IMPACT OF ECHOCARDIOGRAPHIC OPTIMIZATION OF RESYNCHRONIZATION PACE-MAKER USING DIFFERENT PACING MODALITIES AND ATRIOVENTRICULAR DELAYS ON ACUTE HEMODYNAMIC RESPONSE AND LONG TERM PROGNOSIS

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Cardiac resynchronization therapy (CRT) improves ventricular dyssynchrony and is associated with an improvement in life quality and prognosis.

Aim. The aim of study was to examine acute hemodynamic changes with different of CRT device modalities throughout optimization procedure and its impact on one year prognosis.

Material and methods. The study comprised 62 patients with severe left ventricular systolic dysfunction (LVEF 24,6±4,4%, QRS duration 154,71±14,92 ms, NYHA class III/IV 47/15) with implanted CRT device. After implantation and before discharge all the patients underwent optimization procedure guided by Doppler echocardiography. Left (LVPEI) and right (RVPEI) ventricular pre-ejection intervals, interventricular mechanical delay (IVD) and the maximal rate of ventricular pressure rise during early systole (max dP/dt) were measured during left and biventricular pacing with three different atrioventricular (AV) delays. Stroke volume derived from the left ventricular outflow tract velocity–time integral (VTI) of left ventricular outflow tract (LVOT VTI) was measured as well. After one year patients underwent clinical, echocardiographical examination and 6 minute walking test.

Results. After CRT device optimization, optimal AV delay and CRT mode were defined. Left ventricular pre-ejection intervals changed from 175,4±21,5 to 142,6±16,7 ($p < 0,01$), RVPEI from 108,6±18,9 to 127,3±18,3 ($p < 0,001$), IVD from 71,3±14,8 to 24,7±7,6 ($p < 0,001$) and dP/dt from 532,2±74 to 675,2±111 ($p < 0,001$). Left ventricular outflow tract VTI increased after optimization procedure from 18±3,4 to 21±1,5 cm ($p<0,05$).

Conclusions. Echocardiographic optimization procedure emphasizes the individualized approach in CRT optimization procedure in order to derive the best short and long term results.

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Key words: CRT, echocardiographic optimization, heart failure, prognosis, life quality.

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CRT — cardiac resynchronization therapy, CRT-P — cardiac resynchronization therapy pacemaker, CRT-D — cardiac resynchronization therapy pacemaker with an ICD, CARE-HF- Cardiac Resynchronization–Heart Failure study, EDD –end-diastolic diameter, EDV- end-diastolic volume of left ventricle, ESV- end-systolic volume of left ventricle, HF — heart failure, ICD — Implantable cardioverter defibrillator, IVD — inter-ventricular conduction delay, LV- left ventricle, LVEF –left ventricle ejection fraction, LVPEI — pre-ejection interval of the left and ventricle, max dP/dt — maximal rate of ventricular pressure rise during early systole, NYHA — New York Heart Association, PEP LV — pre-ejection interval of left ventricle, PEP RV — pre ejection interval of right ventricle, RV- right ventricle, RVPEI — pre-ejection interval of the left and right ventricle, Six (6) MWD- six minute walking distance, SPWMD — septal-posterior wall motion delay, LVOT VTI — left ventricular outflow tract, VTI — velocity–time integral, VT — ventricular tachycardia, VF — ventricular fibrillation, QoL — quality of life.

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ВЛИЯНИЕ ЭХОКАРДИОГРАФИЧЕСКИХ ОПТИМИЗАЦИИ РЕСИНХРОНИЗИРУЮЩЕЙ ТЕРАПИИ PACE-MAKER, С ИСПОЛЬЗОВАНИЕМ РАЗЛИЧНЫХ МЕТОДОВ СТИМУЛЯЦИИ И АТРИОВЕНТРИКУЛЯРНОЙ ЗАДЕРЖКИ НА ГЕМОДИНАМИЧЕСКИМИ ОТВЕТ И ДОЛГОСРОЧНЫЙ ПРОГНОЗ

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Сердечная ресинхронизирующая терапия (СРТ) улучшает желудочковую диссинхронию и связана с улучшением качества жизни и прогноза заболевания.

Цель. Целью исследования явилось изучение гемодинамических изменений с разными устройствами СРТ, методов оптимизации всей процедуры и ее влияние на один год прогноза.

Материал и методы. В исследование вошли 62 больных с тяжелой систолической дисфункцией левого желудочка (LVEF 24,6±4,4%, длительность комплекса QRS 154,71±14,92 ms, класс NYHA III/IV 47/15) с имплантированными ЭЛТ-устройствами. После имплантации и перед выпиской всем пациентам была проведена процедура оптимизации под контролем допплер-эхокардиографии. Левый (LVPEI) и правый (RVPEI) желудочковый pre-ejection интервалы, межжелудочковая механическая задержка (IVD) и максимальное значение повышения давления в желудочке во время ранней систолы (max dP/dt) были измерены во время лево- и бивентрикулярной электрокардиостимуляции с тремя различными атриовентрикулярными (АВ) задержками. Были измерены ударный объем производный от пути оттока левого желудочка, как и скорость-временной интеграл (VTI) пути оттока левого желудочка (LVOT VTI). После одного года пациенты прошли клиническое, эхокардиографическое исследование и тест 6 минутной ходьбы.

Результаты. После оптимизации СРТ-устройства, оптимальная АВ задержка и режим СРТ были определены. Pre-ejection интервалы левого желудочка изменились от 175,4±21,5 до 142,6±16,7 ($p < 0,01$), RVPEI от 108,6±18,9 до 127,3±18,3 ($p < 0,001$), IVD от 71,3±14,8 до 24,7±7,6 ($p < 0,001$) и dP/dt от 532,2±74 до 675,2±111 ($p < 0,001$). VTI пути оттока левого желудочка возросло после процедуры оптимизации с 18±3,4 до 21±1,5 см ($p<0,05$).

Заключение. Эхокардиографическая процедура оптимизации подчеркивает индивидуальный подход в оптимизации процедуры СРТ в целях определения лучших краткосрочных и долгосрочных результатов.

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Ключевые слова: СРТ, эхокардиографическая оптимизация, сердечная недостаточность, прогноз, качество жизни.

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Introduction

In patients with moderate to severe symptoms of heart failure (HF) and bundle branch block with prolonged duration of QRS complex, cardiac resynchronization therapy (CRT) with or without an implantable cardioverter-defibrillator reduces HF hospitalizations and prolongs survival compared with an optimal medical therapy alone. Moreover, CRT with its dyssynchrony reduction improves symptoms and quality of life (QoL), increases exercise tolerance, and reduces left ventricular dilatation [1–4]. However in a significant number of patients this therapy does not improve symptoms and signs of the disease [5, 6]. The causes of the inadequate response could be the absence of dyssynchrony even if the QRS complex duration is prolonged, inadequate positioning of the electrode or suboptimal parameters of the resynchronization pacemaker [7, 8].

The studies have shown that the basal mechanic dyssynchrony could have the predictive role regarding the hemodynamic response to CRT [9]. In CARE-HF study in the selection of patients for CRT beside recommended parameters for dyssynchrony measurement they have used parameters of the conventional Doppler echocardiography: prolonged pre-ejection interval of the left ventricle (LVPEI >140 ms) and increased difference between pre-ejection intervals of the left and right ventricles (IVD >40 ms) [10].

In the adequately selected patients it has been proved that that the acute obtained required hemodynamic changes could persist during the 6- month follow up period [11]. Adlbrecht et al. in the retrospective analysis showed that echocardiographic optimization of the atrio-ventricular (AV) -interval in patients with CRT was independently associated with improved clinical outcome during 32 months of median follow up [12]. Accordingly, the acute hemodynamic response to CRT measured by the percentage of the change in the value of the basal maximal slope of ventricular pressure increase during the early systole (dP/dt) is associated with the improved clinical parameters independently of the cardiomyopathy aetiology [13]. Beside the advantages of the tissue Doppler in the evaluation of the candidates for this therapy, a conventional Doppler echocardiography is considered as a useful tool not only in the baseline assessment of the patients but also in the individual approach to the non-invasive assessment of the most effective pacing modalities and AV delays [14, 15].

The primary goal of this study was the assessment of the changes in the basal echocardiographic parameters: dP/dt, pre-ejection interval of the left and right ventricle (LVPEI, RVPEI) and their difference (IVD) in optimisation of the resynchronization pacemaker by using the different modalities of the pacing and the atrioventricular delay. Stroke volume derived from the left ventricular outflow tract velocity–time integral (VTI) of left ventricular outflow tract (LVOT VTI) was measured as well. One year after the device implantation we determined mortality rate, number of re-hospitalizations due to worsening of HF, six minute walking distance (6MWD), functional New York Heart Association (NYHA) class and the end-diastolic diameter of the left ventricle (EDD).

Methods

We enrolled 62 patients with chronic systolic heart failure (left ventricle ejection fraction — LVEF <35%) in our study. They were in NYHA class III–IV, with left bundle brunch block (QRS duration >130 ms) and mitral regurgitation which enabled the measurement of the dP/dt.

Before the implantation of the resynchronization pacemaker, patients underwent the coronary angiography in order to determine the aetiology of heart failure.

Atrio bi-ventricular pacemaker with implantable cardioverter defibrillator was implanted in 18 patients, while the others got the atriobi-ventricular device. The resynchronization pacemaker was implanted trans-venal with the left ventricle electrode placed in the anatomically adequate coronary sinus branch with the acceptable threshold pacing and without diaphragm stimulation. The right ventricle electrode was positioned in the apicoseptal region of the right ventricle.

During the first three days, before the hospital discharge, we did the optimisation of the resynchronization pacemaker using the echocardiography Doppler technique. Echocardiographic apparatus General Electric Medical Systems™ Vivid 4 with a sonde of 2.5 MHz was used. By using the pulse Doppler speed of 100 mm/s we analysed the aortic and pulmonary flow. We obtained three values of each parameter and the mean value was taken for the analysis. The pre-ejection interval of the left ventricle (LVPEI) was assessed by the transaortal Doppler flow measurement from the beginning of the QRS complex and transaortal ejection signal. The pre-ejection interval of the right ventricle (RVPEI) was measured from the beginning of the QRS complex to the beginning of the transpulmonary ejection signal. The difference between the LVPEI and RVPEI was determined as an inter-ventricular delay (IVD). The positive value of the IVD was an indicator of the delayed left ventricle ejection, while the negative value of this parameter was considered as an indicator of the delayed ejection of the right ventricle.

Using the continuous Doppler we assessed the mitral flow and by measuring the slope of the mitral regurgitation signal acceleration we determined the dP/dt (16). We tested three values of the AV delay: long 150 ms, intermediate 120 ms and short 90 ms. Intermediate AV delay (120 ms after sensed atrial event) with bi-ventricular pacing was in accordance with the standardized parameters of the CRT device.

As the optimal CRT configuration were considered bi-ventricular or left ventricle pacing and AV delay with the best echocardiographic parameters for each patient.

Continuous variables were presented as a mean value ±1SD, and the ordinary as a frequencies. Student's T test was used for comparison of the basal values during the standard and optimal CRT mode. We correlated interdependence between the measured parameters (Pearson's and Spearman's correlation coefficients were used). Chi-quadrate test was used for the comparison of the frequency distribution between basal and NYHA class and one year after implantation of the CRT. P< 0.05 was considered statistically significant. SPSS 17 for Windows package was used for the analysis.

The study complied with the Declaration of Helsinki and it was conducted in the Clinic for the cardiovascular diseases, Clinical Centre Nis. The Medical Ethical Committee of the Medical Faculty of the University of Nis, Serbia, approved the study protocol. All participants submitted written informed consent.

Results

Demographic data are presented in the Table1. We included in the study patients with significant left ventricle dysfunction (EF=24,60± 4,4%) with manifested heart failure: NYHA III (47, 75,8% of patients) and NYHA IV (15, 24,2% of patients) functional class, Ischemic aetiology was found in 19,4% of patients, non-ischemic in 69,4% of patients and non-compacted cardiomiopathy had 11,2% of patients,

Distribution of the optimal mode of the CRT device is presented in Table 2. The majority of patients (57) had the optimal biventricular pacing. In five patients beside the improvement achieved with the biventricular pacing we found optimal left ventricle pacing. The standardized AV delay of 120 ms was optimal in 25 (40,3%) patients, shortened AV delay of 90 ms was found in 29 (46,7%) patients and increased AV delay of 150 ms was optimal in 8 (13%) patients.

All the measurements were obtained without resynchronization and during the left and biventricular pacing. Basal values and the one obtained after optimization of the LVPEI, RVPEI, IVD, dP/dt, VTI are shown in the Table 3. All the indices of the left ventricle hemodynamic were significantly improved particularly after the CRT device optimization. Pre-ejection interval of the left ventricle and dP/dt were significantly reduced, while, RVPEI, VTI and IVD were significantly increased.

The measured parameters with standardized and optimal AV delays are presented in the Table 3.

We correlated QRS complex duration with echocardiographic parameters in basal conditions and with standardized and optimal CRT device conditions. We found significant correlation between QRS duration with the standardized IVD (p<0.05) which indicates that the wide QRS complex is the predictor of the decreased interventricular delay after CRT device implantation.

After one year follow up period we found significant reduction in the end-diastolic diameter of the left ventricle (from 71,9±7,5 mm to 67,4±6,8 mm, p < 0,001) with significant improvement in NYHA functional class (NYHA II — 44 patients (74,6%), NYHA III — 13 (22,03%) and NYHA IV- 2 patients (3,4%)) (Table 4).

Table 1

Baseline patients' characteristics

age (years ± SD)	61,06±10,00
men / women n (%)	46 (74,2) / 16 (25,8)
non-ishemic cardiomyopathy n (%)	43 (69,4)
ishemic cardiomyopathy n (%)	12 (19,4)
non-compact cardiomyopathy n (%)	7 (11,2)
QRS (ms), (± SD)	154,71±14,9
EF (%) ±SD	24,60±4,4
NYHA III/IV [n (%)]	47 (75,8) / 15 (24,2)

Table 2

Distribution of atrioventricular delay (AV) and optimal cardiac resynchronization therapy (CRT) modality

Pacemaker characteristics	Number of patients (n = 62)	
	n	%
biventricular pacing	57	91,9
left ventricle pacing	5	8.1
prolonged AV delay	8	13
intermediate AV delay	25	40,3
short AV delay	29	46,7

Table 3

Variability of Doppler parameters (r±SD)

Parameter	Baseline value	Secondary conditions	Optimal conditions	Difference baseline vs. Optimal conditions (%)
LVPEI (ms)	175,4±21,5	147,4±16,7*	142,5±13,78**	32,9 (18,7)
RVPEI (ms)	108,6±18,9	124,9±18,7**	127,3±18,3**	18,7 (17,2)
IVD (ms)	71,3±14,8	31,6±6,7**	24,7±7,6**	46,6 (65,3)
dP/dt	532,2±74	622,5±82,9**	675,0±111**	143 (27)
VTI (cm)	18±3,4	20±1,0*	21±1,5*	0,3 (16,6)

* *p*<0,001 between basal and standardized, basal and optimal, optimal and standardized values; ** *p* < 0,01 between standardized and optimal values.

Abbreviations: LVPEI — pre-ejection interval of left ventricle, RVPEI — pre-ejection interval of right ventricle, IVD — difference between LVPEI and RVPEI, dP/dt — change of basal maximal slope of increase in ventricular pressure during the early systole (dP/dt) obtained from the mitral regurgitation signal.

Table 4

Changes of EDD of left ventricle and NYHA functional class after 1-year follow-up

Parameter	Basal conditions	1-year control values	p
EDD (mm), (r' ± SD)	71,92±7,4	67,35±6,8	< 0,001
NYHA II [n (%)]	0 (0)	44 (74.6)	< 0,001
NYHA III [n (%)]	47 (75.8)	13 (22.03)	< 0,001
NYHA IV [n (%)]	15 (24,2)	2 (3,4)	< 0,001

Abbreviations: EDD- end diastolic diameter, NYHA- New York Heart Association.

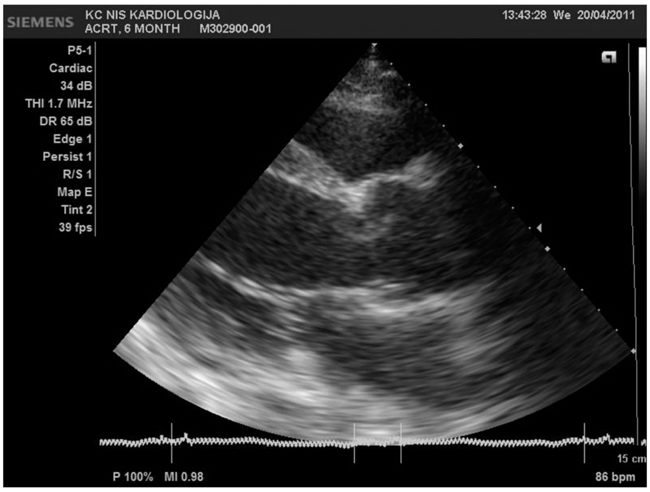

Fig. 1. Left and right ventricle before CRT implantation.

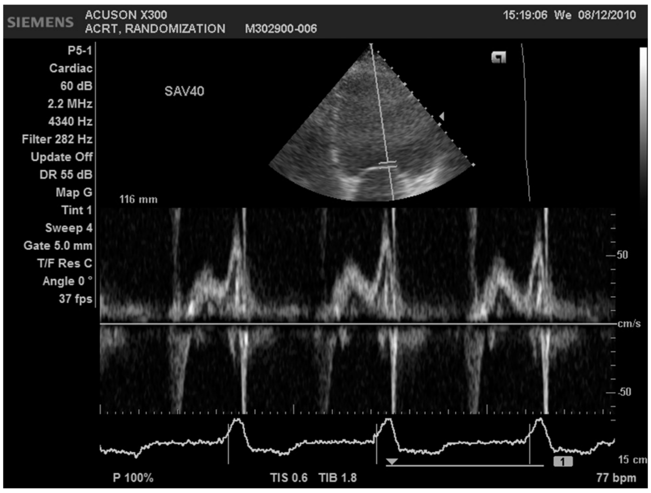

Fig. 3. Echocardiographic presentation of A-V optimization.

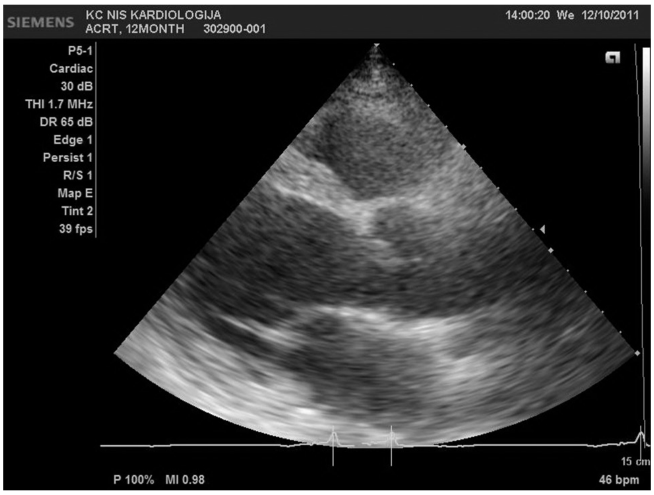

Fig. 2. Left and right ventricle 1 year after CRT implantation.

Fig. 4. Echocardiographic presentation of V–V optimization.

Echocardiographic presentations of left and right ventricle before CRT implantation and one year later are shown in Figure 1 and 2.

Three patients died during follow up period. The majority of patients was not re-hospitalized during one year of follow up (67,7%), while 22,6% had one hospitalization, 6,5% had two hospitalizations and 3,2% three hospitalizations due to worsening heart failure, We measured 6MWD at hospital discharge and after one year of follow up, 6MWD at baseline 222,32±40,35 increased to 302,38±74,8m, p<0,001.

Discussion

Varieties of methods are used clinically for programming the AV delay, with no current consensus as to best practice. Many implanters use empirically program devices to a fixed AV delay interval and optimize only those patients who fail to respond to therapy [17]. Kamdar et al. showed that echocardiography was superior to an algorithm in St Jude medical CRT devices (QuickOptTM) which optimizes device automatically [18].

The most important finding of our study is that easy to obtain and low cost echocardiographic parameters such as pre-ejection intervals of the left and right ventricle (LVPEI, PVPEI) and their difference (IVD) as well as dP/dt, could be very useful in the setting of the optimal mode of resynchronization pacemaker. These lead to short and long term benefits for our patients — decreased LV volumes, improved QoL assessed as a better physical capacity (lower NYHA class and increased 6MWD).

The pre-ejection interval represents the electromechanic delay and isovolumetric time and it is in inverse correlation with the dP/dt (19). In the preliminary MIRACLE study report, LVPEI is defined as a predictor of the CRT treatment efficiency [20, 21]. The interventricular delay is identified as a discordance of the left and right ventricle contractions and it is sought to be the predictor of the CRT treatment efficiency which was used in patients selection in CARE-HF study [3, 22, 23].

In our study we registered the change in values of LVPEI, RVPEI and IVD during the setting of the CRT device which shows that those parameters could be useful in selection of patients for this therapy and in process of the individual setting of these pacemaker parameters.

Ventricular contractility measured as a percentage of the change in the basal maximal slope increase of the ventricular pressure (dP/dt) is a prognostic predictor in patients with heart failure [24]. The change in dP/dt after CRT implantation is the measure of the overall influence of this device on cardiac function [14].

Adamson et al. have showed that the increase of dP/dt is significantly different in patients who have benefit from CRT from those who do not [22]. The invasive determination of dP/dt and pulse pressure in the process of CRT optimization is complicated, unrepeatable and time consuming method [25].

We found significant increase of dP/dt after CRT implantation ($p< 0,001$). Additional increase ($p<0.01$) of this parameter is registered during the process of the CRT optimization.

Number of patients with moderate to severe mitral regurgitation before device implantation was 50 (80%). After CRT pacemaker implantation that number significantly dicreased to 4 (6,7%), $p<0,01$. By influencing on the severity of mitral regurgitation, CRT shows that the increase of dP/dt is the cause but not the consequence of the mitral regurgitation decrease [9, 26, 27]. The effect of the resynchronization therapy on the decrease of mitral regurgitation severity could be direct or late response to the synchrony achievement [28]. The variation in the mitral regurgitation severity caused by the resynchronization therapy do not influence on predictive role of dP/dt. The limitation for using this parameter is the severity of the mitral regurgitation.

According to the literature in our study we showed significant correlation between basal and values of IVD and dP/dt with standard and optimal CRT conditions.

The treatment of significant dyssynchrony is a predictor of better hemodynamic recovery after CRT device implantation. Accordingly, there is significant reduction in end-diastolic diameter of the left ventricle after one year follow-up period with significant improvement in NYHA functional class and 6MWD.

In the majority of patients biventricular and left ventricle pacing with short or intermediate AV delay were the most optimal which is in accordance with previous studies [4, 14, 29]. In small number of patients left ventricular pacing was superior to the biventricular pacing modality. Left ventricular pacing alone may offer theoretical advantages over conventional biventricular pacing, requiring simpler systems that preserve intrinsic conduction via the right bundle branch, however as in previous studies we obtained the best results with biventricular pacing [30, 31]. In 8 (13%) patients optimal increased AV delay was 150 ms. The standard conditions were suitable in 25 (40,3%) patients. In all patients the standard CRT parameters lead to improvement, but with the optimization we achieved additional increase of dP/dt and decrease of IVD.

Mechanical asynchrony of the cardiac function has three determinants: atrioventricular (A-V) dyssynchrony, (V—V) interventricular dyssynchrony, and intraventricular dyssynchrony. Assessment of A-V dyssynchrony is currently used mainly in optimization procedures. However, there are studies demonstrating that each of those types of dyssynchrony may actually affect the outcome of resynchronization therapy. Interventricular dyssynchrony occurs when there is a significant delay between RV and LV activation, which can be crudely denoted by the presence of a wide QRS on the surface electrocardiogram.

Measurement of stroke volume derived from the left ventricular outflow tract velocity–time integral (VTI) of left ventricular outflow tract (LVOT VTI) has been proposed for optimizing both AV and VV delays [32]. On Figure 3 is echocardiographic presentation of AV optimization and on Figure 4 is shown echocardiographic presentation of VV optimization.

Conclusion

Echocardiography may play an important role in patient assessment before CRT and is currently one of the most commonly used non-invasive imaging modalities to provide information on its mechanical effects in heart failure patients. To make echocardiographic techniques a valuable addition also to the clinical field, further improvements in measurement feasibility and reliability, a better understanding of the effects of loading and wall stress, and multicenter validation are required.

The echocardiographic Doppler parameters, such as pre-ejection left/right ventricle interval, and their difference dP/dt are useful in selection of patients for the implantation of CRT and in process of setting the optimal working conditions of this device. The variability in the echocardiographic Doppler parameters according to the conditions of the resynchronization pacemaker could be very useful in the assessment of the optimal treatment. Acute hemodynamic response assessed by echocardiography and expressed as dP/dt change improves the optimization process of this device. The individual approach to optimization process leads to determination of the optimal conditions for each patient. Significant acute improvement could be achieved by optimization of the cardiac resynchronization. Echocardiographic assessment of the acute hemodynamic response to CRT in early post-implantation period could be useful predictor of long-term prognosis in patients with ischemic and non-ischemic cardiomyopathy.

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