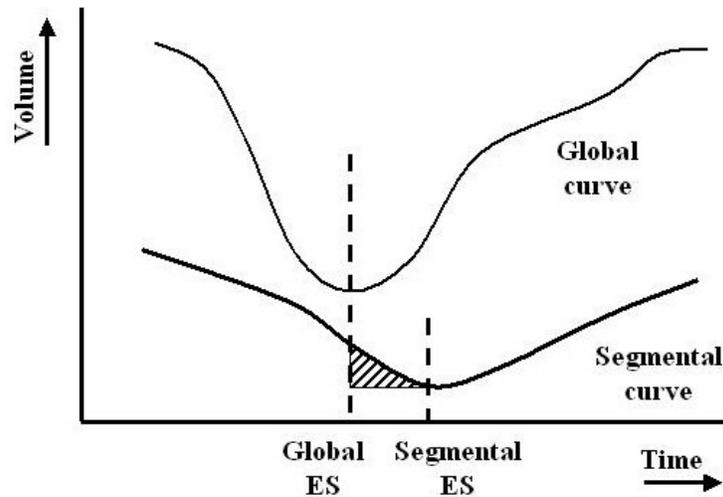
In studies using tissue Doppler imaging to assess mechanical dyssynchrony, it was recognized that there is absence of mechanical dyssynchrony in a significant proportion of heart failure patients with a prolonged QRS duration [5]. Furthermore, there is an important prevalence of mechanical dyssynchrony in heart failure patients with normal QRS duration [6]. Also, it has been shown that there is no clear correlation between QRS duration and mechanical dyssynchrony in heart failure patients [7].

Most methods to quantify LV mechanical dyssynchrony rely on timing of contraction of LV segments, as measured by tissue Doppler imaging [8,9]. These methods can predict response to biventricular pacing better than QRS duration, but for unknown reasons, a substantial group of patients still fail to improve [10,11,12]. This suggests that additional factors may be involved beyond LV mechanical dyssynchrony as assessed with current methods.

A system has been described based on three-dimensional echocardiography (3DE) in combination with semi-automated endocardial border detection, that can be used to evaluate the effects of biventricular pacing therapy [13,14,15]. This system uses segmental time-volume curves which give detailed, regional, quantitative information on each individual LV segment.

In uncontrolled studies, we observed that a proportion of delayed LV segments may contribute only minimally to global LV function because of severely reduced segmental endocardial inward motion. Time-volume curves of these segments exhibit low volume change during the cardiac cycle, with or without a long delay in endocardial inward motion (figure 1). The area under the time-volume curve serves as a correction factor so that values of segments that are hypokinetic, are low, even if they have a long contraction delay

Figure 1. The time-volume loss concept.



A global and a segmental time-volume curve are shown. Clearly, the segment shows delayed endocardial inward motion. Segmental end-systolic time and volume are measured. Furthermore, time between global and segmental end-systole are measured, and volume difference between global and segmental end-systole. Time-volume loss is defined as area under time-volume curve as indicated by the barred area. Thus, a segment with a large delay but with low endocardial inward motion will be assigned a low value, as will a segment with short delay but high inward motion. Only segments with both large delays and high endocardial inward motion, that are expected to yield the most improvement in biventricular pacing, will be assigned high values.

We hypothesise that when these segments are resynchronised by biventricular pacing, the area-under-curve cannot decrease substantially and cardiac function might fail to improve. Therefore, the area-under-curve should demonstrate a more pronounced response to biventricular pacing than parameters that are based on measurement of segmental timing only.

The present study is conducted to compare side-by-side multiple quantitative indices of regional LV function derived by a semi-automated endocardial border detection algorithm using three-dimensional echocardiography of segmental timing alone versus the combination of segmental timing and motion (the area under time-volume curve) in the evaluation of LV mechanical dyssynchrony before and during acute biventricular pacing. Furthermore, the reproducibility of these regional LV indices is examined.

Methods

The study consisted of two parts: a reproducibility study and a pacing study.

Reproducibility study

In 18 consecutive patients who underwent transoesophageal echocardiography for various clinical reasons, 3DE was performed. All patients gave informed consent and the study was approved by the medical ethics committee. In order to assess reproducibility, 3DEs of this patient group were analysed twice by one observer, with an one-month interval.

Pacing study

Twelve patients with a biventricular pacemaker who were in sinus rhythm were studied with the pacemaker on and off. After implantation the pacemaker was switched to AAI mode at a lower rate of 40-50 beats per minute, resulting in absence of paced complexes. Patients returned after approximately 3 weeks to undergo AV optimisation, which was performed by switching the pacemaker to DDD mode and programming the AV interval that was associated with the longest LV filling time as measured by transmitral Doppler 16. Then the pacemaker was temporarily switched back to AAI mode and patients underwent 3DE. After completion of the first acquisition, the pacemaker was reprogrammed to DDD mode with the optimal AV interval, and a second acquisition was performed.

Three-dimensional echocardiography

For 3DE, a commercially available HP SONOS 5500™ ultrasound machine and transoesophageal echocardiography probe (Hewlett Packard, Andover MA, USA) were used. 3DE was performed using a built-in rotational acquisition algorithm described earlier [17]. Briefly, a long-axis view of the left ventricle with minimal foreshortening in all scan planes was generated. Using onset of QRS-complex and respiratory gating, 3DE was performed with either 60 or 36 slices, using, respectively, a 3- or 5 degree interval at 25 frames/sec. Images were stored on MO-disk for subsequent analysis.

Analysis

A TomTec™ workstation with TomTec 4DLV analysis™ software (TomTec GmbH, Munich, Germany) was used for analysis. Based on image quality, 8 to 9 approximately evenly spaced slices were selected from the data set. After manual input of locations of mitral and aortic valves and the apex, both in end-diastole and end-systole, the software projects an oval in the LV cavity of which size and shape were adjusted manually to an approximate fit. The software then detects the endocardial borders automatically throughout the cardiac cycle, with a possibility for manual correction, and extrapolates the 3D endocardial surface. For visual assessment a cine-loop of surface and borders was projected on-screen that could be rotated for viewing at different angles. End-diastole and end-systole were defined as the moments of maximal and minimal volume. LV volumes and ejection fraction were generated automatically by the software.

LV dyssynchrony

The software automatically divides the LV into 1440 segments and calculates the following parameters:

- 1- LV end-diastolic and end-systolic volumes
- 2- Global end-systolic time, defined as time between onset of QRS-complex and moment of minimal LV volume
- 3- Latest-earliest time interval (L-E), defined as time between the first and the last segment's moment of minimal volume
- 4- Segmental minimal volume, defined as minimal volume of individual segments
- 5- Segmental end-systolic time, defined as time between onset of QRS-complex and moment of minimal volume of each individual segment
- 6- Systolic dyssynchrony index (SDI), defined as the standard deviation of moments of minimal volumes of all segments.
- 7- Pre-systolic time-volume loss (Pre-STV). Of each segment showing segmental end-systolic time before global end-systolic time, segmental end-systolic time and minimal volume are measured. Furthermore, volume at the moment of global end-systole is measured and time between segmental and global end-systole (figure 1). Pre-STV is the sum of all segmental values.
- 8- Post-STV was defined accordingly.

We also calculated the following additional parameters:

- 9- Systolic time-volume loss (STV), defined as the sum of pre- and post-STV.
- 10-Pre-systolic dyssynchrony index (Pre-SDI), defined as the standard deviation of time between onset of QRS-complex and moment of segmental minimal volume of those segments only that reached minimal volume before global end-systolic time.
- 11-Post-systolic dyssynchrony index (Post-SDI) was defined accordingly.
- 12-Sum of segmental times (SUM), defined as the sum of times between global and segmental end-systole. This was a positive value for each segment, irrespective whether segmental or global end-systole came first.

Statistical analysis

Continuous variables are expressed as average \pm 1 standard deviation. Reproducibility was assessed by Bland-Altman analysis (bias \pm 2 standard deviations). Correlations were assessed by linear regression. Comparison of data was performed by two-sided student's T-test. A value of $p < 0,05$ was considered statistically significant.

Results

Reproducibility study

Eighteen patients (age 64 ± 15 years, 10 male, ejection fraction $38 \pm 17\%$ (range 15 - 68%), QRS duration 134 ± 40 ms (range 76 - 204 ms), of whom 4 patients were without cardiac abnormalities) were included. Of these 18 patients, a subgroup of 7 patients had a biventricular pacemaker and they were studied with the pacemaker on and off, thus, a total of 25 3DEs were acquired. In 5 patients, 3DE analysis was not possible because of motion artifacts (n=1), the development of bigeminy during acquisition (n=1), and mitral valve calcifications partly concealing the endocardial border (n=3), resulting in 20 echocardiograms available for reproducibility analysis. Acquisition time was approximately 3 minutes per LV. After a training period, analysis time was approximately 30 minutes per LV.

Reproducibility is shown in table 1. At segmental level, timing-derived parameters showed acceptable reproducibility. Because of skewed distribution, global end-systolic time was different from average segmental end-systolic time. All volume-derived parameters showed good reproducibility.

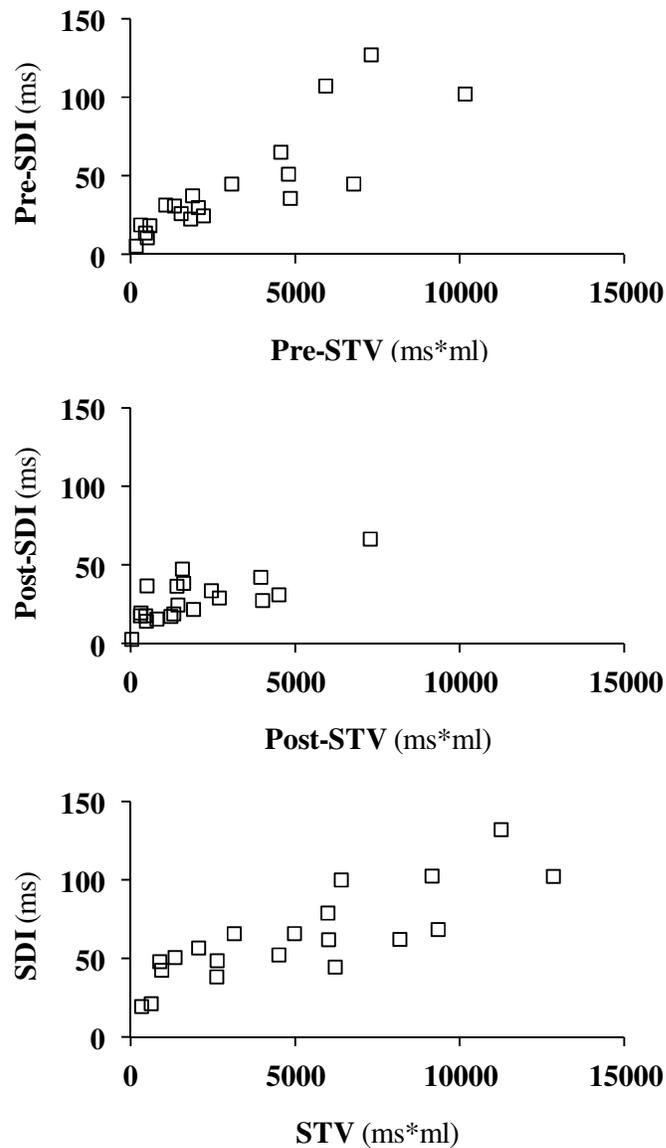
Table 1. Reproducibility.

(n=20)	Value (Average \pm 1 SD)	Intra-observer variability, absolute (Bias \pm 2 SD)	Intra-observer variability, percentual (Bias \pm 2 SD)
LV enddiastolic volume (ml)	145 \pm 54	-1 \pm 12	-1 \pm 8
LV endsystolic volume (ml)	98 \pm 57	0 \pm 12	0 \pm 12
Segmentl minimal volume (ml)	5,2 \pm 3,4	0,2 \pm 1,8	4 \pm 35
Global endsystolic time (ms)	416 \pm 60	-2 \pm 50	0 \pm 12
Segmentl endsystolic time (ms)	407 \pm 102	-9 \pm 146	-2 \pm 36
L-E (ms)	249 \pm 135	46 \pm 193	18 \pm 78
SUM (ms)	903 \pm 390	102 \pm 336	11 \pm 37
SDI (ms)	72 \pm 35	10 \pm 36	14 \pm 50
Pre-SDI (ms)	51 \pm 39	15 \pm 59	29 \pm 116
Post-SDI (ms)	35 \pm 22	2 \pm 28	6 \pm 80
STV (ms*ml)	5496 \pm 4055	556 \pm 1552	10 \pm 28
Pre-STV (ms*ml)	3501 \pm 3320	552 \pm 2103	16 \pm 60
Post-STV (ms*ml)	1995 \pm 1790	4 \pm 1066	0 \pm 53

See text for abbreviations

Correlation between pre-SDI and Pre-STV, post-SDI and Post-STV and (total) SDI and STV is shown in figure 2. The respective r-values were 0,86, 0,74 and 0,83 ($p < 0,001$ for all).

Figure 2. Correlation between dyssynchrony index and time-volume loss



Correlation between (top) pre-SDI and Pre-STV; (center) post-SDI and Post-STV; and (bottom) SDI and STV.

Pacing study

For baseline patient characteristics, see table 2.

Table 2. Baseline patient characteristics.

(n=12)	Average \pm 1 SD
Age (years)	66 \pm 8
Male/female	9 / 3
Ischemic/non-ischemic	6 / 6
Ejection fraction (%)	26 \pm 8
QRS duration (ms)	150 \pm 34
NYHA class	2,9 \pm 0,7
Diuretics (%)	100
Betablockers (%)	83
ACE-inhibitors/ARBs (%)	91
Spirinolacton (%)	50
Digoxin (%)	50

During pacing, LV volumes remained unchanged (table 3). L-E and SUM decreased significantly during pacing ($p=0,007$ and $p=0,02$, respectively). SDI decreased significantly as well ($p=0,05$). Pre-SDI decreased significantly ($p=0,05$), whereas the decrease in post-SDI was not statistically significant. Post-SDI was smaller than pre-SDI, but the difference was not statistically significant.

STV decreased significantly ($p=0,001$). This decrease was caused by pre-STV, which decreased significantly ($p=0,002$) whereas post-STV remained unchanged. At baseline, post-STV was significantly smaller than pre-STV ($p=0,04$). Considering the difference between STV at baseline and during acute pacing, reproducibility was quite sufficient to discriminate. Values of individual patients of selected variables are shown in figure 3.

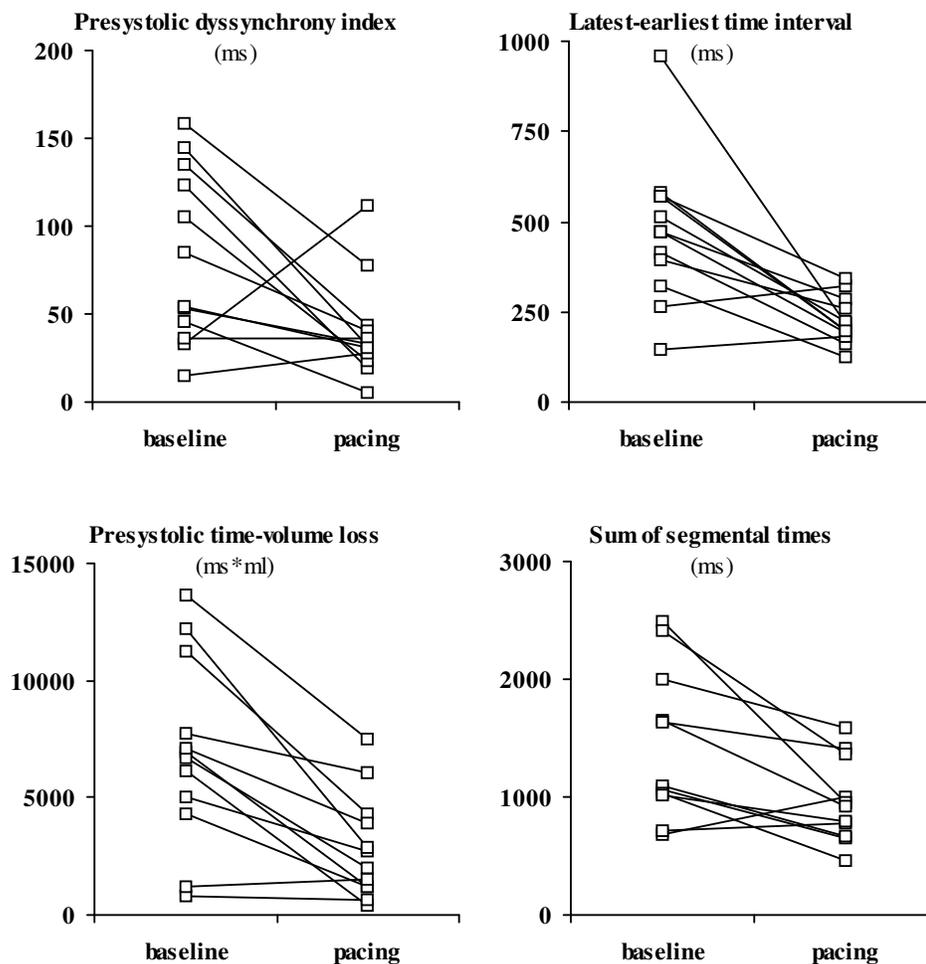
In this small patient cohort, the correlation between pre-STV before pacing and change in ESV after pacing failed to reach statistical significance ($r=0,58$; $p=0,08$) [18].

Table 3. Pacing.

(n=12)	Baseline (average \pm 1 SD)	Pacing (average \pm 1 SD)	Percentual change	p-value
LV end-diastolic volume	151 \pm 39	160 \pm 49	+ 6,0	0,39
LV end-systolic volume	113 \pm 39	116 \pm 43	+ 2,7	0,78
Global end-systolic time	402 \pm 25	438 \pm 53	+ 9,0	0,12
L-E	472 \pm 213	225 \pm 68	- 52,3	0,007
SUM	1381 \pm 650	964 \pm 352	- 30,2	0,02
SDI	113 \pm 60	69 \pm 24	- 38,9	0,05
Pre-SDI	85 \pm 54*	41 \pm 31	- 51,8	0,05
Post-SDI	56 \pm 49	40 \pm 17	- 28,6	0,28
STV	10178 \pm 4327	6064 \pm 2316	- 40,4	0,001
Pre-STV	6914 \pm 4171**	2872 \pm 2326	- 58,5	0,002
Post-STV	3264 \pm 2311	3193 \pm 1979	- 2,2	0,33

See text for abbreviations; * p=0,14 for pre- vs post-SDI at baseline; ** p=0,04 for pre- vs post-STV at baseline

Figure 3. Values of individual patients of selected variables.



Discussion

The main finding of this study is that STV is more sensitive to dynamic changes during acute biventricular pacing than other regional indices of LV dyssynchrony. During acute biventricular pacing, decrease in (pre-) STV was highly significant. L-E, SUM and (pre-) SDI decreased significantly as well. Furthermore, mechanical dyssynchrony was assessed in diastole; post-SDI and time-volume loss were low at baseline and did not change significantly during acute biventricular pacing.

The present study investigates cardiac dyssynchrony fundamentally differently from all previous studies. It shows feasibility of measuring mechanical dyssynchrony in terms that are not only dependent of segmental timing, but also on segmental endocardial inward motion. This method has moderate reproducibility, which in the future may improve as endocardial surface detection software becomes more accurate.

Zhang et al showed that SDI decreased from 70 to 46 ms during acute biventricular pacing [15]. Time-volume loss was not assessed and a differentiation between pre- and post-SDI was not made. A prerequisite for a standard deviation to be useful is a normal distribution of the data. In measurements of SDI however, presence of a small number of segments with a long delay might cause skewed distribution, impairing usefulness of a standard deviation. This weakness is intrinsic to all standard-deviation based models of dyssynchrony. Time-volume loss is based on a 16-segment model in which values of all segments are summed. Furthermore, since basal segments contribute more to endocardial inward motion, their contribution to the total value of time-volume loss is greater than that of apical segments. This is in contrast to methods that use only timing parameters and where every segment contributes equally to the final standard deviation or summed value.

Krenning et al showed that L-E decreased from 147 to 103 ms during acute biventricular pacing [19]. Time-volume loss was not assessed either, but segments showing volume change $< 20\%$ during the cardiac cycle were excluded from analysis. In our patients, L-E decreased from 472 to 225 ms. These absolute values are considerably larger, but we did not exclude segments with a low volume change. Conceivably, segments that are severely hypokinetic might also be severely delayed. A different explanation might be that time-volume curves of severely hypokinetic segments largely run horizontal and that minor

artefacts that do not reflect true volume change, might mistakenly be identified as segmental end-systole. Thus, in these segments, end-systole is randomly distributed over the cardiac cycle and L-E does not reflect true segmental end-systolic times. However, given the large and significant decrease of L-E during acute biventricular pacing, a major role for measurement error in our study is highly unlikely.

Pre- and not post-STV decreased during acute biventricular pacing. In a tissue Doppler study on biventricular pacing by Yu et al, peak systolic contraction in 6 basal segments was delayed homogeneously to a timing close to that of the latest segment, so that regional variation was abolished [8]. In hemodynamic studies on biventricular pacing, an increased positive dP/dT , and an increased (i.e., more negative) negative dP/dT have been reported [20,21,22]. It might be speculated that in biventricular pacing, at the start of systole late segments are activated earlier, causing an increase in dP/dT . This opposes contraction of other segments which then take longer to complete contraction. By the end of systole, the majority of segments finish contraction simultaneously. An increased positive dP/dT could be consistent with early activation of delayed segments, and an increase in negative dP/dT could be consistent with a homogeneous delay of 6 basal segments and a decrease in pre-STV.

In this study, we describe different responses to biventricular pacing in late systole and early diastole. It appears that biventricular pacing primarily decreases pre-STV, with no change in post-STV. However, at baseline post-STV was significantly less than pre-STV and may not have been of major importance. Since post-STV occurs during early diastole, it may serve as a measure of LV diastolic function.

Limitations

We defined end-systole as the moment of minimal LV volume. No attention was given to opening or closing of mitral and aortic valves for practical reasons.

Close examination of time-volume curves revealed that in some cases, segments seemed to “overtake” other segments, i.e. endocardial inward motion started later, was faster, and ended earlier. We did not assess peak endocardial inward velocity as a marker of dyssynchrony. In a tissue Doppler study however, standard deviation of times to peak myocardial velocity (which occurs in mid-systole) demonstrated superiority over peak

myocardial displacement (which occurs at the end of systole) in prediction of response to biventricular pacing [23]. We could not assess if the same segments were delayed at baseline and during pacing, and we did not correlate 3DE-, to Doppler parameters of dyssynchrony.

The present data suggest that in cardiac dyssynchrony, time-volume-based methods might potentially be superior to methods that are based on timing alone, because wall motion is more completely described. These findings needs to be re-addressed in a larger study, in which follow-up is performed as well. Furthermore, studies are needed regarding events that are similar to pre- and post-STV, but may occur at end-diastole.

Conclusions

The use of transoesophageal three-dimensional echocardiography in combination semi-automated endocardial border detection and generation of segmental time-volume curves is feasible, although reproducibility is moderate with current software. Time-volume loss measurements integrate segmental timing and endocardial inward motion and might provide more comprehensive information on LV dyssynchrony than methods that are based solely on timing. It is more sensitive to dynamic changes during acute biventricular pacing than other regional indices of LV dyssynchrony.

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