European Journal of Echocardiography (2008) **9**, 235–240
doi:10.1016/j.euje.2007.03.026

CLINICAL/ORIGINAL PAPERS

Poor agreement of echographic measures of ventricular dyssynchrony

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Received 26 December 2006; accepted after revision 16 March 2007; online publish-ahead-of-print 11 May 2007

KEYWORDS
Dyssynchrony;
Echocardiography;
Tissue Doppler imaging;
Cardiac resynchronization therapy

Echocardiography is playing an increasing role in patient selection for cardiac resychronization therapy (CRT). The most frequently used techniques for evaluating inter- and intraventricular dyssynchrony are standard echocardiography and tissue Doppler imaging (TDI). Whether these techniques give concordant results is unknown. We studied 44 patients with a left ventricular ejection fraction of $\leq$0.35. Dyssynchrony was evaluated by standard echocardiography using the techniques described in the CARE-HF trial (interventricular mechanical delay and delayed motion of the posterior wall). Dyssynchrony was also measured by pulsed-wave TDI using delay to onset (Sm_o) as well as to peak (Sm_p) sustained systolic motion of the right ventricular free wall and of 4 basal segments of the left ventricle. A control group of 40 subjects with normal systolic function was studied for determining cutoff values. Agreement between standard echocardiography and TDI was poor for diagnosing inter- and intraventricular dyssynchrony ($\kappa < 0.33$ for all comparisons). None of the patients had evidence of intraventricular dyssynchrony when evaluated for delayed posterior wall motion, whereas dyssynchrony was seen in 15/44 (34%, $p = 0.001$) patients using left ventricular dispersion of $Sm_o > 20$ ms. Parameters using Sm_p were highly variable with poor reproducibility, making them unsuitable for evaluating dyssynchrony. In conclusion, our study indicates that there is poor agreement between standard echocardiography and TDI for diagnosing dyssynchrony.

Introduction

Detection of dyssynchrony by echocardiography has been proposed for improving patient selection before cardiac resynchronization therapy (CRT).[1] A multitude of echographic techniques exist for diagnosing dyssynchrony, the most frequent of which are standard echocardiography (with pulsed-wave Doppler and M-mode), and tissue Doppler imaging (TDI). The former technique was applied for patient selection in the CARE-HF trial,[2] and has the advantage of being widely available and simple to use in clinical practice. On the other hand, TDI has been the focus of growing attention, as it may quantify dyssynchrony more accurately than standard echocardiography. However, there is currently no consensus on which method to use, and direct head-to-head comparison of these techniques is lacking. Our aim was therefore to investigate whether standard echocardiography and TDI gave concordant results for evaluating inter- and intraventricular dyssynchrony.

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Methods

Study population

Forty-six consecutive patients addressed to the echocardiography laboratory of our institution were evaluated. Patients were included if they had an LVEF of $\leq$0.35 (by visual evaluation) and were in sinus rhythm. QRS width was not a criterion, as it has previously been shown that mechanical dyssynchrony may be present in patients with a narrow QRS.[3] Of these patients, 2 were excluded due to suboptimal image quality. A control group of 40 subjects (19 males, age 49 $\pm$ 13 years) with normal left ventricular systolic function, sinus rhythm, a narrow QRS (<120 ms), and without structural heart disease was also studied in order to obtain normal cutoff values of the echographic parameters. Patients with bundle branch block were excluded from the control group as mechanical dyssynchrony may result from intraventricular conduction delay.

The protocol was approved by the institutional ethics committee, and all patients gave informed consent to participate in the study.

Echocardiography

All echographic data were acquired by a single experienced observer (H.M.) in order to reduce variability of the recordings, using a Philips (Andover, MA) Sonos 7500 echocardiograph with an S3 probe. Digital echocardiograms were recorded according to the American Society of Echocardiography guidelines.[4]

Standard echocardiography

The same techniques as those described in the CARE-HF study[2] were used. Pulsed-wave Doppler samples were placed at the leaflet tips of the aortic and pulmonary valves in the apical 5-chamber view and the parasternal short-axis view, respectively. The aortic and pulmonary pre-ejection intervals were defined as the delay between the onset of the QRS complex and onset of flow. Interventricular dyssynchrony was calculated as the difference between these intervals, otherwise referred to as the interventricular mechanical delay (IVMD). Intraventricular dyssynchrony was evaluated by delayed motion of the posterior wall. Dyssynchrony was present if the delay to maximal excursion of the posterior wall by M-mode in the parasternal long-axis view exceeded the delay to left ventricular filling by pulsed-wave Doppler at the mitral valve leaflet tips in the apical 4-chamber view (the Q–E interval).

TDI

Pulsed-wave TDI samples (with 250 Hz pulsed-rate frequency) were placed on the basal segments of the free wall of the right ventricle and of 4 segments of the left ventricle in the apical 2- and 4-chamber views. At each point, delays between QRS onset and onset of the Sm (Systolic motion) wave (Q–Sm_o interval) as well as to peak sustained velocity (Q–Sm_p interval) were measured (*Figure 1*). Both Sm_o,[5–8] and Sm_p[9] have been used for evaluating dyssynchrony using pulsed-wave TDI, but whether they yield the same results is as yet not known. Interventricular delay was defined as the maximal delay between measurements of the right and left ventricle.[8] Intraventricular delay was defined as the maximal difference between any 2 of the 4 measurements of the left ventricle.[5,8–11] In addition, we also measured the difference of Sm_p between the septal and lateral walls of the left ventricle, otherwise known as the septal to lateral delay (SLD). This parameter has been described using colour-Doppler TDI, with a delay of $\geq$60 ms predicting response to CRT.[12]

All recordings were performed at end-expiration during normal breathing. Gain and filter settings were adjusted to optimize the images, and the sweep speed was set to 100 mm/s. A single observer (H.M.) measured the data offline using digital calipers with dedicated software (EnconCert, Philips, Andover, MA). Each parameter was averaged over 3 consecutive beats, and the data were rounded off to the nearest 5 ms for easier interpretation. The same observer repeated the recordings and measurements in 16 patients to assess intra-observer reproducibility. A second experienced observer (H.B.), blinded to the results of the first observer, performed additional recordings and measurements in 12 of these patients, in order to assess inter-observer reproducibility. All the data were acquired during the same session.

Statistical analysis

The Shapiro–Wilk test indicated that the results did not have a Gaussian distribution. Due to positive skewness, we used the 90th percentile for obtaining cutoff values of the parameters from the control population. The Mann–Whitney and Chi-square tests were used for comparing continuous and nominal variables respectively, between the control and patient groups. We used the McNemar test for comparing results of dyssynchrony obtained by the different techniques. Linear regression was used for correlating values of dyssynchrony between standard echography and TDI. Agreement was evaluated using the Kappa statistic. Reproducibility was assessed using the Bland–Altmann method. Data are expressed as mean $\pm$SD. A two-sided p value of <0.05 was considered statistically significant.

Results

The patient population demographics are shown in *Table 1*.

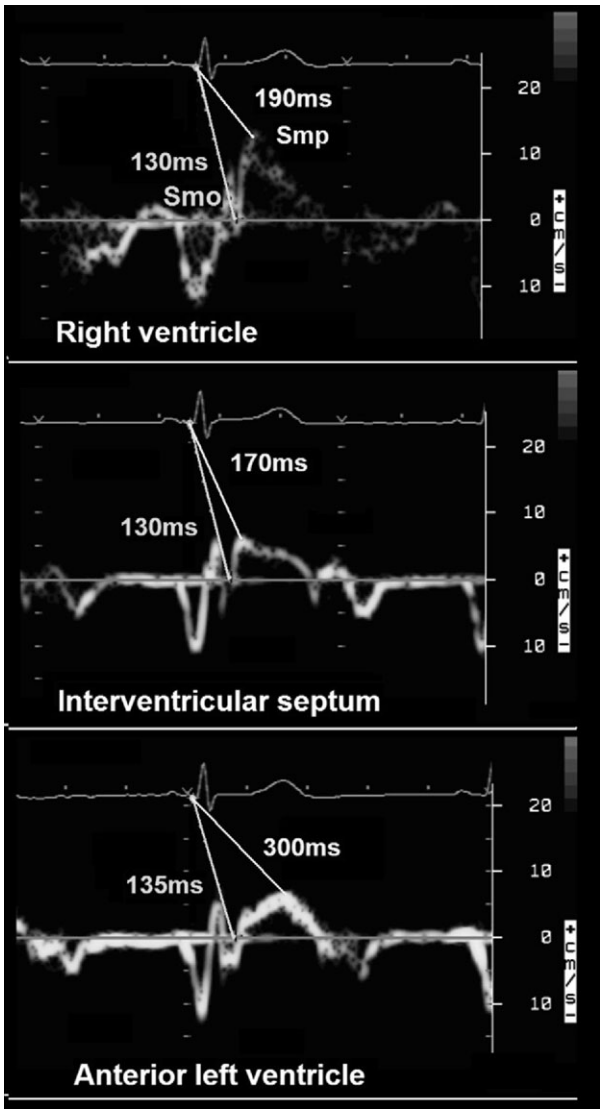

Figure 1 Measurement of the Q–Sm_o and Q–Sm_p intervals in a control subject. Note absence of significant inter- or intraventricular delay with Sm_o, and considerable delay when measuring Sm_p.

Reproducibility of the measurements

As expected, intra-observer reproducibility was better than for inter-observer reproducibility (*Table 2*). Intra-observer reproducibility was good for IVMD and parameters using Sm_o (with 95% limits of agreement of about $\pm$20 ms). Inter-observer reproducibility for parameters using Sm_p was very poor, with differences in measurements of up to 100 ms due to disagreement in interpreting the point of maximal sustained velocity in polyphasic or relatively flat velocity curves.

Normal limits for dyssynchrony

Cutoff values for dyssynchrony obtained from the control group (rounded off to the nearest 5 ms) were as follows: For standard echocardiography, dyssynchrony was present for an IVMD $>$ 30 ms. None of the control subjects had delayed posterior wall motion. For TDI, interventricular dyssynchrony was present for a delay in Sm_o of $>$25 ms,

Table 1 Patient population demographics

	Patients ($n = 44$)
Age (years)	67 ± 14
Sex (M/F)	31/13
Ischemic/nonischemic cardiomyopathy	22/22
History of diabetes	14
History of hypertension	25
LVEF (%)	26 ± 6
NYHA I/II/III/IV	5/13/19/7
QRS duration (ms)	125 ± 35
QRS $>$ 120 ms	20
Bundle branch block (left/right/indeterminate)	14/4/2

Table 2 Inter- and intra-observer reproducibility of different parameters of dyssynchrony

95% limits of agreement	Intra-observer reproducibility ($n = 16$)	Inter-observer reproducibility ($n = 12$)
IVMD (ms)	−27 to 26	−43 to 41
Interventricular Sm_o (ms)	−20 to 19	−45 to 85
Intraventricular Sm_o (ms)	−19 to 17	−38 to 54
Interventricular Sm_p (ms)	−36 to 20	−96 to 19
Intraventricular Sm_p (ms)	−51 to 35	−103 to 41

Table 3 Results of the different parameters of dyssynchrony in the control and patient groups

	Controls ($n = 40$)	Patients ($n = 44$)	P
Individual measurements			
APEI (ms)	87 ± 21	121 ± 31	<0.001
APEI $>$140 ms	0 (0%)	9 (23%)	NA
PPEI (ms)	85 ± 20	106 ± 18	<0.001
Q–Sm_o RV (ms)	115 ± 17	131 ± 33	0.010
Q–Sm_o septum (ms)	109 ± 18	147 ± 31	<0.001
Q–Sm_o LV lateral (ms)	112 ± 20	152 ± 33	<0.001
Q–Sm_o LV anterior (ms)	110 ± 19	147 ± 29	<0.001
Q–Sm_o LV inferior (ms)	112 ± 19	156 ± 32	<0.001
Q–Sm_p RV (ms)	199 ± 33	210 ± 31	0.128
Q–Sm_p septum (ms)	181 ± 35	222 ± 45	<0.001
Q–Sm_p LV lateral (ms)	188 ± 41	230 ± 48	<0.001
Q–Sm_p LV anterior (ms)	184 ± 45	219 ± 40	<0.001
Q–Sm_p LV inferior (ms)	186 ± 35	230 ± 47	<0.001
Interventricular dyssynchrony			
IVMD (ms)	13 ± 12	27 ± 23	0.002
Interventricular delay by Sm_o (ms)	14 ± 8	40 ± 35	<0.001
Interventricular delay by Sm_p (ms)	53 ± 27	51 ± 38	0.28
Left intraventricular dyssynchrony			
Delayed posterior wall motion	0 (0%)	0 (0%)	NA
Dispersion of Sm_o (ms)	9 ± 6	24 ± 25	0.001
Dispersion of Sm_p (ms)	43 ± 33	50 ± 35	0.92
Septal to lateral delay $>$ 60 ms	6 (15%)	8 (18%)	0.56

APEI = aortic pre-ejection interval; PPEI = pulmonary pre-ejection interval; RV = right ventricle; LV = left ventricle.

and intraventricular dyssynchrony for a delay of $>$20 ms. As concerns results for Sm_p, results were extremely heterogeneous within the control group, with average values of inter- and intraventricular delay being higher than for Sm_o ($p < 0.001$ for both). Due to this heterogeneity, we did not use Sm_p for analysis of dyssynchrony in the patient group, except for calculating SLD. It should be noted that 6 (15%) control subjects had an SLD $>$60 ms. Results of all parameters, other than those involving Sm_p, were significantly different between control and patient groups (*Table 3*).

Interventricular dyssynchrony

TDI trended to show dyssynchrony more often that standard echocardiography, and differences were significant when cutoffs of $>$40 ms for IVMD and $>$25 ms for TDI were used (*Table 4*). Agreement between the measurement techniques was poor ($\kappa < 0.33$ for all comparisons). Correlation between the IVMD and interventricular dyssynchrony assessed by Sm_o was poor ($r^2 = 0.13$, *Figure 2*). This was essentially due to poor correlation between the pulmonary pre-ejection interval and Q–Sm_o of the right ventricle ($r^2 = 0.10$), as the correlation between APEI and maximal Q–Sm_o interval of the left ventricle was good ($r^2 = 0.67$).

Intraventricular dyssynchrony

None of the patients had evidence of intraventricular dyssynchrony when studied for delayed posterior wall motion. However, dyssynchrony was found in 34% of the patients when using the cutoff of dispersion of $Sm_o > 25$ ms obtained from the control group ($p < 0.001$) and in 25% of patients when using the previously reported cutoff of $>$40 ms[5] ($p = 0.008$, *Table 4*). An example of discordant diagnosis of inter- and intraventricular dyssynchrony in a single patient is shown in *Figure 3*.

Agreement of parameters of interventricular dyssynchrony according to QRS duration

The patient population was divided into 2 groups according to QRS duration $\leq$ or $>$120 ms. There was a nonsignificant trend in greater interventricular dyssynchrony in patients with a wide QRS (IVMD 22 ± 18 ms vs 32 ± 27 ms, $p = 0.41$, and RV–LV Sm_o 32 ± 32 ms vs 48 ± 38 ms, $p = 0.30$). Agreement for diagnosis of interventricular dyssynchrony was compared between standard echocardiography and TDI for each group (*Table 5*). Although agreement was poor for all parameters in both groups, it was consistently worse in patients with a narrow QRS. Analysis of agreement was limited to parameters of interventricular dyssynchrony, as none of the patients

Table 4 Agreement between standard echocardiography and TDI for diagnosing dyssynchrony in the patient population

Standard echo criterion	*n* (%)	TDI criterion	*n* (%)	*P*	κ
Interventricular dyssynchrony					
IVMD $>$ 30 ms[a]	13 (30)	RV—LV $Sm_o > 25$ ms[a]	20 (45)	0.17	0.10
		RV—LV $Sm_o > 38$ ms[5]	14 (32)	1.00	0.20
IVMD $>$ 40 ms[2]	10 (23)	RV—LV $Sm_o > 25$ ms[a]	20 (45)	0.021	0.24
		RV—LV $Sm_o > 38$ ms[5]	14 (32)	0.39	0.32
Intraventricular dyssynchrony					
Delayed posterior wall motion[2]	0 (0)	LV $Sm_o > 20$ ms[a]	15 (34)	$<$0.001	NA
		LV $Sm_o > 40$ ms[5]	11 (25)	0.001	NA
		SLD $Sm_p > 60$ ms[12]	8 (18)	0.008	NA

RV—LV Sm_o = maximal delay between Sm onset (Sm_o) of the right ventricular free wall and any of 4 left ventricular basal segments. LV Sm_o = maximal delay between the 4 left ventricular basal segments. SLD = Septal to lateral delay measured using Sm peak (Sm_p). The Kappa statistic was not applicable for intraventricular dyssynchrony, as there were no positive cases with echocardiography.

[a]Cutoff derived from the control group. All other cutoffs are derived from the cited references.

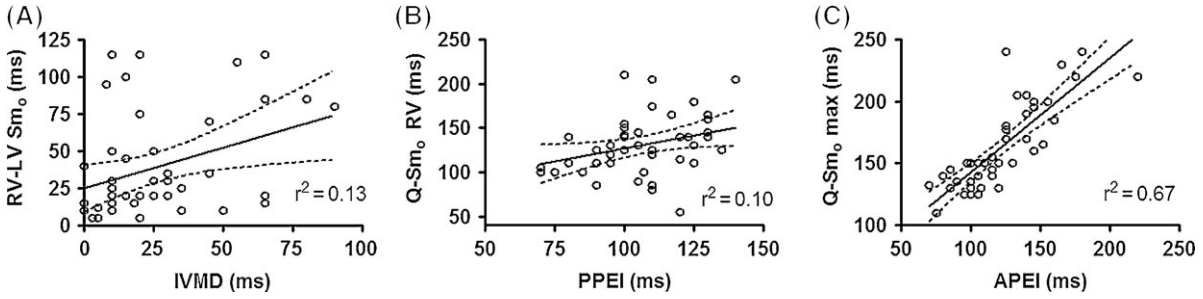

Figure 2 (*A*) Correlation (with 95% confidence intervals) of the interventricular mechanical delay (IVMD) plotted against interventricular dyssynchrony assessed by maximal difference in Sm_o (RV—LV Sm_o). (*B*) Correlation between the pulmonary pre-ejection interval (PPEI) and Q–Sm_o of the right ventricle. (*C*) Correlation between the aortic pre-ejection interval (APEI) and the maximal Q–Sm_o of the left ventricle.

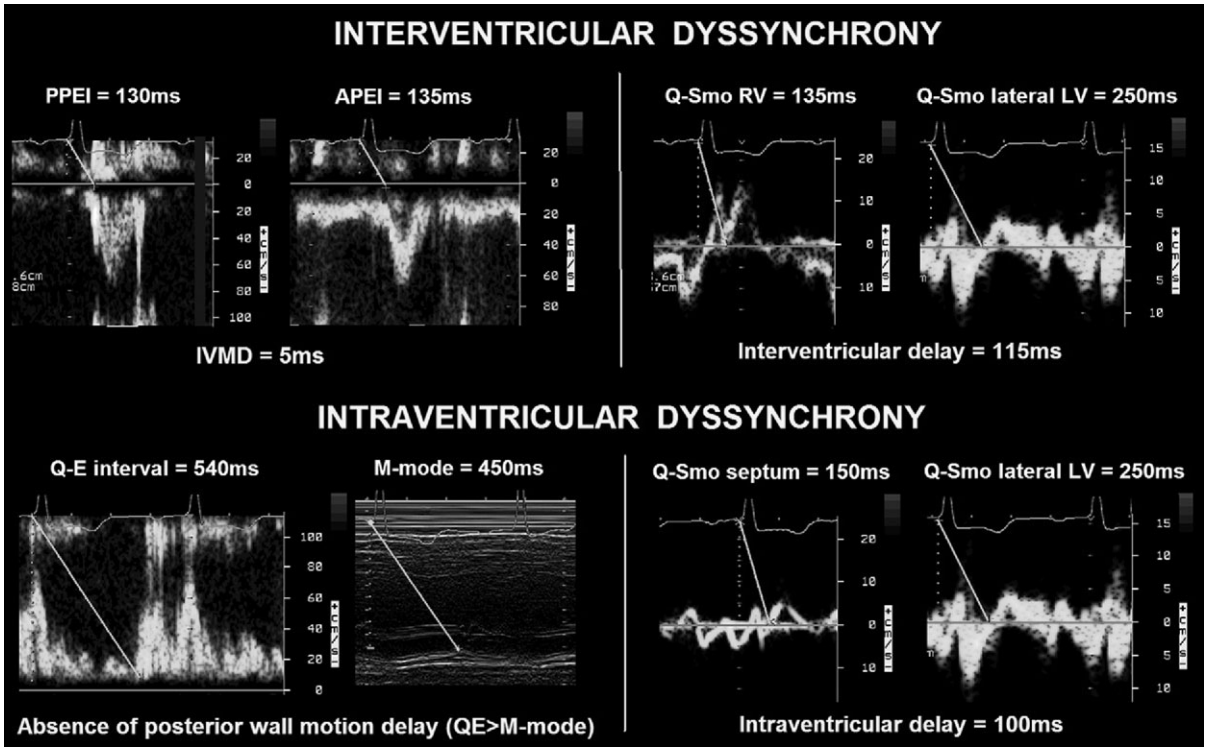

Figure 3 Discordance in diagnosis of inter- and intraventricular dyssynchrony between standard echocardiography and TDI in a single patient. Note that this patient has a narrow QRS. (IVMD = Interventricular mechanical delay; PPEI = Pulmonary pre-ejection interval; APEI = Aortic pre-ejection interval; RV = Right ventricle; LV = Left ventricle).

Table 5 Agreement between standard echocardiography and TDI for diagnosing interventricular dyssynchrony in patients with normal and wide QRS complexes

Standard echo criterion	TDI criterion	Kappa statistic	
		QRS ≤ 120 ms ($n = 24$)	QRS > 120 ms ($n = 20$)
IVMD > 30 ms	RV—LV Sm_o > 25 ms	0.17	0.31
	RV—LV Sm_o > 38 ms	0.05	0.20
IVMD > 40 ms	RV—LV Sm_o > 25 ms	0.03	0.42
	RV—LV Sm_o > 38 ms	0.17	0.30

showed intraventricular dyssynchrony using the M-mode criterion (making the Kappa statistic non-applicable).

Discussion

Our study shows for the first time that diagnosis of dyssynchrony differs considerably in a given patient according to whether the technique being used is standard echocardiography or pulsed-wave TDI. This lack of agreement between measurement techniques may be due to several reasons: (1) The physical parameters being measured are different. Pulsed-wave Doppler at the valvular level measures blood flow, whereas TDI measures wall motion. Even though these 2 parameters are inter-related (i.e. blood flow results from wall motion), this relationship is complex. For instance, even though TDI may indicate that a particular left ventricular myocardial segment has delayed motion as compared to the right ventricular free wall, this segment may be of limited functional importance, leading to diagnosis of interventricular dyssynchrony by TDI but not by the IVMD. Conversely, onset of motion of the basal right and left ventricular segments may be relatively synchronous by TDI, but if the left ventricular apex is dyskinetic or has delayed contraction, aortic ejection may be retarded, resulting in a prolonged IVMD. In addition, pulsed-wave TDI only measures longitudinal wall motion, and ignores radial and circumferential components that may also play a part in delayed ejection. (2) M-mode of the posterior wall only analyses motion of a single left ventricular segment, whereas 4 segments of the left ventricle were analysed using TDI. It is therefore understandable that delayed posterior wall motion (used to diagnose intraventricular dyssynchrony in the CARE-HF study[2]) was unable to show evidence of dyssynchrony. Also, M-mode recorded in the parasternal long-axis view refers to radial motion, whereas TDI recorded in the apical view refers to longitudinal motion. (3) Evidence of delayed motion by pulsed-wave TDI is not synonymous of delayed contraction (better analysed by strain imaging), and may be passive in nature. (4) Interpretation of standard echocardiography is relatively straightforward, whereas that of TDI is more complex. Low velocity signals may make it difficult to correctly mark onset (and especially peak) Sm velocity, and this may lead to measurement error.

Our study shows the importance of the value used as a cutoff for defining dyssynchrony. We compared cutoff values obtained from our control population with those reported in the literature (*Table 4*). There are no large series that define normal values for Doppler pre-ejection delays or pulsed-wave TDI. Normal cutoffs for inter- and intraventricular delay using Sm_o were reported by Bader *et al.*[5] in 25 subjects and were found to be longer than in those derived from our control population. Differences in sample size (with 40 control subjects in our study) may explain these differences. In agreement with our data, Pai and Gill[13] found *average* values of Q–Sm_o to be very similar in basal segments of the septal, lateral, inferior and anterior walls of the left ventricle in 20 normal individuals, but they did not report left ventricular Q–Sm_o *dispersion* in their study.

Our data also indicate that Sm_o should be used for pulsed-wave TDI measurements, and not Sm_p, as the latter measurement is highly variable in the control population (with the presence of an SLD > 60 ms in 15% of the group), and has poor reproducibility. In agreement with our findings, Jansen *et al.*[14] have reported poorer reproducibility of Sm_p compared to Sm_o and have also found the former parameter to be less accurate for predicting reverse remodelling. However, it has to be borne in mind that studies measuring delay to peak sustained velocity using colour-Doppler TDI have shown to predict response to CRT,[3,11,12] which suggests that colour-Doppler TDI and pulsed-wave TDI may not be used interchangeably. Peak systolic velocity is less clearly visualized with pulsed-wave TDI compared to colour-Doppler TDI, which may explain these differences.

Study limitations

We only analysed pulsed-wave TDI, and not colour-Doppler TDI for which many parameters of dyssynchrony have been described. However, as the latter technique is not available on all echocardiographs, pulsed-wave TDI is often used in clinical practice. Pulsed-wave TDI also has better temporal resolution, with a pulsed-rate frequency of 250 Hz compared to about 100 Hz with colour-Doppler TDI (depending on the imaging sector used).

The control population was not matched for age and sex to the patient group, and may therefore have yielded inappropriate cutoff values for dyssynchrony. However, it has previously been shown that dyssynchrony is not related to age in control subjects.[10] We also used cutoff values obtained from previous studies in our analysis, which did not affect the results. The population size was relatively limited due to the number of parameters studied in each patient. However, the results very clearly indicated lack of agreement of the different echographic parameters of dyssynchrony, and it is unlikely that findings would have differed with a larger population. Finally, presence of class III or IV heart failure was not mandatory in our patient population, as our aim was to compare echographic techniques for evaluating dyssynchrony in patients with systolic dysfunction, and not to evaluate prevalence of dyssynchrony in candidates for CRT.

Conclusions

Whether echographic markers of dyssynchrony are able to improve patient selection for CRT is controversial.[1,15,16] More important than the presence or absence of dyssynchrony *per se* is the ability of a particular parameter for

predicting response to CRT. Multicentre trials such as the PROSPECT study[17] may help to identify these markers. However, we will have to wait for randomized studies that evaluate robust, reproducible parameters which should then be validated in large cohorts of 'real world' consecutive patients to confirm the role that echocardiography will play in patient selection for CRT. In the meantime, it is important that the techniques used for measuring dyssynchrony are accurately reported, as they are not interchangeable.

Acknowledgements

I. Vieira, RN, was funded by a research grant by Medtronic.

Conflicts of interest: None of the authors has any potential conflict of interest.

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