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REAL-TIME THREE-DIMENSIONAL TRANSTHORACIC ECHOCARDIOGRAPHY IN QUANTIFICATION OF LEFT VENTRICULAR DYSSYNCHRONY

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Aim. To compare endocardial and epicardial left ventricular (LV) pacing using real-time electrocardiography (ECG)-synchronized three-dimensional echocardiography (3DE).

Methods. Experimental intraoperative study included 88 points obtained from 12 patients with compensated heart failure of II-IV functional class NYHA (LV ejection fraction < 35%) and cardiac resynchronization therapy indications - ECG pattern of complete left bundle branch block (LBBB) and QRS complex duration > 150 ms. During isolated LV pacing as part of cardiac resynchronization therapy implantation procedure endocardial and epicardial stimulation points matched under fluoroscopic control using quadripolar coronary sinus leads and endocardial electrodes for temporary pacing were obtained. The overall number of corresponding pacing sites included 44 endocardial and 44 epicardial stimulation positions. The mean age of patients was 68.5 [63; 73.5] years, 83% males (n=10). Before study enrollment, 12-channel ECG, echocardiography, and a six-minute walk test were performed for all participants along with cardiac magnetic resonance imaging and control coronary angiography if indicated. The prevalence of coronary heart disease was 50% (n=6) while dilated cardiomyopathy was the most common etiology of chronic heart failure in other cases. Intraoperative ECG with estimation of paced QRS complex morphology at each point was registered via LabSystem Pro Electrophysiological Recording System (Bard Electrophysiology, USA). 3DE was performed using TomTec and Philips Qlab 3DQ Advanced software (Philips Medical Systems, USA).

Results. Three-dimensional parametric imaging of LV regional segmental excursion and myocardial contractility using 3DE revealed statistically significant difference in semi-quantative parameters such as ExcAvg (p<0.001), ExcMax (p=0.001), ExcMin (p<0.001) and LV ejection fraction based on 3D modelling (p=0.003) while endocardial pacing was more beneficial. During the course of endocardial stimulation, the 3DE dyssynchrony index estimated at the 2nd stimulation site was also significantly lower (p=0.03). Identical dyssynchrony parameters valid for the 16 and 12-segment 3D models (SDI-16, Tmsv-12SD) (at p=0.06) demonstrated only a tendency for significant difference. The duration of QRS complex at the time of endocardial pacing was significantly shorter (<190 [179;215] ms) (p=0.0008). Semi-quantitative and quantitative 3DE parameters showed the benefit of endocardial pacing resulting in cardiac contractility improvement with less dyssynchrony and LV volume reducing during intraoperative period.

Conclusion. Endocardial pacing has potential benefit over the epicardial pacing represented by intraoperative dynamics of LV global and local contractility, intraventricular dyssynchrony estimated by 3DE and also ECG criteria. 3DE is helpful in more precise and reproducibile determing of late activation zone for target LV lead placement that is more manoeuvrable in case of endocardial stimulation.

Key words: cardiac resynchronization therapy; endocardial pacing; epicardial pacing; left ventricular lead; three-dimensional real-time echocardiography; mechanical dyssynchrony

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To date, cardiac resynchronization therapy (CRT) has been successfully used in patients with chronic heart failure (CHF) of NYHA functional class II-IV (New York Heart Association), with ejection fraction (EF) less than 35% and QRS complex dilation on surface electrocardiography (ECG) greater than 130 ms. The incongruence between electrophysiologic indicators and echocardiographic manifestations, coupled with the sustained high percentage of individuals who do not respond favorably to therapy, underscores the continual quest for factors that govern the efficacy of Cardiac Resynchronization Therapy (CRT). Common factors contributing to inadequate or absent response to CRT encompass imperfect criteria for patient selection, extensive myocardial scarring, suboptimal programming parameters of the device, ventricular electrode misplacements, and a low proportion of genuinely achieved biventricular stimulation. Encountering challenges in implanting a left ventricular (LV) electrode within the desired target zone is not uncommon, often attributed to anatomical constraints within the coronary sinus. These challenges necessitate the exploration of alternative stimulation modalities, such as surgical epicardial approaches (minithoracotomy or thoracoscopic) or endovascular endocardial techniques (transapical or transseptal, including approaches through the interventricular septum).[1-3]. Considering the limitations associated with the thoracoscopic approach, including the requirement for general anesthesia in patients with severe congestive heart failure (CHF), challenges in achieving optimal electrode positioning, and the inherent risks of surgical and infectious complications, there has been a growing body of research focusing on the exploration of alternative endocardial methods for electrode implantation [1-10]. There is conflicting evidence that endocardial stimulation has several advantages:

- more rapid spread of excitation through LV myocardium,
- absence of a perverse pattern of LV activation,
- better LV filling and systolic function [11],
- better acute hemodynamic effect [12],
- epicardial stimulation may be more arrhythmogenic than endocardial stimulation [13], as it contributes to prolongation of the QT interval duration and an increase in transmural dispersion of repolarization [14],
- ventricular electrical storm more often during epicardial stimulation [15];
- endocardial stimulation reduces repolarization dispersion [16] compared with stimulation from epicardially located branches of the coronary sinus.

3D-echoCG was chosen as the main technique for intraoperative assessment of stimulation efficiency and comparison with the zones of the most late activation [17-24] because of its ease of application, high reproducibility, and visualization.

Purpose: To compare endocardial and epicardial left ventricular stimulation using real-time ECG-synchronized three-dimensional echocardiography.

METHODS

The pilot study included 12 patients with sinus rhythm, medically compensated class II-IV CHF, EF less than 35% and QRS complex duration more than 150 ms, prepared for implantation of CRT device. All patients underwent standard ECG, echoCG, six-minute walk test, coronarography, and, if indicated, cardiac magnetic resonance imaging to determine the volume of viable myocardium. Characterization of the patients is presented in Table 1. All patients were informed and gave consent to participate in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the local Ethical Committee (meeting #35 of 28.02.2018).

Implantation of the CRT system was performed under fluoroscopic control using standard radiologic projections (straight, left oblique, right oblique). The right atrial electrode was positioned in the auricle of the right atrium, and the right ventricular electrode was positioned in the area of the septum interventriculaire, apex of the right ventricle. LV epicardial quadripolar Quartet epicardial electrode (St. Jude Medical, USA) was implanted into one of the branches of the coronary sinus. To perform endocardial stimulation, we performed puncture of the right femoral artery and guided a temporary ten-pole diagnostic electrode into LV by retrograde transaortic access. Amplitude was calibrated as a function of stimulation threshold and compared with that during epicardial stimulation: nominally 3-3.5 V or twice the stimulation threshold. Under fluoroscopic control, the matching of the stimulating pole of the electrode with the points of epicardial stimulation was performed sequentially. Temporary isolated LV stimulation from each point was performed with registration of the duration and morphology of the stimulated QRS complex, performing transesophageal 3D-echoCG.

EchoCG control was performed transesophageally on a Philips CX50 (Philips Medical Systems, USA) with

Table 1.

General characteristics of patients in the study group

Number of patients, n	12
Number of stimulated points	88
Age, years	68.5 [63;73.5]
Male gender, n (%)	10 (83%)
Ischemic genesis of CHF, n (%)	6 (50%)
Non-ischemic genesis of CHF, n (%)	6 (50%)
Coronary heart disease, n (%)	11 (91%)
History of myocardial infarction, n (%)	6 (50%)
Revascularization in history, n (%)	8 (67%)
No history of revascularization, n (%)	4 (33%)
II f.c. CHF (NYHA), n (%)	3 (25%)
III f.c. CHF (NYHA), n (%)	7 (58%)
IV f.c. CHF (NYHA), n (%)	2 (17%)
QRS duration, ms	171 [158.5; 181]
LVEF, ml	240 [177; 275.5]
LV ESV, ml	174.5 [117.5; 212.5]
LVEF, %	27 [18; 28]
Mitral regurgitation. n (%)	9 (75%)
Mild mitral regurgitation, n (%)	7 (58%)
Moderate mitral regurgitation, n (%)	2 (17%)
Mitral valve replacement, n (%)	1 (8%)
8 isolated stimulation points, n (%)	9 (75%)
6 isolated stimulation points, n (%)	2 (17%)
4 isolated stimulation points, n (%)	1 (8%)

Notes: hereinafter CSF - chronic heart failure, f.c. - functional class. EDV - end-diastolic volume, ESV - end-systolic volume, LV - left ventricle, EF - ejection fraction.

a 3D-matrix X5-1 (Philips, USA) transesophageal transducer. The study was performed according to an abbreviated protocol with mid-esophageal projection, left chamber positions in 2-, 3-, and 4-chamber projections, and 3D echoCG, with optimal frame rate, image sweep for 2 and 4 cardiac beats, and 2D speckle-tracking echoCG. All frames obtained in different EchoCG modes during each stimulation were saved for further processing. Data analysis was performed using TomTec and Philips Qlab 3DQ Advanced software packages (Philips Medical Systems, USA). Global longitudinal strain index was calculated using speckle-tracking echoCG, and global and segmental systolic function was assessed by 3D-echoCG data analysis, visualization of polar maps superimposed on a 16-segment cardiac model with identification of the zones of the most late activation, segmental assessment of the time to reach the minimum regional volume with determination of the total systolic dyssynchrony index, which has a high prognostic value in the description of MD [19, 21, 23] and for determination of which it is necessary to calculate the standard deviation of the intervals between the beginning of the QRS complex and the moment of reaching the minimum regional systolic volume for the 16-segment LV model (Tmsv16-SD). This figure is similarly calculated for the 12- and 6-segment model. Additionally, the maximum time difference between the onset of QRS and the time when the minimum regional systolic volume was reached (Tmsv16-Dif, Tmsv12-Dif, Tmsv6-Dif) was determined. All of the above parameters are normalized as a percentage of QRS duration. To visualize the regional endocardial motion to the central axis, drawn from the basal sections to the apex, the endocardial excursion parameters (ExcAvg, ExcSD, ExcMah, ExcMin, also expressed using color coding (blue color encodes the motion to the central axis, red - away from it, black - no motion) were calculated using «time-volume» curves [24-29].

Statistical analysis

Statistical processing of ECG monitoring data and calculated data obtained by 3D-echoCG and STE was performed using Statistica 10 (StatSoft Inc., version 10.0.228.8, Oklahoma, USA) and 13 (StatSoft Inc., Trial version, Oklahoma, USA) using nonparametric mathematical criteria Kolmogorov-Smirnov (if the whole sample, 88 points, was chosen as the basis), Wilcoxon for paired dependent samples (2 samples of 44 points were chosen as the basis, depending on the type of stimulation). Data are presented as Me [25th percentile; 75th percentile] or absolute number (%). A mixed statistical analysis of variance ANOVA was used to determine the relationship between the output data, with the possibility of leveling individual patient

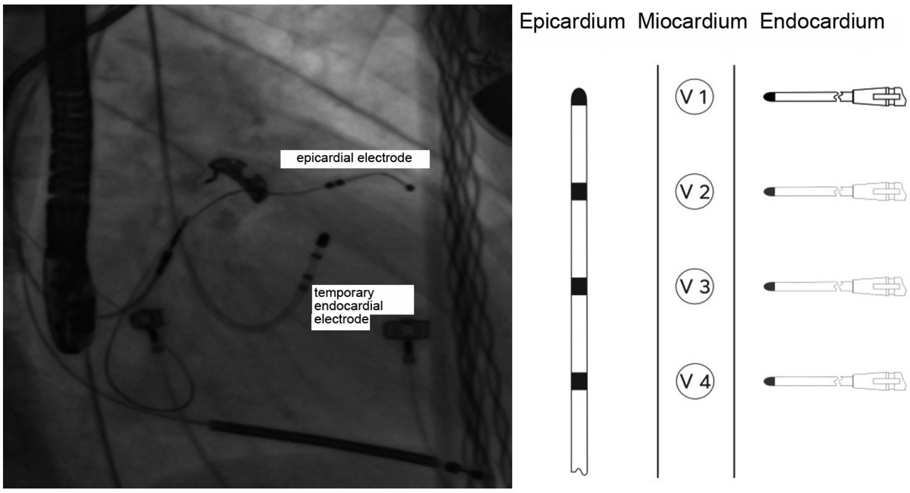

Fig. 1. Implantation of quadripolar epicardial and temporary endocardial electrode (right oblique position) and schematic representation of comparison of stimulation points during epi- and endocardial stimulation, where V1, V2, V3, V4 are points of isolated LV stimulation.

Table 2.

Comparison of values of the main ECG and echocardiogram parameters for epicardial and endocardial stimulation

	Epicardial ECS	Endocardial ECS	P
QRS, ms	218 [197;246]	190 [179;215]	0.0008
3D EDV, ml	172 [134.3;189.6]	177 [142.6;189.3]	0.22
3D ESV, ml	133.6 [101;158.8]	138.3 [104.8;156.3]	0.82
3D EF, %	23.1 [21;25]	25.2 [22;29.8]	0.009
ExcAvg, mm	2.7[1.7;3.7]	4.9 [3.6;6.4]	0.0002
ExcMax, mm	10.2 [7.9;13.5]	14.2 [11.4;15.9]	0.0036
ExcMin, mm	-6.9 [-9.5;-3.2]	-3.2 [-5; -1.9]	0.0004
ExcSD, mm	3.8 [2.9;5.4]	5.3 [3.6;5.6]	0.08
Tmsv-16SD, ms	17 [10.4;24.7]	11.4 [6.3;21.7]	0.13
Tmsv-12SD, ms	16.5 [8.4;25.7]	13.4 [1.2;21]	0.21
Tmsv-6SD, ms	17.2 [7.1;27.9]	13 [1.1;25.3]	0.21
Tmsv-16Dif, ms	48.5 [27;68.2]	50.9 [20.7;69.2]	0.7
Tmsv-12Dif, ms	39.4 [24.3;64.8]	50.1 [5.3;68.1]	0.7
GLS, %	-4.5 [-7;0.6]	-8.1 [-9.3;-6.4]	0.004

Notes: ExcAvg, ExcMax, ExcMin, ExcSD - mean, maximum, minimum values and standard deviation of endocardial excursion to the central axis respectively, Tmsv-16SD, Tmsv-12SD, Tmsv-6SD - time to reach minimum regional volume for 16-, 12- and 6-segment LV model, Tmsv-16Dif and Tmsv-12Dif - maximum time difference between QRS onset and the moment of reaching the minimum regional systolic volume for 16- and 12-segment model, GLS - global longitudinal strain.

characteristics that were combined into a random effects group to avoid statistical errors (due to the fact that data were collected from the same patient up to 8 times). Correlation analysis for nonparametric criteria was performed according to Spearman. P values less than 0.05 were considered statistically significant.

RESULTS

In 12 patients, 4 to 8 stimulation points were investigated for each patient, totaling a sample of 88 points investigated. In 9 patients all 4 epicardial and 4 endocardial stimulation points were studied, in 2 patients only 2 points were studied, and in 1 patient only 3 points were studied because of high stimulation thresholds or because of anatomic features of the coronary sinus. The scheme of the study execution is presented in Fig. 1. No complications were identified during implantation of the CRT system and endocardial left ventricular stimulation.

When comparing all epicardial points with all endocardial stimulation points, significant differences were demonstrated by semiquantitative parametric indices of segmental and total LV myocardial contractility calculated by 3D-echoCG: ExcAvg, mm, ExcMax, mm, ExcMin, mm, by EF, %, as well as by global longitudinal two-dimensional stretch, % and by QRS complex duration, ms. According to the data calculated by analyzing ECG monitoring, 2D speckle-tracking EchoCG and 3D EchoCG, the following results were found (Table 2).

Stimulated QRS duration ranged from 137 to 312 with a median of 204 [184;240] ms. The maximum QRS length was recorded during stimulation of basal LV sections (point 4 - proximal electrode contact). QRS duration was significantly shorter for endocardial stimulation and was 190 [179;215] ms, while for epicardial stimulation it was 218 [197;246], (p=0.0008, at p<0.05).

When examined in more detail, at each matched comparison point, significant differences were demonstrated at point 2 stimulation (p=0.033), at p<0.05 (Figure 2). The global strain score was -6.5[-10.9; -15.4] for the whole sample, and was significantly different (p=0.004) for epicardial (-4.5 [-7;0.6]) and endocardial (-8.1 [-9.3; -6.4]) stimulation. Significant differences were also demonstrated when analyzed at different stimulation points. At point 1 (p=0.003) and 2 (p=0.004) at p<0.005 (Figure 3).

3D-EchoCG parameters

The systolic dyssynchrony index or Tmsv-16SD, ranged from 6.90 to 38.20. The sample mean was 24.15±3.75, 17.8±5.4 for epicardial stimulation, and 13.9±5.7 for endocardial stimulation. No significant differences were found, but a tendency to favor endocardial over epicardial stimulation was demonstrated (p=0.06) at p<0.05. However, the same index calculated for the 6 segment model showed a significant difference in favor of endocardial stimulation at stimulation point 2 (p=0.018) at p<0.05, as illustrated in the sweep diagram below (Figure 4).

The obtained semi-quantitative parametric three-dimensional indices of segmental excursion and myocardial contractility such as ExcAvg (p<0.001), ExcMach (p=0.001), Exmin (p<0.001) as well as LV EF indices using three-dimensional echocardiography (p=0.003) [18] differed significantly depending on the method of stimulation, showing the advantage of endocardial stimulation. For ExcAvg at points 1 and 2 (p=0.021 and p=0.011) (Figure 5), for ExcMax at points 1 and 4 (p=0.02 and p=0.03), and for ExcMin at point 2 (p=0.011) (Figure 6).

Thus, all obtained semiquantitative parametric 3D-EchoCG indices of myocardial segmental excursion, contractility, and dyssynchrony, as well as data from ECG methods assessing intraventricular dyssynchrony and global strain, were better with endocardial stimulation. The data obtained using the different mathematical criteria applicable in this model were found to be comparable.

DISCUSSION OF FINDINGS

Technically, CRT is represented by three stimulating electrodes, two of which are stimulation electrodes located in the right chambers and the last one is for LV stimulation. Of practical interest is the positioning of the LV electrode, which in the «classical» transvenous technique of implantation is limited by the anatomy of the venous channel and the possibility of its fixation in the target vein [26, 27]. The influence of ventricular electrode placement on the effectiveness of CRT was first discussed by E.K.Heist et al. (2005). In the study of F.M.Merchant et al. (2010), it was shown a significant increase in mortality, a decrease in

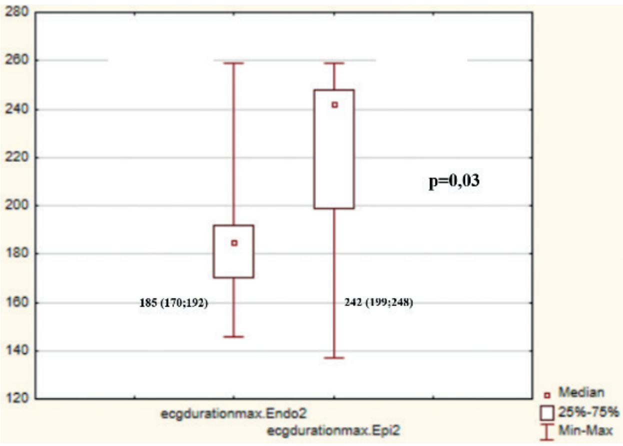

Fig. 2. Swing diagram demonstrating the difference in QRS duration for endo- and epicardial stimulation.

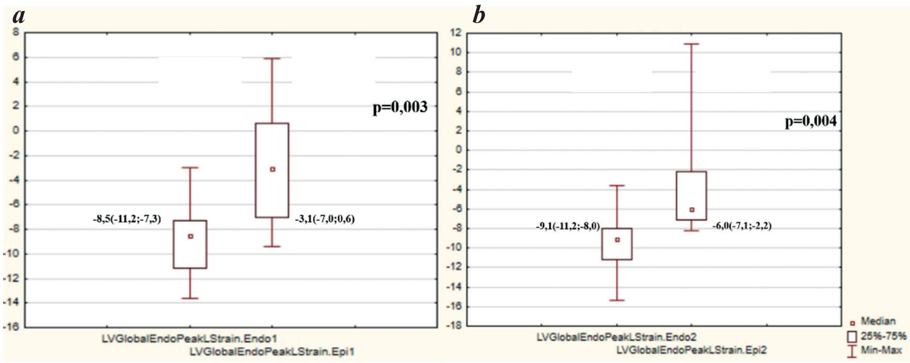

Fig. 3. Scatter plots showing the difference in global longitudinal strain (GLS) values for endo- and epicardial stimulation at points 1 (a) and 2 (b).

the degree of reverse LV remodeling and worsening of the functional class of CHF in the group with apical position of the LV electrode [29]. In the early days of CRT devices, only direct visualization techniques (radiography or fluoroscopy) were used at the time of device implantation or in case of suspected electrode dislocation or fracture, but were not so convenient for dynamic follow-up [30]. In the works of C.Ypenburg et al. [31] attempts were made to optimize the choice of stimulation zone on the basis of determination of zones of myocardial mechanical dyssynchrony on the basis of late activation zones [32] obtained by tissue Dopplerography. The TARGET study also confirmed the dependence of clinical and hemodynamic parameters on matching the LV pole of the electrode with the zone of late activation [32, 33]. Currently, there are techniques of three-dimensional EchoCG with more accurate and reproducible results of determining the zones of late activation of LV myocardium and the index of intraventricular dyssynchrony to determine the target segment for LV stimulation [18, 25].

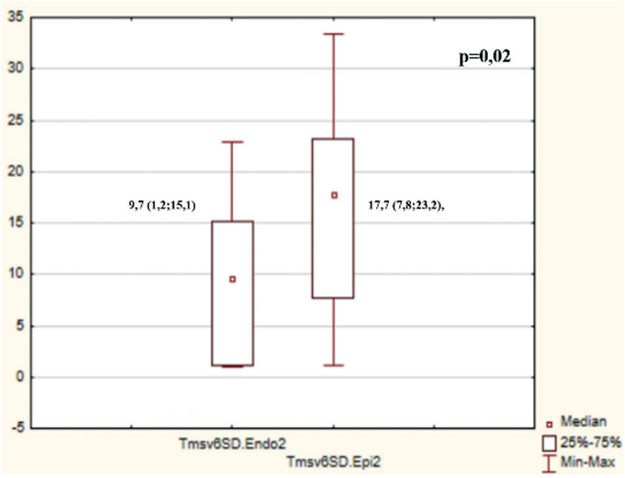

Fig. 4. Scatter plot showing significant differences in 3D dyssynchrony index for the 6-segment model (Tmsv-6SD) for endo- and epicardial stimulation.

The final location of the left ventricular electrode depends primarily on the anatomy of the coronary sinus veins, the presence or absence of diaphragmatic stimulation in the patient, and the properties and stability of the position of the electrode itself [34, 35]. In 8-10% of cases, according to various data, there is a failure of LV electrode implantation by transvenous method [34, 35]. One of the actively studied variants of isolated left ventricular (LV) stimulation is the technique of endocardial stimulation using different types of endocardial electrodes [36] and electrodeless systems [38, 39]. Endocardial stimulation has been reported to result in faster and physiologic LV activation compared to standard epicardial stimulation, less its proarrhythmogenic effect, lower risk of ventricular electrical storm and better acute hemodynamic effect [12-15]. The ALSYNC study, despite some limitations such as lack of a control group, significant differences in the cohort of patients who had the CRT system implanted repeatedly, 5 (3.6%) cases of ischemic stroke, and 14 (10.3%) transient ischemic attacks, demonstrated the efficacy of endocardial LV stimulation in patients who are nonresponders or in patients with technical difficulties of LV electrode placement [36]. An additional advantage of endocardial stimulation is the absence of restrictions in the choice of implantation point due to anatomical variants of the coronary sinus structure.

The use of different types of electrodes for endocardial stimulation has some limitations, such as the need for continuous anticoagulant therapy. Although the risk of thromboembolic complications and acute cerebral circulatory failure (2.5 cases per 100 patients per year) [3] is close to the risk of acute

a ***b***

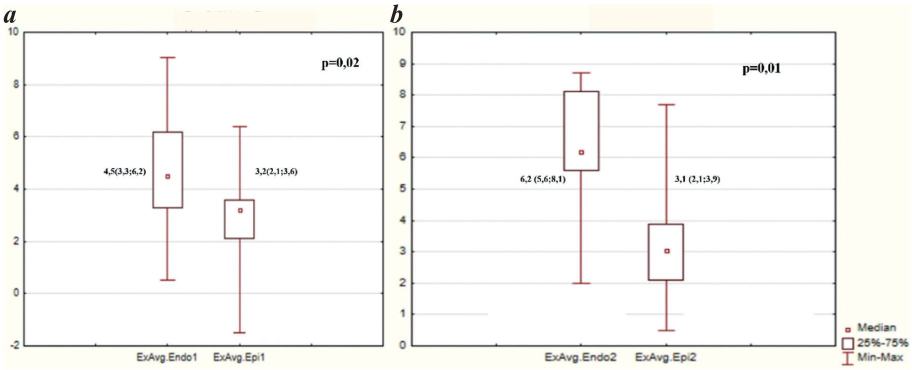

Fig. 5. Scatter plots showing significant differences on the average 3D index of left ventricular segmental contractility (ExcAvg) for endo- and epicardial stimulation at points 1 (a) and 2 (b).

a ***b*** ***c***

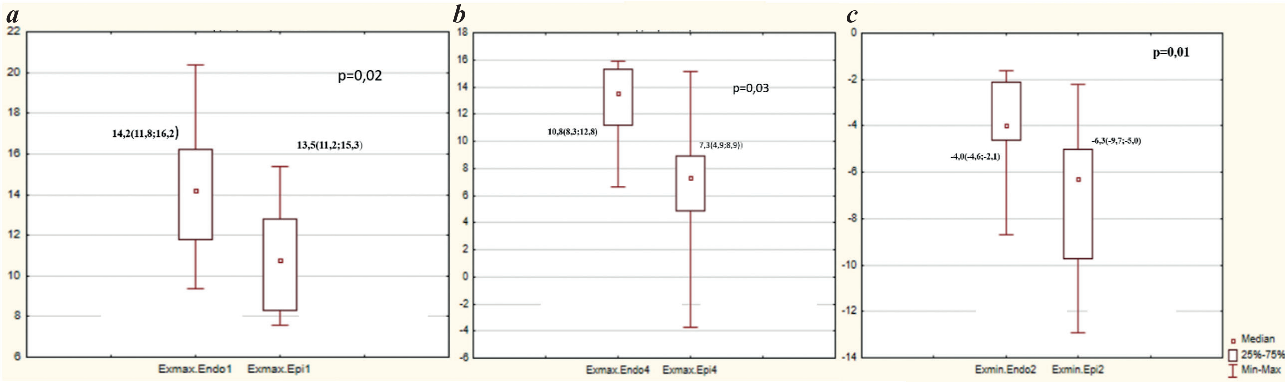

Fig. 6. Scatter plots showing significant differences in 3D values of maximum ExMax for points 1 (a) and 4 (b) and minimum ExMin at point 2 (c) of left ventricular endocardial excursion for endo- and epicardial stimulation.

cerebral circulatory failure in the group of patients with CHF and LVEF <28% [41].

At the same time, the advent of wireless LV endocardial stimulation systems has provoked a new wave of interest in studying this issue (SOLVE-CRT studies, 2021-2023), as endothelialization of the device completely removes the issue of lifelong anticoagulant therapy and the risk of acute cerebral circulatory failure [38, 39].

In our work, a temporary diagnostic LV electrode delivered retroaortically was used for endocardial LV stimulation. For epicardial stimulation, a quadripolar electrode with a controlled stimulation vector was used. Real-time three-dimensional EchoCG was used to assess left ventricular response parameters with evaluation of global and segmental myocardial contractility parameters such as Tmsv16-SD, Tmsv12-SD, Tmsv6-SD, and Tmsv16-Dif, Tmsv12-Dif and Tmsv6-Dif to assess intraventricular mechanical dyssynchrony and segmental contractility parameters (ExcAvg, ExcSD, ExcMah, ExcMin, Excursion Threshold) measured in mm, also expressed using color coding and identification of zones of most late activation [24-30].

Thus, the parameters of left ventricular response to endo- and epicardial stimulation were studied and compared, and a significant advantage of endocardial stimulation was demonstrated within the intraoperative study by assessing the data of global and segmental myocardial contractility, reduction of QRS duration as a criterion of electrical dyssynchrony and a significant reduction of one of the indices of mechanical dyssynchrony (Tmsv-6). More modest results were obtained for the systolic dyssynchrony index, which may be due to the small sample size.

Endocardial LV stimulation may be considered as an alternative to epicardial stimulation in repeat patients, in case of lack of response to CRT or in patients with abnormal or absent coronary sinus branches in the target area. The study and development of the methodology requires further accumulation of material.

Limitations of the study

The limitation of the study is the small sample size. The design did not involve the use of navigation for precise oppositional positioning of endocardial and epicardial electrodes.

CONCLUSION

1. Endocardial stimulation in the acute experience has an advantage in terms of better LV response, reduced degree of dyssynchrony, and reduced LV volumes as measured by real-time three-dimensional EchoCG.
2. The duration of QRS complex during endocardial stimulation is significantly shorter, which confirms the greater propagation velocity of LV myocardial excitation.
3. Endocardial stimulation is not limited in the choice of position in the target zone of the LV, in contrast to epicardial stimulation, in which the anatomy of the coronary sinus determines the possibilities of selecting the stimulation point.

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