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Validation of rapid automated tissue synchronization imaging for the assessment of cardiac dyssynchrony in sinus and non-sinus rhythm

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Aims Cardiac resynchronization therapy is showing benefits for an increasing number of indications but fails to predict response in up to 20–30% of subjects. Echocardiographically assessed dyssynchrony has been proposed as a potential stratifier but current methods are time-consuming and suffer poor reproducibility, thus limiting their clinical utility. This study compared the accuracy, time efficiency, and reproducibility of automated tissue synchronization imaging (Auto TSI) vs. established manual tissue velocity imaging (TVI) techniques for the assessment of intra-ventricular dyssynchrony in sinus and non-sinus rhythm.

Methods and results Fifty consecutive stable systolic heart failure patients on optimal guideline-based medical therapy underwent intra-ventricular dyssynchrony assessment [time to peak velocity (Ts), septal to lateral delay (SLD), and dyssynchrony index (DI)] with TVI and Auto TSI techniques, enabling the assessment of agreement, time efficiency, and reproducibility. Statistical analyses included Pearson's correlation, Bland–Altman's statistics, and coefficient of reproducibility. There was excellent agreement between Auto TSI and TVI for the measurement of Ts [$r = 0.92$, $P < 0.001$, limits of agreement (LOA): −27.3 to 56.5 ms], SLD ($r = 0.94$, $P < 0.001$, LOA: −41 to 49 ms), and DI ($r = 0.89$, $P < 0.001$, LOA: −12.2 to 12.6 ms) which persisted irrespective of cardiac rhythm [Ts: sinus ($n = 32$) $r = 0.93$, $P < 0.001$; non-sinus ($n = 18$) $r = 0.91$, $P < 0.001$]. Automated TSI was more time efficient (3 ± 1 vs. 14 ± 2 min, $P < 0.001$) and demonstrated superior reproducibility: intra-observer (5.5 vs. 9.6%) and inter-observer variability (9.5 vs. 13.4%).

Conclusion Automated TSI enables rapid, reproducible intra-ventricular dyssynchrony assessment and overcomes some of the limitations of conventional techniques in sinus and non-sinus rhythm.

Keywords Echocardiography • Heart failure • Cardiac resynchronization therapy • Dyssynchrony

Introduction

Cardiac resynchronization therapy (CRT) is a proven therapy for systolic heart failure patients to reduce morbidity and mortality in those who remain symptomatic despite optimal medical therapy.[1,2] Current guidelines recommend CRT therapy in subjects with New York Heart Association (NYHA) class III–IV, reduced left ventricular (LV) systolic function [LV ejection fraction (LVEF) ≤ 35%] and QRS prolongation (≥120 ms) on electrocardiogram with sinus rhythm (Class I, Level A), QRS prolongation of ≥150 ms in NYHA class II (Class I, Level A), concomitant indication for permanent pacing (first implant or upgrading conventional pacemaker) (Class IIa, Level B), or permanent atrial fibrillation (AF) with an indication for atrio-ventricular node ablation (Class

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IIa, Level B).[3,4] However, these guidelines fail to successfully predict a positive response to CRT in 20–30% of subjects.[1,5–7]

Although several studies have demonstrated the superiority of mechanical dyssynchrony assessment over QRS duration for the prediction of response to CRT,[8,9] the role of echocardiographic determined dyssynchrony remains controversial. Echocardiography has achieved promising results in expert centers,[6,10–12] but the recent multicentre PROSPECT study reported major reliability issues with existing echocardiographic techniques for dyssynchrony assessment and cast doubt on the value of echocardiographic dyssynchrony for predicting response to CRT.[13,14]

A multitude of echocardiographic measures of dyssynchrony have been advocated; however, to date, there is no consensus as to the optimal technique. Recently published guidelines have advised that a variety of methods may be used and acknowledge the need for further studies.[15] Current colour-coded tissue Doppler imaging (TDI) techniques, such as tissue velocity imaging (TVI), are most commonly used, but require manual post-processing of data, thus are time-consuming, prone to operator error, and inconsistent interpretation. Tissue synchronization imaging (TSI) is a parametric tool derived from tissue Doppler images, which automatically detects peak positive myocardial velocities and calculates time to peak velocity (Ts) with reference to the QRS complex. Automated TSI (Auto TSI) is a dyssynchrony assessment tool, which provides a simple, comprehensive dyssynchrony assessment with minimal manual input, further expediting analysis and reducing the opportunity for operator error.

The aim of this study was to compare the accuracy, time efficiency, and reproducibility of Auto TSI with the established manual TVI techniques for the assessment of intra-ventricular dyssynchrony in systolic heart failure patients. In particular, we aimed to assess agreement between TVI and Auto TSI techniques, for the measurement of Ts and the two most commonly performed intra-ventricular dyssynchrony indices: septal to lateral delay (SLD) and dyssynchrony index (DI) in both sinus and non-sinus rhythms. In addition, we aimed to compare analysis time and reproducibility of TVI and Auto TSI techniques.

Methods

With the widening range of indications for CRT, the study population consisted of 50 consecutive systolic heart failure patients on stable optimal medical therapy, referred from a tertiary teaching university hospital's heart failure service for echocardiography. Age, gender, heart failure aetiology, NYHA class, medications, cardiac rhythm, QRS duration, and LVEF were recorded. The study was approved by our institutional Human Research Ethics Committee.

Echocardiography methods

Studies were performed with commercially available echocardiography equipment (Vivid-7 GE Vingmed Ultrasound, Norway). Standard two-dimensional echocardiography was performed by experienced echocardiographers as per the recommendations of the American Society of Echocardiography.[16] Tissue Doppler imaging was performed using standard apical views as previously described[17] and analysed offline using a customized software package (Echopac 6, GE Vingmed Ultrasound). The event-timing tool was employed on the aortic Doppler spectrum of three consecutive heartbeats to document the aortic valve opening and closure times, with reference to the start of the QRS complex. This defined the aortic ejection phase, during which measurements of peak velocity were recorded.

Colour-coded tissue Doppler imaging for intra-ventricular dyssynchrony assessment

Colour-coded TDI loops of five beats duration were recorded from the three standard apical views (two, three, and four chamber), enabling offline analysis with both TVI and TSI algorithms. For image optimization, gain settings, filters, and pulse repetition frequency were manipulated to optimize colour saturation. Maximal frame rates were achieved by adjusting sector width and depth.

For TVI analysis, a 6 mm sample volume was placed in six basal and six mid-segments of the LV. The event-timing tool was used to record Ts from the onset of the QRS complex on three consecutive beats. Mean Ts was calculated for each of the 12 myocardial segments. Dyssynchrony was evaluated by the measurement of SLD[6] and the 12-segment DI.[18]

For Auto TSI analysis, an initial qualitative assessment of the digital loop was performed to establish the degree and distribution of dyssynchrony and to select a representative beat for further analysis. For non-sinus rhythm, e.g. AF, an R–R interval representative of the mean heart rate was selected. With the TSI Ts tool, a cursor was placed in the centre of the six basal and mid-LV segments as obtained from the three standard apical views. Measurements were carried out at the TSI end-frame. When a wide range of colours was present within a small spatial region, the myocardial velocity curves (from a 6 mm region of interest) were interrogated and Ts manually determined. Manual interrogation was required in $<3\%$ of segments and added <1 min to analysis time. Echopac 6 software package automatically calculated a range of dyssynchrony indices including SLD and all segment standard deviation (DI) and presented Ts results in a colour-coded 'bull's eye' diagram (*Figure 1*).

Echocardiograms were analysed for cardiac dyssynchrony by a cardiologist experienced with both TVI and Auto TSI techniques. Automated TSI analysis was performed blinded to the TVI results.

Reproducibility analysis

For the assessment of intra-observer and inter-observer variability, we calculated the coefficient of reproducibility for the Ts measurement. For the determination of intra-observer variability, repeat (blind) analysis was performed a minimum of 4 weeks after the initial assessment with the corresponding technique. For inter-observer variability, studies were analysed by a second independent cardiologist blinded to the results of the primary observer. Intra-observer and inter-observer variability were 5.5 and 9.5% for Auto TSI and 9.6 and 13.4% for TVI, respectively.

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation. Paired sample *t*-tests were performed for comparison of continuous variables. Pearson's correlation statistics were performed to examine the relationship between dyssynchrony techniques. The Bland–Altman analysis assessed the level of agreement between dyssynchrony techniques. The Bland–Altman plots demonstrate the mean difference between the techniques (bias) and the 95% limits of agreement (LOA) (mean difference $\pm$ two standard deviations). A value of $P < 0.05$ was

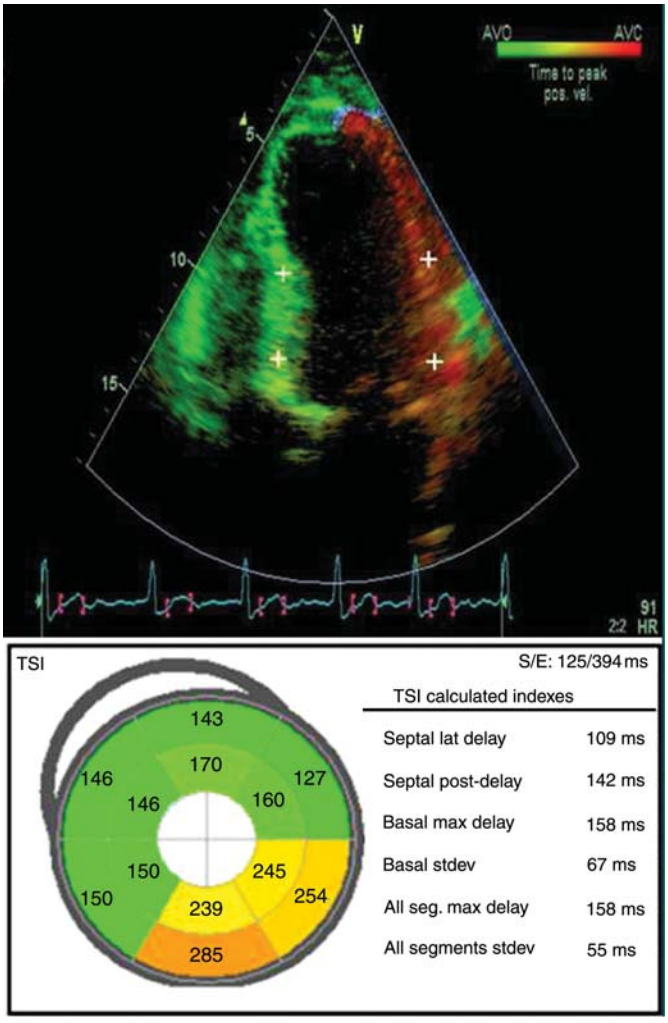

Figure 1 Automated TSI technique. Transthoracic echocardiogram (apical four chamber) demonstrating cursor placement for Auto TSI analysis; the bull's eye diagram for Ts measurements and Auto TSI calculated dyssynchrony indices. Ts, time to peak velocity; TSI, tissue synchronization imaging.

considered statistically significant. Statistical analysis was performed using SPPS 16.0 statistical software package.

Results

The baseline characteristics of subjects are displayed in *Table 1*. The majority of the patients were males with an ischaemic aetiology. There was a high utilization of optimal guideline-based medical therapy with the majority of subjects being ≥NYHA class II (86%), with an LVEF ≤ 35% (50%, LVEF range 14–63%) and left bundle branch block (54%). Thirty-two patients were in sinus rhythm and 18 patients in non-sinus rhythm (AF, $n = 9$; paced rhythm, $n = 9$). At baseline, six patients had received a dual-chamber pacemaker for high-degree atrio-ventricular block and three patients had received an implantable defibrillator for ventricular tachycardia. At final follow-up (mean follow-up 2.5 years), 17 (35%) subjects had had a biventricular pacemaker inserted since the baseline echocardiographic study.

Comparison of tissue velocity imaging and automated tissue synchronization imaging dyssynchrony assessment

Measurements were possible in 1181 of 1200 myocardial segments (98.4%). A comparison of Ts was feasible on 585 of 600 myocardial segments (97.5%). Fifteen segments were considered unsuitable for comparison due to poor image quality. There was a strong correlation between TVI and Auto TSI techniques ($r = 0.92$, $P < 0.001$) (*Figure 2A*), which was present in subjects with LVEF ≤ 35% ($r = 0.93$, $P < 0.001$) and LVEF > 35% ($r = 0.92$, $P < 0.001$). A Bland–Altman analysis revealed a small bias reflecting marginally higher Ts measurements by Auto TSI (TVI: 194 ± 54 ms, Auto TSI: 179 ± 55 ms, $P < 0.001$). The Bland–Altman plots demonstrate a strong agreement for Ts measured with TVI and Auto TSI throughout the range of Ts values (95% LOA: −27.3 ms to 56.5 ms; *Figure 2B*). Importantly, Auto TSI enabled a large and significant reduction in dyssynchrony analysis time when compared with

TVI assessment (Auto TSI: 3.2 ± 1.2 min, TVI: 13.9 ± 2.2 min, $P < 0.001$).

The assessment of SLD was feasible in 49 of 50 patients (98%). *Figure 3A* demonstrates a strong correlation between the TVI and Auto TSI measurements of SLD ($r = 0.94$, $P < 0.001$). The Bland–Altman plots (*Figure 3B*) demonstrate no significant measurement bias and good agreement between techniques across the range of values measured (95% LOA: −41.1 to 49.1 ms).

Table 1 Patient characteristics

Characteristic	*n* = 50
Age (years)	67.7 ± 10.0
Male, *n* (%)	44 (88)
Left ventricular ejection fraction (%)	34 ± 7.7
Aetiology, *n* (%)	
Ischaemic	35 (70)
Non-ischaemic	15 (30)
New York Heart Association class, *n* (%)	
I	7 (14)
II	25 (50)
III	17 (34)
IV	1 (2)
Cardiac rhythm, *n* (%)	
Sinus rhythm	32 (64)
Non-sinus rhythm	18 (36)
QRS duration (ms)	1.6 ± 36
Left bundle branch block, *n* (%)	27 (54)
Medications, *n* (%)	
β-Blocker	46 (92)
ACE-inhibitor or angiotensin receptor blocker	49 (98)
Spironolactone	24 (48)

Values are mean ± SD unless otherwise stated.

The assessment of the DI was feasible in all subjects. *Figure 4A* illustrates a strong correlation between the Auto TSI and TVI methods for the assessment of the DI ($r = 0.89$, $P < 0.001$). The Bland–Altman plots (*Figure 4B*) demonstrate no significant measurement bias and excellent agreement between techniques across the range of values measured (95% LOA: −12.2 to 12.6 ms).

Cardiac rhythm-based analysis of Ts measurements revealed an excellent correlation between the TVI and Auto TSI techniques, irrespective of the cardiac rhythm: sinus rhythm ($r = 0.93$, $P < 0.001$) and non-sinus rhythm ($r = 0.91$, $P < 0.001$).

Discussion

In this study, the measurement of intra-ventricular mechanical dyssynchrony with the Auto TSI technique showed an excellent agreement with dyssynchrony measured by the validated TVI technique, irrespective of cardiac rhythm status with superior reproducibility and analysis time. A major finding of this study was that Auto TSI reduced the opportunity for interpretation error, but maintained the ability to rapidly interrogate raw tissue velocity data.

Recent reported CRT studies in AF,[19,20] right ventricular pacing,[21–24] narrow QRS complex,[9] and NYHA class I/II[25] with LVEF ≤40%[26,27] will lead to expanded CRT indications. This is likely to result in a much larger population of potential CRT candidates, highlighting the need for improved, time efficient methods of the assessment of dyssynchrony and prediction of response to CRT.[3,4,19–24,26–28] Although echocardiographic dyssynchrony assessment is a promising prognostic marker, its generic utilization is limited by a necessity for extensive training and expertise to ensure high-quality, reproducible results. With analysis of 585 paired myocardial segments, two dyssynchrony methods, and the inclusion of patients with AF and paced rhythm, this study provides the most comprehensive direct comparison of the Auto TSI technique with established TVI methods.

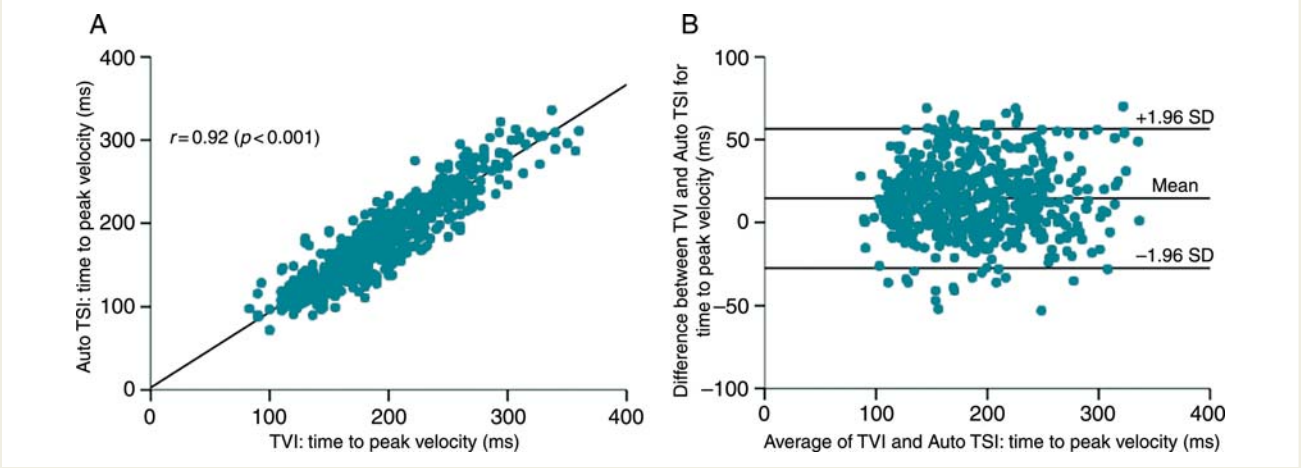

Figure 2 Comparison of manual TVI and Auto TSI Ts measurements. Scatter plot (*A*) and Bland–Altman's plot (*B*) comparing manual TVI and Auto TSI measurements of Ts from six basal and six mid-ventricular segments. Pearson's correlation is reported in the upper left corner of the scatter plot. TVI, tissue velocity imaging; TSI, tissue synchronization imaging.

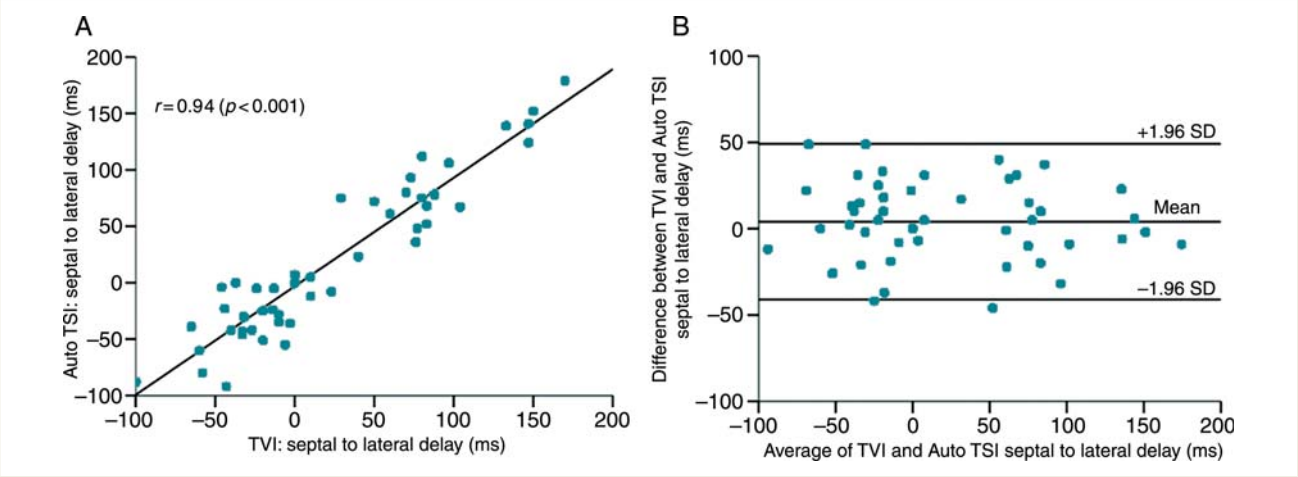

Figure 3 Comparison of manual TVI and Auto TSI SLD. Scatter plot (*A*) and Bland–Altman's plot (*B*) comparing manual TVI and Auto TSI measurements of SLD. Pearson's correlation is reported in the upper left corner of the scatter plot. TVI, tissue velocity imaging; TSI, tissue synchronization imaging.

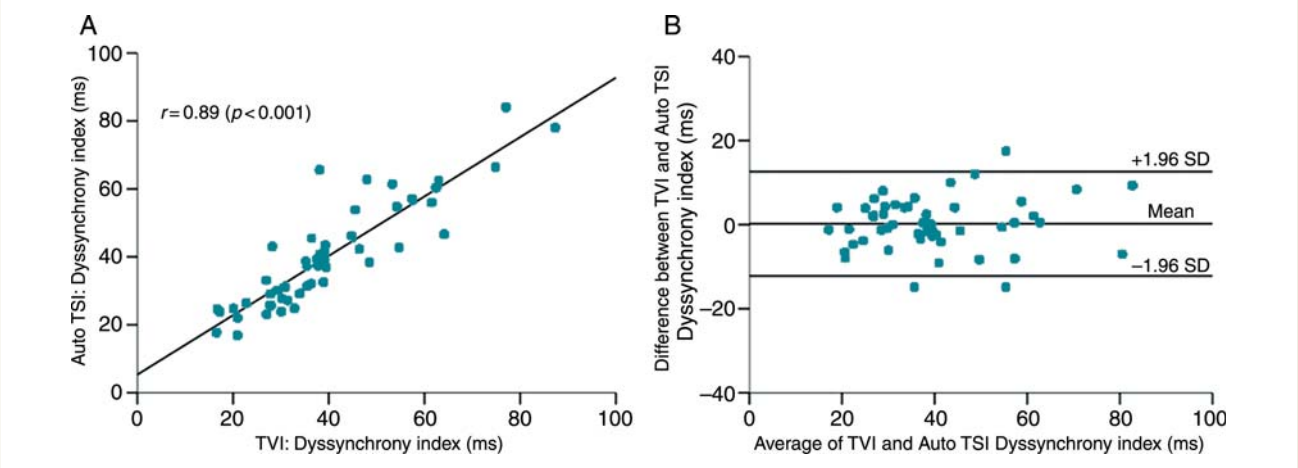

Figure 4 Comparison of manual TVI and Auto TSI DI. Scatter plot (*A*) and Bland–Altman's plot (*B*) comparing manual TVI and Auto TSI measurements of the 12-segment DI. Pearson's correlation is reported in the upper left corner of the scatter plot. TVI, tissue velocity imaging; TSI, tissue synchronization imaging.

A small bias in Ts measurement between techniques reflects a systematic difference in designation of the QRS onset and is unlikely to affect dyssynchrony results, which are dependent on the difference between segments rather than absolute values.

Standard TSI techniques have proven to be effective for the detection of intra-ventricular dyssynchrony and prediction of acute and long-term response to CRT.[29–31] To the authors' knowledge, only one study has compared TSI with automated software to manual colour-coded TDI for quantification of intra-ventricular dyssynchrony.[32] Van de Veire *et al.*[32] found a strong correlation between automated TSI and colour-coded TDI measurements of Ts; however, comparison was limited to just two myocardial segments per patient and one technique (SLD), whereas in our study, up to 12 segments per patient were compared with multiple measures of dyssynchrony (SLD and DI).

Numerous echocardiographic techniques have been proposed for the assessment of intra-ventricular dyssynchrony. However, PROSPECT identified that outside of expert centres, reduced test reproducibility and marked intra-observer variability limited the clinical utility of many echocardiographic techniques.[14,33] This study shows that there are several potential advantages of Auto TSI over existing dyssynchrony techniques utilized in PROSPECT. In particular, the automated processing algorithm reduces the impact of operator skill and improves reproducibility, while reducing analysis time. Intra-observer and inter-observer reproducibility were 5.5 and 9.5%, respectively, for the Auto TSI method and 9.6

and 13.4%, respectively, for the TVI method. Reproducibility for both techniques were superior to those reported in PROSPECT.[14]

Limitations of this study

The study design focused on the assessment of the accuracy and reliability of the Auto TSI technique in comparison to the established TVI technique for evaluation of intra-ventricular dyssynchrony. The enrolment of consecutive heart failure patients enabled the assessment of Auto TSI across a broad range of dyssynchrony values, cardiac rhythms, and LV function, but resulted in inclusion of some patients without a current class I indication for CRT. Consequently, the capacity of Auto TSI to predict response to CRT was not assessed in this study.

Conclusions

Automated TSI provides a simple, rapid, and comprehensive assessment of intra-ventricular dyssynchrony in both sinus and non-sinus rhythm. Dyssynchrony measurements are comparable between Auto TSI and TVI techniques; however, Auto TSI assessment improves time efficiency with superior reproducibility.

Conflict of interest: none declared.

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