ORIGINAL ARTICLE

Evaluation of echocardiographic optimization of cardiac resynchronization therapy using VTI parameters

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Abstract: Cardiac resynchronization therapy (CRT) can improve left ventricular function and symptoms of heart failure by restoring synchronous left ventricular (LV) contractions. Although this improvement is achieved in the majority of patients, some 30% of those who underwent CRT remain non-responders. A number of methods have been tested to improve the rate of responders and convert non-responders into responders, among which different echocardiographic methods. The aim of this study was to establish whether echocardiographic parameters of mitral and aortic velocity time integral (VTI) can help to optimize CRT settings. 27 patients with CRT have been included in the study; demographic, clinical (blood pressure, laboratory parameters, etiology of heart failure, comorbidities, ECG), therapeutic and echocardiographic (standard measurements, LVDFT/RR, IMD, SPWMD, aortic and mitral-VTI, LVEF, dp/dt, GMI) parameters were assessed. Patients underwent echocardiography to determine dyssynchrony parameters with actual CRT, without CRT and with optimized CRT settings, which was carried out using the aortic and mitral-VTI. Our results indicate that echocardiographic optimization using VTI parameters did not improve mechanical dyssynchrony and acute left ventricular function parameters in patients with CRT and should be considered only in selected cases of CRT non-responders, associated with other optimization methods.
Keywords: CRT, echocardiograpic optimization, Mi-VTI, Ao-VTI, non-responders

Rezumat: Terapia de resincronizare cardiacă (TRC) poate îmbunătăți funcția ventriculară și simptomele insuficienței cardiace prin corectarea asincronismului cardiac. Cu toate că TRC s-a dovedit benefică în majoritatea cazurilor, aproximativ 30% dintre pacienți rămân non-responsivi. O serie de metode au fost testate pentru a îmbunătăți rata de răspuns și de a converti pacienții non-responsivi, printre care și diferite metode ecocardiografice. Scopul studiului nostru a fost stabilirea rolului parametrilor ecocardiografici - de integrala velocitate-timp (IVT) mitrală si aortică - în optimizarea setărilor TRC. 27 de pacienți cu TRC au fost incluși în studiu, cu evaluarea caracteristicilor demografice, clinice (tensiune arterială, parametrii de laborator, etiologia insuficienței cardiace, comorbidități, ECG), terapeutice și a parametrilor ecocardiografici (măsurători standard, LVDFT/RR, IMD, SPWMD, IVT mitrală si aortică, FEVS, dp/dt, IMG). Au fost determinați și analizați comparativ parametrii de asincronism ecocardiografic cu 4 setări de stimulare diferite: setarea TRC actuală, cu TRC oprit și cu setări TRC optimizate cu ajutorul IVT mitral respectiv aortic. Rezultatele obținute indică faptul că optimizarea ecocardiografică, folosind parametrii IVT, nu are efect benefic asupra asincronismului mecanic și a parametrilor funcției ventriculare stângi la pacienții cu TRC, prin urmare, ar trebui luată în considerare numai în cazuri selecționate de pacienți non-responsivi și asociată altor metode de optimizare.
Cuvinte cheie: TRC, optimizare ecocardiografică, Mi-ITV, Ao-ITV, non-responderi

INTRODUCTION

Chronic heart failure (HF) is one of the most common cardiovascular pathologies in developed countries. Besides medical treatment, interventional treatment using devices that target left ventricle dyssynchrony are gaining more and more attention. Electrical dyssynchrony (atrioventricular and interventricular conduction delays that manifest as left bundle branch block (LBBB), right bundle branch block (RBBB) or other conduction abnormalities on the ECG) and mechanical dyssynchrony (with three aspects of atrioventricular, interventricular and intraventricular dyssynchrony) leads to a spectrum of pathophysiological alterations of the LV function, causing a decrease in the efficacy of LV contractility and thus reducing stroke volume[1].

In HF patients who remain symptomatic despite optimal medical therapy, cardiac resynchronization the-

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rapy is a valuable option to improve left ventricular contractility and symptoms of heart failure.

Cardiac resynchronization therapy (CRT) can help improve left ventricular systolic function and symptoms of heart failure by restoring the normal AV and intraventricular conduction patterns and synchronous contractility[2]. According to current guidelines, CRT has class I indication in HF patients with NYHA class II-IV symptoms, who are in sinus rhythm, have a left ventricular ejection fraction (LVEF) <35%, LBBB morphology with QRS duration >120 ms and are symptomatic despite optimal medical therapy for HF[3].

However, about 30% of patients do not respond clinically to CRT and 45% show no evidence of reverse remodeling or clinical improvement despite meeting the guideline criteria[4,5]. It is yet unclear why this issue occurs. Despite evidence that several parameters are correlated with response to CRT, none of these can accurately predict individual response to CRT[6-8]. The occurrence of this important category of non-responder patients, in whom CRT fails to achieve the desired response, is an intensely researched issue that remains to be solved. A number of methods to convert non-responders into responders have been studied and tested. CRT optimization based on ventriculo-ventricular delay (VVD) settings according to the narrowest QRS complex on ECG after implantation, and the difference between biventricular pacing and pre-implantation ECG, as tested by Vidal et al. showed a good correlation to echocardiographic parameters, but did not supply data on improvement of LVEF or reverse remodeling[9].

Some studies suggest that echocardiography can help optimize resynchronization settings in non-responders. Attempts have been made for echocardiographic optimization, because of its affordability and large availability. Ritter's method, measuring largest stroke volume or residual LV dyssynchrony had only mild benefit in comparison to standard CRT settings[10-12].

The aim of this study was to assess whether two echocardiographic parameter (Mi and Ao-VTI) can help to optimize CRT settings and to establish which of these parameters is the most efficient. The authors have chosen to assess mitral and aortic VTI parameters because they reflect the global function of the left ventricle and do not require special technical background or training, thus they are largely available.

MATERIALS AND METHODS

27 patients with heart failure and previously implanted CRT device were enrolled in a prospective study, aimed to establish acute hemodynamic response and optimal AV and VV delay settings for their CRT device, with the help of echocardiography. All of the patients were examined between August 2013 and December 2014, at the Department of Cardiology, Emergency Institute of Cardiovascular Diseases and Transplantation Târgu Mureș, being admitted for follow-up visits (authors own cases). Demographic (age, sex, height, weight, body mass index, smoking status), clinical (blood pressure, laboratory parameters, etiology of HF, comorbidities, ECG data including rhythm, atrioventricular and intraventricular conduction delays, characteristics of the implanted device), therapeutic and echocardiographic parameters were registered. Only patients with sinus rhythm were evaluated, VTI optimization in patients with atrial fibrillation being considered too difficult to perform.

All of the patients underwent a baseline echocardiographic examination and a set of dyssynchrony parameters were recorded under four different settings: with actual CRT parameters (actual stimulation parameters after implantation), without CRT pacing (native rhythm, with device stimulation turned off) and with stimulation parameters optimized using mitral and aortic velocity time integral (VTI). Immediately post-implant devices were programmed using electric criteria, taking in account native AV conduction (PR interval), conduction delay between RV and LV lead, intramural conduction time, width and morphology of the QRS complex (R wave in lead V1); before discharge, echocardiographic evaluation of the transmitral inflow profile also was performed.

The standard schedule during this examination was the following: device interrogation with the specific programming device for each CRT (recording native rhythm, native atrio-ventricular delay, actual paced AV and VV delay), standard echocardiographic study with chamber quantification and functional assessment, measurement of a first set of dyssynchrony parameters (with actual post-implantation AVD and VVD settings). The following parameters were assessed: left ventricular diastolic filling time/ RR ratio (LVDFT/RR), left ventricular preejection period (LVPEP), right ventricular preejection period (RVPEP), interventricular mechanical delay (IMD), septal to posterior wall motion delay (SPWMD), mitral time-velocity integral and aortic time-velocity integral, dp/dt (when mitral regurgitation was present), left ventricular ejection fraction (LVEF) using Simpson's biplane method, isovolumetric contraction time (IVCT), isovolumetric relaxation

time (IVRT), ejection time (ET) and global myocardial performance index (the sum of isovolumetric contraction time and isovolumetric relaxation time divided by ejection time). A second set of these dyssynchrony parameters was assessed under native rhythm, after the CRT stimulation was turned off.

After these recordings, an attempt for echocardiographic optimization using mitral and aortic velocity time integral (VTI) was performed: starting from a baseline AV delay of 100 msec (or below of this level, if the actual setting values were lower) and gradually increasing AV delay by 20 msec at a time (baseline AV delay, +20, +40, +60, +80 msec respectively) and measuring aortic and mitral VTI parameters for each of these AV delay, concomitantly with different VV delay settings, ranging from -20 msec ("RV first"), through 0, +20, +40, +60 and finally +80 msec or "LV only" in devices that allowed this setting.

After establishing the best mitral and aortic VTI parameters, a third set of dyssynchrony parameters were assessed with matching stimulation parameters (AV delay and VV delay optimized for "Best Mi" VTI) and a fourth set of dyssynchrony parameters were determined based on "Best Ao" VTI optimized AV and VV delay.

Echocardiographic evaluation and measurements were performed with a General Electric Vivid S5TM device (System SW v3.0.16, using SW v10.3.0 build 144 application), by the same examiner in each of the cases to reduce inter-examiner variations, with patients in supine position with the reading/programmer head placed above the central unit of the CRT device. Three programmer devices were used, namely BiotronikTM (PSW 1402.A/1 software), MedtronicTM (2090/2.9 software) and St. Jude MedicalTM (3330 software v21.1.2). In the case of aortic and mitral VTI measurements, a pause of 3 minutes was interposed after each adjustment of AV and VV delay to allow proper hemodynamic adaptation, after which VTI parameters were assessed in inspiratory apnea.

Echocardiographic parameters were measured according to previously validated methods, as follows:

- LVDFT/RR: left ventricular diastolic filling time is measured based on the transmitral pulsed wave velocity curve, from apical four chamber view, from the start of the E wave until the end of the A wave, RR interval is measured between the peaks of two successive QRS complexes.
- IMD (interventricular mechanical delay): is quantifiable as the time difference between pre-ejection periods for left and right ventricles, (i.e. the interval from the beginning of the QRS complex to the beginning of ejection through the aortic/pulmonary valves) measured by PW-Doppler method, IMD = left ventricular pre-ejection period (LVPEP) - right ventricular pre-ejection period (RVPEP)
  SPWMD (septal-to-posterior wall motion delay) is obtained in parasternal short axis sections at the level of papillary muscles in 2D guided – M mode
- Mi-VTI (mitral velocity-time integral): determined by pulsed wave transmitral velocity curves, from apical four chamber view, as shown in Figure 1.
- Ao-VTI (aortic velocity-time integral): determined by pulsed wave Doppler method at the left ventricular ejection tract, below the aortic valves,

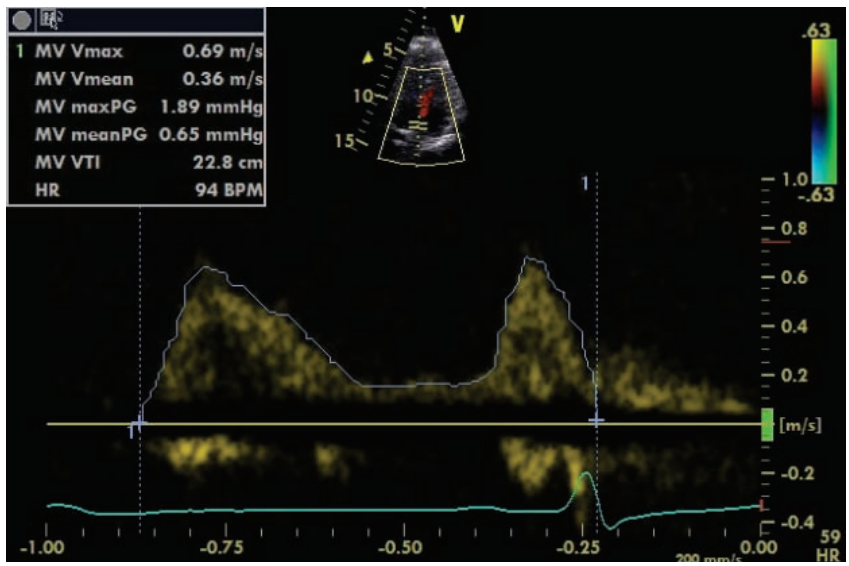

Figure 1. Echocardiographic measurement method of Mi-VTI.

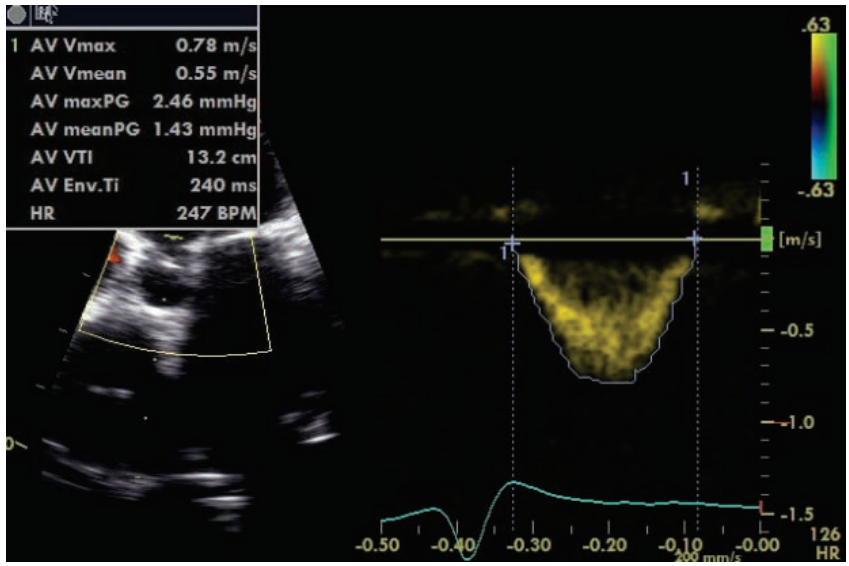

Figure 2. Echocardiographic measurement method of Ao-VTI.

from apical 5 chamber view, as shown in Figure 2
- dp/dt: measured based on the CW Doppler curve, where mitral regurgitation was present
- LVEF was determined using Simpson's biplane method from apical four and two chamber views
- GMI (global myocardial index): calculated as the sum of IVCT and IVRT, divided by ET, according to the formula: GMI=(IVCT+IVRT)/ET, measured by pulsed wave Doppler, from apical 5 chamber view.

The study was approved by the hospital's ethics committee, written informed consent was obtained from each of the enrolled patients.

Data management and statistical analysis: data was recorded in Microsoft Office Excel 2003. Data are represented as mean ± SD. Calculations and statistical analysis were performed using Microsoft Office Excel 2003 and GraphPad InStat 3.06, applying Kolmogorov-Smirnov's goodness-of-fit test and using Student's paired t-test for comparing the native and basal-paced data group, respectively repeated measure ANOVA with Bonferroni post-test or Friedman test with Dunn post-test for comparing the basal-paced and the two optimized ("best with Mi-VTI" and "best with Ao-VTI") data group.

RESULTS

Demographic and clinical characteristics of the patients are summarized in Table 1. Relevant comorbidities of the patients are included in Table 2. The most frequent comorbidities were arterial hypertension and hypercholesterolemia.

Besides CRT, patients received medical therapy for heart failure according to current ESC guideline recommendations, as shown in Table 3. All patients received beta-blocker therapy with carvedilol, an average daily dose of 22.1 mg. 88.8% of patients received RAAS antagonists, mostly ramipril (70.37%, average dose of 4.16 mg), 2 patients were treated with perindopril and

Table 1. Basic demographic and clinical characteristics of the studied group	
Mean age (years) ± SD	62.85 ± 10.30
Male	66.66 %
Urban	74.07 %
Ischemic	18.51%
Non-ischemic	81.48%
LBBB	100 %
Average systolic BP (mmHg) ± SD	118.51 ± 14.33
Average diastolic BP (mmHg) ± SD	73.70 ± 5.47

Table 2. Prevalence of comorbidities (%)	
Arterial hypertension	44.44
Paroxysmal atrial fibrillation	29.62
Prosthetic valve implant	11.11
First degree AV block	37.03
History of myocardial infarction	7.40
Pulmonary hypertension	22.22
Diabetes mellitus type II	25.92
Obesity	22.22
Hypercholesterolemia	43.47
Hypertriglyceridemia	19.04
COPD	14.81
Chronic kidney disease	7.40
Past smokers	29.62

3 patients with candesartan. All patients were treated with spironolactone (average daily dose 43.75 mg) and 81.48 % received furosemide (average daily dose 44 mg).

Basic echocardiographic parameters are shown in Table 4. Mean LV ejection fraction was 32.25% (SD: 6.79 %, limits 20-43 %). The average time passed from the implantation, at the moment of examination, was 1.3 years (between 3 months and 4 years).

Figure 3 and Figure 4 show the distribution of AVD and VVD in our group, under three different settings: basal-paced and the two best settings determined by VTI optimization ("best with Mi-VTI" and "best with Ao-VTI" respectively). The mean AVD under the three different setting was (msec. ± SD): 92.92 ± 20.50 for basal-paced setting, 115.91 ± 26.53 for Mi-VTI optimization and 110.45 ± 26.88 for Ao-VTI optimization. The most frequent VVD found was +80 msec or "LV only" under each of the settings (with 77.77%, 37.03% and 59.25 % respectively).

Figure 5 shows the percentual improvement of dyssyncrony parameters with basal-paced CRT rhythm (before optimisation) compared to native rhythm (with the CRT device turned off). Table 5 shows the statistical (p) values for these dyssynchrony parameters.

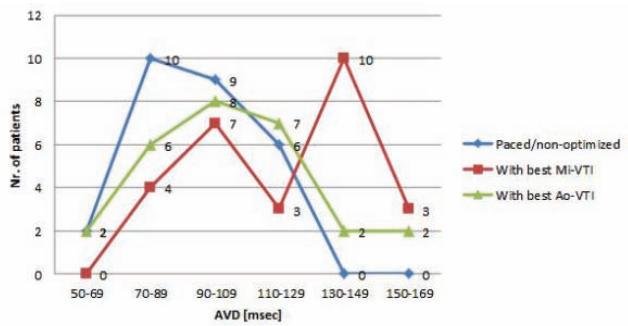

Figure 3. Distribution of the atrio-ventricular delay under the three settings.

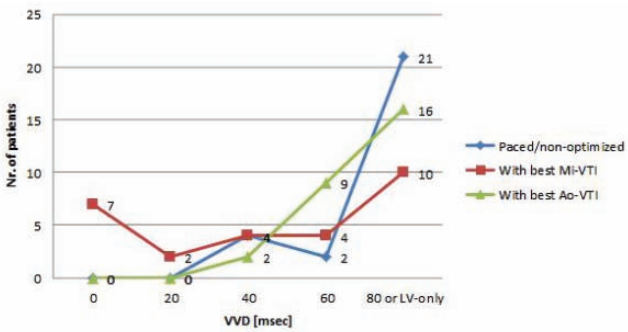

Figure 4. Distribution of the ventriculo-ventricular delay under the three settings.

Figure 6 and Figure 7 shows the improvement or worsening of LV dyssynchrony parameters after optimization of AVD and VVD with Mi-VTI and Ao-VTI respectively, expressed in percents, compared to basal-paced setting before optimization. Table 6 summarizes the statistical (p) values for these dyssynchrony parameters.

DISCUSSIONS

As shown in Figure 5 and Table 5, cardiac resynchronization therapy proved its benefits on each and every studied parameter, though the difference was statistically significant only in the case of LVDFT/RR, IMD and GMI. As in many other studies, CRT proved to have also in this case series a positive acute effect on mechanical dyssynchrony and LV function parameters.

Regarding optimization, the results were far below expectations. As Figure 6 and Figure 7 shows, practically the only positive effect was demonstrated on the two VTI parameters, quite explicable due to the fact that these were the parameters based on, and for which the CRT settings were optimized. In case of all the other parameters, except small benefits on IMD (with Mi-VTI) and SPWMD (with Ao-VTI) respectively, the

Table 3. Cardioactive drug therapy (%)	
Beta-blockers (Carvedilol)	100
ACEI or ARBs	88.88
Furosemide	81.48
Spironolactone	100
Amiodarone	37.03
Digoxin	7.40
Ivabradine	18.51
Aspirine	70.37
Statins	55.50
Oral anticoagulant (OAC)	48.14

Table 4. Mean echocardiographic parameters (± SD)	
Left ventricle (mm)	66 ± 13.66
Interventricular septum (mm)	10.91 ± 2.02
Posterior wall of LV (mm)	11.33 ± 2.05
Aortic ring (mm)	21.27 ± 2.53
Ascending Aorta (mm)	33.8 ± 2.58
Left atrium (cm²)	23.87 ± 6.09
E/A	0.86 ± 0.51
Right ventricle (mm)	32.91 ± 9.03
Right atrium (cm²)	17.52 ± 5.88
Inferior vena cava (mm)	15.22 ± 6.22
Mitral regurgitation	100 %
Aortic regurgitation	36 %
Tricuspid regurgitation	76 %
Pulmonary regurgitation	24 %
RV/RA gradient (mmHg)	24.00 ± 10.31
Ejection fraction of LV (%)	32.25 ± 6.79

Table 5. Statistical analysis of LV dyssynchrony parameters with and without CRT (native rhythm with the CRT device turned off versus basal-paced rhythm before optimization)

	Native	Paced	p
LVDFT/RR	0.47 ± 0.08	0.53 ± 0.05	0.0019
LVPEP	163.08 ± 30.15	145.5 ± 39.18	0.2905
RVPEP	98.75 ± 23.13	123.91 ± 51.63	0.1834
IMD	64.33 ± 17.25	21.58 ± 38.65	0.0016
SPMWD	165.55 ± 62.67	134.22 ± 76.06	0.2750
MI VTI	19.97 ± 6.29	21.03 ± 5.64	0.0895
Ao VTI	15.69 ± 4.17	16.30 ± 4.26	0.3167
dP/dT	451.15 ± 114.71	579.24 ± 169.03	0.1925
LVEF	29.33 ± 10.77	31.90 ± 8.91	0.1865
IVCT	147.54 ± 52.53	102.72 ± 80.21	0.0406
IVRT	144.54 ± 30.68	134.72 ± 36.44	0.2163
ET	253.18 ± 39.59	263.00 ± 40.68	0.1616
GMI	1.2 ± 0.35	0.93 ± 0.31	0.0044

results were negative both with Mi-VTI and Ao-VTI optimization, furthermore in some cases the worsening was even statistically significant (LVDFT/RR, IVRT and GMI after optimization with Mi-VTI).

Based on this case series, echocardiographic optimization of cardiac resynchronization therapy using Mi and Ao-VTI parameters showed no benefit and should be considered only in individual cases, especially in non-responders to CRT with standard pacing settings, perhaps correlated with other optimization methods, such as TDI Doppler imaging techniques using myocardial strain and strain rate 13 and cardiac MRI, which can help better identify patterns of dyssynchrony 14, although these methods have limited applicability due to their lack of availability and high costs.

In addition, there is a concern regarding reproducibility and averaging of mitral and aortic VTI measurements for multiple beats15. Furthermore, the time-consuming nature of echocardiographic optimization and relatively high variability of parameters, partially dependent also on the degree of experience of the examiner, is considered one of the major disadvantages of the procedure, thus limiting the use of these parameters in routine clinical practice. This is one of the reasons why many authors consider that it should be used only in selected cases, where standard settings of CRT fail to achieve the expected response[3].

When echocardiographically assessing CRT patients, especially non-responders, demonstrating mechanical dyssynchrony is the main target, but other aspects as clinical response, dynamic dyssynchrony, contractile reserve and the presence of myocardial scar tissue should not be disregarded. In addition, lead placement and its optimization is also an important issue and should always be considered when assessing non-responders, especially in patients with ischemic cardiomyopathy[16].

Optimization based on avoidance of apical lead placement and targeting latest activated area showed likely benefit by reducing hospitalization for HF and improving the rate of responders[17-20].

Our results correspond partially with findings from the literature, which in itself consists of controversi-

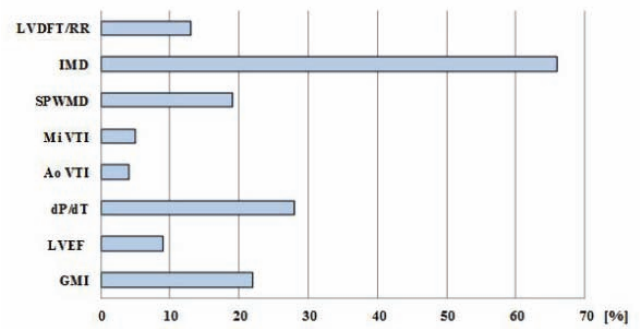

Figure 5. Percentual improvement of dyssynchrony parameters with basal-paced CRT rhythm compared to native rhythm (with the CRT device turned off).

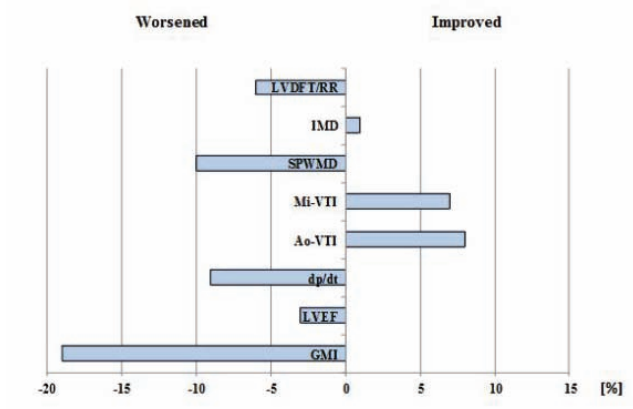

Figure 6. Percentual improvement or worsening of LV dyssynchrony parameters, after optimization with Mi-VTI compared to basal-paced setting before optimization.

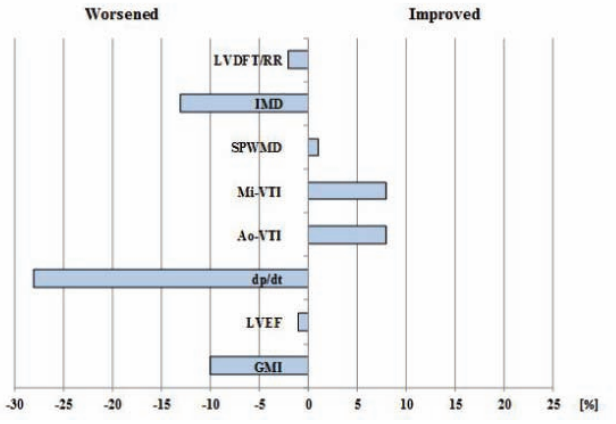

Figure 7. Percentual improvement or worsening of LV dyssynchrony parameters after optimization with Ao-VTI compared to basal-paced setting before optimization.

al conclusions in this field. Small randomized clinical trials and experimental studies found improvement in the left ventricular systolic function, heart failure symptoms, reducing hospitalizations and a positive change in the quality of life after optimization with AV and VV delay. Sawhney et al. have identified that AV delay optimization using the aortic-VTI improves the three-month clinical outcome more than a 120 ms programmed empiric AV delay[10]. Similar results were described by Kerlan et al., who compared echocardiographic AV delay optimization guided by the aortic-VTI versus the mitral inflow method and concluded that AV delay optimization with aortic-VTI for patients with severe heart failure, provides considerably more improvement[21]. Other studies emphasize the importance of mitral-VTI. Jansen et al. and Thomas et al. had similar findings when comparing the use of mitral-VTI to aortic-VTI guided optimization, claiming that the mitral-VTI method is reliable and affordable in everyday clinical practice and adequate in improving response to CRT[15,22].

Contrarily, results from large multicentre trials, that assessed the utility of aortic and mitral VTI for optimization of CRT, showed no significant benefit compared to other optimization methods. According to the FREEDOM[23,24], CLEAR[25], SMART-AV[12], Adaptive CRT[26,27], DECREASE-HF I and Responde CRT[28] trials, the difference of benefits between automatic electrical, device-based algorithms (*SmartDelay and QuickOpt for AV delay and Expert-Ease, Quick-Opt, Peak endocardial acceleration for VV delay-based optimization*) and echocardiographic CRT optimization remains uncertain. Correspondingly, our results suggest that AV and VV delay optimization do not provide improvement in echocardiographic parameters of patients with CRT.

Therefore, as stated in ESC guidelines, current evidence does not support AV and VV optimization routinely in all patients receiving CRT. However, in non-responders, evaluation of AV and VV delay may be recommended, in order to correct suboptimal device settings[3]. The same conclusions were published in a recent, leading review conducted by Daubert, so that the systematic routine optimization of the AV and VV delays in all CRT system recipients is not warranted[29].

In actual practice, ESC guidelines recommend to first programme a fixed 100–120 ms AV delay, without VV interval. However, in subgroups of patients, especially in the presence of a long interatrial delay, the intervals should be optimized after the implantation. Further echocardiographic evaluations and optimizati-

Table 6. Statistical analysis of LV dyssynchrony parameters between the three settings: basal-paced before optimization, optimized with Mi-VTI and optimized with Ao-VTI (using repeated measure ANOVA with Bonferroni post-test 1 or Friedman test with Dunn post-test 2 - according to normality of data)

	Paced	Optimized		p	p <0.05 (post-test)
		With Mitral VTI	With Aortic VTI		
LVDFT/RR[1]	0.53 ± 0.05	0.50 ± 0.06	0.52 ± 0.05	0.0268	A vs B (-)
LVPEP[1]	145.50 ± 39.18	149.72 ± 33.19	141.09 ± 37.20	0.6233	
RVPEP[2]	123.91 ± 51.63	128.36 ± 49.99	116.64 ± 54.25	0.6291	
IMD[2]	21.58 ± 38.65	21.36 ± 33.97	24.45 ± 43.97	0.5992	
SPMWD[1]	134.22 ± 76.06	147.55 ± 59.44	132.22 ± 72.07	0.7645	
MI VTI[2]	21.03 ± 5.64	22.52 ± 8.74	22.65 ± 8.83	0.4966	
Ao VTI[1]	16.30 ± 4.26	17.54 ± 4.02	17.65 ± 3.56	0.0119	AvB & AvC
dP/dT[1]	579.24 ± 169.03	526.82 ± 80.79	418.58 ± 68.16	0.4393	
LVEF[1]	31.90 ± 8.91	31.01 ± 10.70	31.70 ± 12.87	0.9192	
IVCT[2]	102.72 ± 80.21	130.36 ± 71.05	126,73 ± 75,24	0.0701	
IVRT[1]	134.72 ± 36.44	152.27 ± 41.49	143.73 ± 35.67	0.0269	A vs B (-)
ET[1]	263.00 ± 40.68	268.18 ± 55.77	280.18 ± 56.00	0.1886	
GMI[1]	0.93 ± 0.31	1.11 ± 0.39	1.02 ± 0.34	0.0241	A vs B (-)

(-) statistically significant difference but not in the desired direction

ons are advised in case of non-responders to CRT[3,29].

Most studies agree that one parameter cannot be singled out as a predictor of favorable outcome or successful optimization, instead a series of parameters should be used when echocardiographically evaluating CRT patients[3].

In conclusion, echocardiographic optimization using VTI parameters did not improve mechanical dyssynchrony and acute LV function parameters in patients with CRT, thus should be considered only as a complementary tool in selected cases of CRT non-responders, associated with other optimization methods.

Conflict of interest: none declared.

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