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Comparison between IEGM-based approach and echocardiography in AV/PV and VV delay optimization in CRT-D recipients (Quicksept study)

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ABSTRACT

Background: AtrioVentricular (AV) and InterVentricular (VV) delay optimization can improve ventricular function in Cardiac Resynchronization Therapy (CRT) and is usually performed by means of echocardiography. St Jude Medical has developed an automated algorhythm which calculates the optimal AV and VV delays (QuickOpt™) based on Intracardiac ElectroGrams, (IEGM), within 2 min. So far, the efficacy of the algorhythm has been tested acutely with standard lead position at right ventricular (RV) apex. Aim of this project is to evaluate the algorhythm performance in the mid- and long-term with RV lead located in mid-septum.
Methods: AV and VV delays optimization data were collected in 13 centers using both echocardiographic and QuickOpt™ guidance in CRTD implanted patients provided with this algorhythm. Measurements of the aortic Velocity Time Integral (aVTI) were performed with both methods in a random order at pre-discharge, 6-month and 12-month follow-up.
Results: Fifty-three patients were studied (46 males; age 68 ± 10y; EF 28 ± 7%). Maximum aVTI obtained by echocardiography at different AV delays, were compared with aVTI acquired at AV delays suggested by QuickOpt. The AV Pearson correlations were 0.96 at pre-discharge, 0.95 and 0,98 at 6- and 12- month follow-up respectively. After programming optimal AV, the same approach was used to compare echocardiographic aVTI with aVTI corresponding to the VV values provided by QuickOpt. The VV Pearson Correlation were 0,92 at pre-discharge, 0,88 and 0.90 at 6-month and 12- month follow-up respectively.
Conclusions: IEGM-based optimization provides comparable results with echocardiographic method (maximum aVTI) used as reference with mid-septum RV lead location.

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1. Background

Although Cardiac Resynchronization Therapy (CRT) has become a standard treatment in chronic heart failure patients with Left Ventricular (LV) systolic dysfunction, intraventricular conduction delay and NYHA class II to IV, despite optimal medical therapy [1], about 30–40% of patients still do not to respond to treatment [2–8]. The role of sensed and paced atrio-ventricular (PV/AV) and inter-ventricular (VV) delays optimization remains controversial. The 2013 ESC guidelines on CRT do not recommend a routine AV and VV optimization, which should be restricted to non-responders and to patients with ischemic heart disease [1–10]. Optimization has been performed using echocardiography, which, however, is time- and skill-costly and can be hampered by a relevant intra- and inter-observer variability [11–13]. This fact has prompted a series of alternative methods for optimization, among which Intracardiac ElectroGraMs (IEGM)-based algorithms [14–16] have gained most attention. The QuickOpt™ (St Jude Medical, ST Paul, MN, USA) is an automatic IEGM-based algorithm incorporated in CRT devices, validated for optimizing AV and VV delays [14,17,18]. However, no serial assessment over time has been performed to test the relation between IEGM- and echo-generated optimal values of AV, PV and VV intervals. Furthermore, right ventricular (RV) lead has been predominantly located at the apex, and the QuickOpt™ reliability in "non-apical" RV pacing sites has not been highlighted yet.

The QuickSept study has been designed to evaluate the efficacy of QuickOpt™ algorithm in a population of patients implanted with a CRT system with defibrillator capabilities (CRT-D) with the RV lead in a mid-septal position, at Hospital discharge at six-month and at one-year follow-up, by comparing AV and VV intervals calculated by IEGM with those determined by echocardiographic (ECHO) measurements.

2. Materials and methods

2.1. Population

Between January 2011 and January 2012, in 13 Italian Laboratories 53 patients were implanted with a CRT-D system according to current guidelines indications [19]. All patients gave written informed consent. Baseline patients' features are shown in Table 1. Main inclusion criteria were: stable and safe placement of an active–fixation RV lead on mid-interventricular septum; achievement of an efficacious LV intravenous pacing from a Coronary Sinus (CS) branch. St Jude Medical (Saint Paul, Minnesota MN, USA) manufactured CRT-D systems with QuickOpt™ algorithm were implanted: models CD3211-36 Promote Plus, CD3215-36 Promote Accel, CD3239-40 Promote Quadra, 3251-40 Unify Quadra and 3235-40 Unify, with the single or dual-coil active fixation leads Durata mod. 7120Q and 7122Q. Enrolment was accomplished at pre-discharge from hospital after recovery from implant. At hospital discharge and after at each follow-up, AV, PV and VV intervals were programmed as designated by the ECHO assessment.

Table 1
Baseline features of study population (n = 53). LVEF: Left Ventricular Ejection Fraction; ESV: End Systolic Volume; EDV: End Diastolic Volume.

Baseline features	Mean ± SD or %
Gender (M)	46 (86.8%)
Age (years)	68 ± 10
LVEF (%)	28 ± 7
ESV (ml)	148 ± 70
EDV (ml)	198 ± 79
Ischemic cardiomyopathy	47.2%
Dilated cardiomyopathy	39.6%
Hypertensive cardiomyopathy	3.8%
Myocardial non-compaction	1.9%
Etiology not reported	7.5%

2.2. Aims

Primary end-point was to evaluate the relationship between the series of aortic flow Velocity Time Integral (aVTI) values calculated by the two methods at the PV, AV, and VV interval settings recommended by both the QuickOpt™ and the standard ECHO optimization in CRT-D patients, at three index times: pre-discharge, at 6-month and at 12-month follow-ups.

Secondary end-point was to define the correlation between the optimal AV, PV and VV intervals defined by ECHO, using aVTI measurements and by the QuickOpt™ algorithm, IEGM-based.

2.3. Right ventricular and left ventricular lead positioning

Defibrillation lead was implanted in the mid interventricular septum in all patients.

CS lead was implanted using current conventional technique.

2.4. Echocardiographic measurements

ECHO and Doppler measurements were performed at hospital discharge, at 6-month and 12-month follow-ups. Transducer and sample volume were maintained in the same position as far as possible during the entire series of AV, PV or VV programming [20]. Acquisition of aortic Doppler flow velocities was performed digitally. The optimal AV, PV, and VV delay by the ECHO method was defined as the delay associated with the largest average aVTI. Aortic VTI measurements were obtained in accordance with the American Society of Echocardiography guidelines [12]. A random sample (average 2 ECHO for each Laboratory at discharge) of echocardiographic exams pre-discharge, 6 months and one year follow-up was evaluated off-line for each center by a Core-lab. The reproducibility in aVTI measurements was determined as the inter- and intra-center (that is: between echocardiographers) using variability coefficient (CV).

2.5. aVTI and IEGM acquisitions

AV and VV interval optimization was carried out by each participating center by calculating the aVTI on pulsed Doppler of transaortic flow. Using the VTI method the best matching of AV and VV intervals was determined at each patient's evaluation. Transducer and sample volume were maintained in the same position as far as possible during the entire series of AV/PV or VV programming [12,20]. Acquisition of aortic Doppler flow velocities was performed digitally. With patients in a stable clinical condition, three aVTI measurements for each combination of AV, PV and VV (see Table 2) programmed values were performed 2 min after the programming of delays, excluding both premature beats and post-premature contraction beats. From the sampled aortic flow, pre-ejections components were excluded, which corresponded to atrial and isovolumetric ventricular contractions. The sequence of acquisitions of aVTI with different AV and VV intervals was single-blind and randomly decided by the attending electrophysiologist, in order to keep the echocardiographer unaware of the programmed delay.

2.6. Statistical analysis

Categorical variables describing the patient population are expressed as absolute numbers and percentages, while continuous

Table 2
aVTI measures were carried out with different AV, PV and VV delays. The table shows the delays used during Echocardiographic measurements.

aVTI[a] measures with DDD atrial rate >10bpm spontaneous rate:	
QuickOpt AV/PV[b]	QuickOpt VV
QuickOpt AV/PV ± 20	QuickOpt VV ± 10
QuickOpt AV/PV ± 40	QuickOpt VV ± 20
QuickOpt AV/PV ± 60 (max AV/PV = 200 ms)	QuickOpt VV ± 40

[a] aVTI: aortic Velocity Time Integral.
[b] AV/PV_Atrio-Ventricular Delay.

variables are shown as means [with standard deviations (SD)] or medians (with quartiles) for continuous variables.

Nonparametric Wilcoxon-Mann-Whitney and Wilcoxon signed rank (for paired data) tests were used for non-normally distributed variables. The primary endpoint was assessed by means the linear correlation analysis by the Pearson product-moment correlation coefficient to assess the agreement between the ECHO-based and the IEGM-based aVTIs for each of the AV/PV, and VV delay determinations.

The secondary endpoint was assessed by means the Bland–Altman [21] plot method, to test whether the overlap between the series of values given by the two techniques was congruent. It was deemed as clinically acceptable to have a difference not wider than 30 msec in measurements of AV and VV intervals.

Intra and inter-observer reproducibility of echocardiographic measurements were reported as CV calculated using the formula: CV = ¼ (SD/arithmetic mean of measurements)/100, where SD is the standard deviation of residuals (measurement 1 - measurement 2) [21]. CV value less than 5% was considered to indicate a good reproducibility.

The software Microsoft Office Excel 2007 was employed for data storage and analysis.

3. Results

3.1. Electrical results

Fifty-three patients were enrolled. Rv lead was in septal position in all patients. Atrial lead was implanted in appendage in 98% of the patients. LV lead was implanted in 26 (49%) patients in a lateral vein, in 1(2%) in an antero-lateral vein, in 4 (7%) in a middle vein, in 10 (20%) in a postero vein and in 12 (22%) in a postero-lateral vein.

Leads electrical parameters were acceptable after implant procedure and stable at follow-up (Table 3). Neither RV lead dislodgement nor failures in electrical therapies delivery nor arrhythmic death occurred.

3.2. Comparison between aVTI after optimizing PV and AV intervals by echocardiography and by QuickOpt™

Optimal mean PV and AV values, obtained from the best aVTI which were calculated by both IEGM-based and echocardiographic method, showed a good correlation at hospital discharge and at 6-month and 12-month follow-up. Correlation coefficients were always above 94% (Table 4). The close linear relationship between the values of maximum aVTI calculated with both methods at discharge and after 12 months is showed in Fig. 1.

3.3. Comparison between aVTI after optimizing interventricular (VV) intervals by echocardiography and by QuickOpt™

At the optimized VV intervals, the values of aVTI calculated by both IEGM and echocardiographic method showed a good correlation, with a coefficient above 88% at the three index times (Table 5). The relationship between the maximum aVTI calculated with both methods at discharge and at 12-month follow-up is showed in Fig. 2.

As expected the overall difference between the best aVTI and the worst aVTI is significant for AV ($p < 0.001$), PV ($p < 0.001$) and VV ($p < 0.001$). Different Delay produced significant different in VTI Values.

4. Secondary end point

4.1. Comparison between optimal PV/AV intervals measured by echocardiographic method and by QuickOpt™

Using Bland-Altman plot analysis, in any single patient the clinically acceptable correlation between echo- and IEGM-generated PV/AV optimized measures showed a progressive improvement. Cases where differences in mean's variations were less than 30 ms were 52% at discharge and became 61% and 65% at six- and twelve-month follow-up (Fig. 3).

4.2. Comparison between optimal VV intervals measured by echocardiographic method and by QuickOpt™

The analysis of values given by the two techniques, performed using the Bland–Altman plot, demonstrated that the clinically acceptable congruence between them was substantially stable during the follow-up. The corresponding difference less than 30 ms between the two techniques were 56% at discharge, and 51% and 48% at 6- and 12-month follow-up respectively (Fig. 4).

4.3. Intra and inter-observer reproducibility of echocardiographic measurements

Intra and inter-observer reproducibility of aVTI measurements, reported as coefficient of variation (CV), are displayed in Table 6. The aVTI determined at LVOT measurement resulted reproducible, being both intra- and inter-observer CV less than 5% in all follow-ups.

4.4. Discussion

In a selected population of CRT-D patients with a mid-septal

Table 3
Left and Right Leads electrical measurements at pre-discharge, 6-month (6 m FU) and 12-month follow-Ups (12 m FU). No failure in sensing, pacing and defibrillation therapy was found during the Study.

	Pre-discharge (mean ± SD)	6 m FU (mean ± SD)	12 m FU (mean ± SD)
RV[a] wave amplitude (mV)	10.88 ± 4.76	10.05 ± 5.03	9.91 ± 5.28
RV Pacing threshold (V × 0.5 ms)	0.56 ± 0.51	0.69 ± 0.42	0.68 ± 0.46
LV[b] Pacing threshold (V × 0.5 ms)	1.16 ± 0.6	1.5 ± 1	1.5 ± 1.18

[a] RV: Right ventricle.
[b] LV:Left Ventricle.

Table 4
aVTIs obtained with optimal AV/PV intervals calculated with Echo-based and IEGM-based QuickOPt method at pre-discharge, 6-monthfollow-Up (6 m FU) and 12-month follow-Up (12 m FU); Pearson correlation analysis showed a good correlation between aVTIs obtained with both methods; Median and quartiles (25, 75) of AV/PV Optimal Delay; there aren't significant differences between the two methods.

		aVTI (cm) Mean ± SD	Pearson coefficient value	Optimal delays median; Interquartile 25; 75 (ms)	P value
AV delay pre-discharge	Max Echo	20.8 ± 6.7	0.96	170[130; 190]	P = 0.9
	IEGM	19.2 ± 9.7		150 [150; 170]	
PV delay pre-discharge	Max Echo	23 ± 8	0.94	120[85; 150]	P = 0.4
	IEGM	21.2 ± 7.3		110 [100; 130]	
AV delay 6 m FU	Max Echo	22 ± 6	0.95	160[142.5; 190]	P = 0.67
	IEGM	20 ± 6		160[150; 170]	
PV delay 6 m FU	Max Echo	25 ± 8	0.94	120[100; 140]	P = 0.59
	IEGM	23 ± 7		110[100; 120]	
AV delay 12 m FU	Max Echo	22.9 ± 8.8	0.98	165[150; 190]	P = 0.38
	IEGM	21.7 ± 8		160[150; 170]	
PV delay 12 m FU	Max Echo	26 ± 10	0.97	110[80; 140]	P = 0.69
	IEGM	24 ± 9		110[100; 120]	

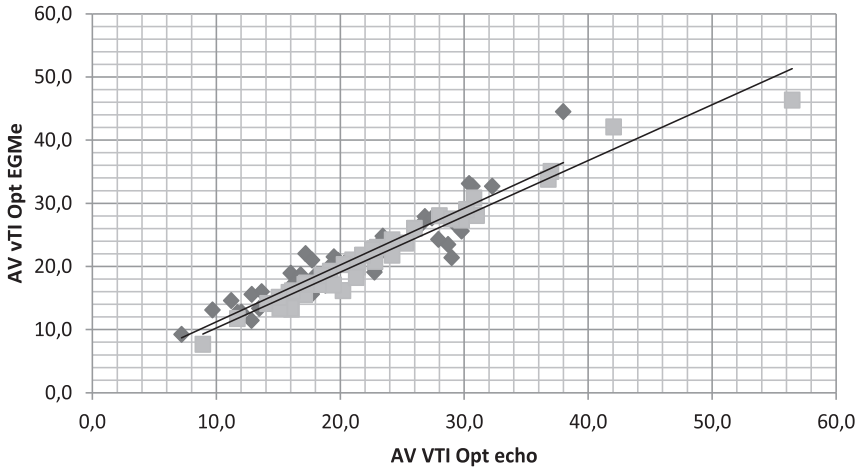

Fig. 1. Correlation between aVTI (cm) calculated with optimal AV/PV intervals optimized by Echo and QuickOpt™ method's at pre-discharge and at 12 month Follow up (upper line). The correlation between the two methods is always good.

Table 5
aVTIs obtained with optimal VV intervals calculated with Echo-based and IEGM-based QuickOpt™ method at pre-discharge, 6-month follow-Up (6 m FU) and 12.month follow-Up (12 m FU). Pearson correlation analysis showed a good correlation between aVTIs obtained with both methods.

		aVTI (cm) Mean ± SD	Pearson
VV delay pre-discharge	Max Echo	23.2 ± 8	0.92
	IEGM	20.8 ± 7.1	
VV Delay 6 m FU	Max Echo	24.9 ± 7.5	0.88
	IEGM	21 ± 6.7	
VV Delay 12 m FU	Max Echo	25.9 ± 10	0.91
	IEGM	22 ± 8	

placement of RV lead, the Quicksept study showed that aVTI values at the optimized AV/PV and VV intervals as determined by ECHO method and by QuickOpt™ algorithm -based method were quite well correlated, and that this correlation was maintained in long-term follow-ups. Previously published works have validated the IEGM-based algorithm for optimizing AV and VV delays, in an acute and single-time setting and with RV lead at the apex. Most prospective, small sample and non-randomized studies have demonstrated that the QuickOpt™ -generated acute optimization was comparable with the ECHO-based one as far as long-term response to CRT was concerned, and that the QuickOpt™ method resulted faster and easier to perform than ECHO-guided optimization [13–17]. On the other hand other studies was reached a discordant conclusion, The FREEDOM [23] results presented at Heart Rhythm Society in 2010 showed no statistically significant difference between echo and QuickOpt approaches.

In Quicksept, ECHO aVTI was used for ECHO-based optimization of AV and VV intervals. In the Pearson correlation analysis, comparing aVTI values, which were obtained by measuring AV and VV intervals by echocardiography and IEGM-based QuickOpt™ algorithm, the level of correspondence resulted around 90% at all three index times (above 90% at AV evaluation, above 88% at VV evaluation), with a fairly linear correlation.

However, a further analysis by means of Bland-Altman plot on ECHO-derived and QuickOpt™ –generated data regarding AV intervals found that, at most, only in 52% of cases at discharge, 61% at 6 months follow up and 65% at 12 months follow-up were the percent difference between measurements supplied by the two methods below 30 msec – the predefined upper limit of clinical insignificance. Moreover, when VV intervals were analyzed, this

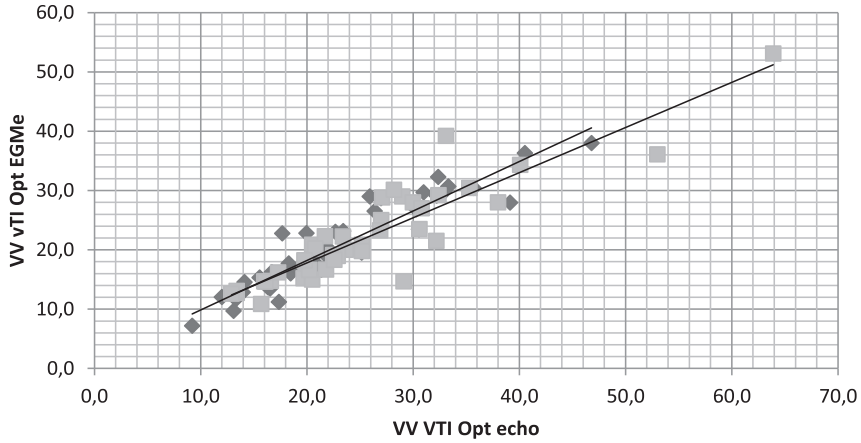

Fig. 2. Correlation between aVTI (cm) calculated at the optimized VV intervals obtained by Echo and QuickOpt™ method's at pre-discharge and at 12-month follow-up (upper line). The correlation between the two methods was always good.

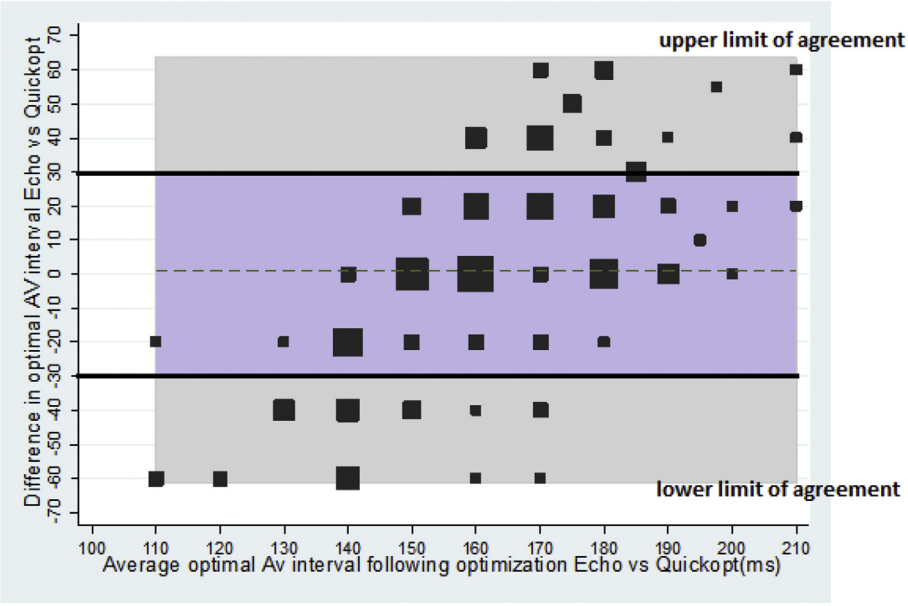

Fig. 3. Bland-Altman plot of differences in optimal atrioventricular interval measured by echocardiography and by QuickOpt at Phd, 6 and 12-month follow-up. Grey zone indicate average, upper and lower limit of agreement (1.13 msec ± 31 msec; IC 95% −61 msec + 63 msec). Colored area indicates clinically acceptable margins of difference between the two tecniques (0 ± 30 msec). Although there was no statistical difference between the two methods, the clinically acceptable margins of difference between them (0 ± 30 msec) showed a low concordance (64%).

figure decreased to around half the cases in all the follow-ups time.

This finding suggests that optimal aVTIs determined by the two methods were similar even with a remarkable difference in AV and VV intervals, and that, consequently, there could be a wide variations among the programmed settings in the same patients. In measurements of VV intervals by the two methods there was a poor correlation depending on the ventricle which was paced first with 50% of discordance (Fig. 5).

Discrepancy between echo- and QuickOpt™ -calculated aVTIs being fairly well correlated and corresponding AV and VV intervals being scarcely correlated could be due to the fact that even wide variations of AV and VV delays can elicit small hemodynamic effects When we study AV delays, the hemodynamic effect can also be influenced by the VV delay. The inter-ventricular and intra-ventricular delays are influenced by different factors, too.

This might be caused in our opinion by the very short time allowed for the CRT device to work with each predefined setting of AV and VV intervals (in our study 2 min, but in other study only 30 s). A sort of slower hemodynamic adaptation to mechanical consequences of a certain programming could be invoked. It can be also hypothesized that methods for measuring aVTI require a longer period of pacing to produce measurable different hemodynamic effects.

On the other hand, 2-min interval allowed before each aVTI measurement represented a reasonable standard utilized in other studies, and longer "adaptive" times would have been barely manageable, due to the remarkable duration of each echocardiographic examination.

In conclusion, previous reports on QuickOpt™ performance in optimizing AV and VV intervals in acute settings and with apical placement of RV lead were substantially confirmed by our observations in Quicksept study, which demonstrated the same reliability of QuickOpt™ in mid- and long-term follow-up when RV lead had been placed exclusively in the mid-septum [14–18,22].

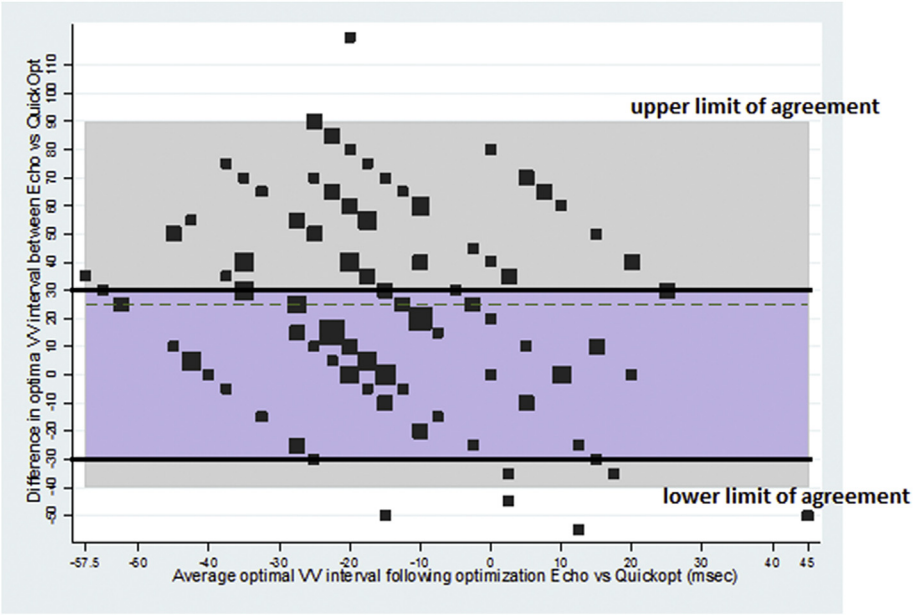

Fig. 4. Bland-Altman plot of differences in optimal VV interval measured by echocardiography and by QuickOpt at Phd, 6 and 12-month follow-up. Grey zone indicate average, upper and lower limit of agreement (25 msec ± 33 msec; IC 95% −40 msec + 90 msec). Colored area indicates clinically acceptable margins of difference between the two tecniques (0 ± 30 msec). Although there was no statistical difference between the two methods, the clinically acceptable margins of difference between them (0 ± 30 msec) showed a low concordance (56%).

Table 6
Variability coefficient (mean), its standard deviation (+SD) and its range, between both inter- and intra-center echocardiographic measurements of aVTI. All values are less than 5%, demonstrating a good reproducibility between echocardiographic examinations.

	CV%	SD	Range
Pre-Discharge	4.7	+1.05	2.9–6.6
6-Month follow-up	4.8	+1.15	2.7–7.4
12-Month follow-up	4.3	+0.6	3.2–5.5

CV: Variability coefficient.

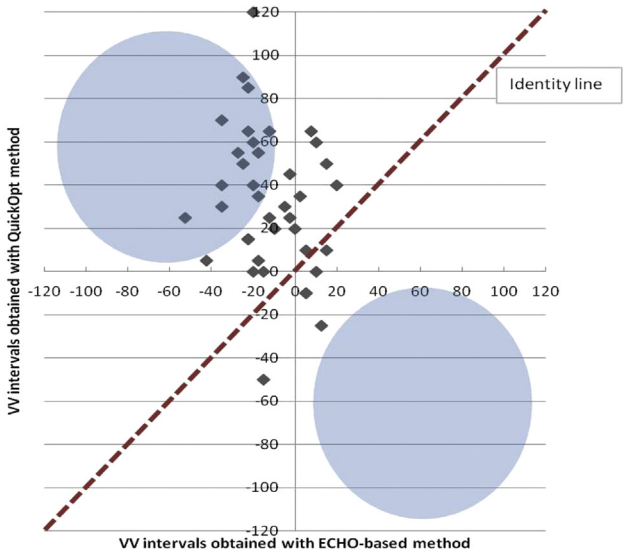

Fig. 5. Correlation of optimal VV intervals measured with ECHO and QuickOpt method. In 50% of cases the ventricle paced first was different. In this analysis 13 patients with VV intervals equal to 0 msec as calculated by either method were excluded. Blue colored area represents the conflict zones between the two methods. In general the larger the advance of the left ventricle, the wider the error between the two methods.

5. Study limitations

This study was a small prospective Registry with a limited population: findings need confirming on a wider scale and with a randomized design. The criteria for response to CRT were mostly clinical, but response was not used to further investigate into optimization methods and no comparison between responders and non-responders as regards optimization was attempted. AorticVTI suffers from well-known intrinsic limitations for optimizing AV/VV intervals [24]: other authors have proposed other indices, among which the maximal VTI of mitral inflow has gained most attention [25]. On the other hand, there was no clue that aVTI use hampered either of the methods taken into consideration unequally, and its limits can be supposed not to have altered substantially the results of methods' comparison.

Author's disclosure

None.

Appendix A

QuickSept Research Group

The following investigators participated in the study design, conduction and publication in addition to paper's authors:

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