Europace Advance Access published April 12, 2013

Europace
doi:10.1093/europace/eut068

CLINICAL RESEARCH

Assessment of optimal right ventricular pacing site using invasive measurement of left ventricular systolic and diastolic function

Vlastimil Vančura[1,2]*, Dan Wichterle[2,3], Vojtěch Melenovský[2], and Josef Kautzner[2]

[1]Department of Cardiology, Complex Cardiovascular Centre, University Hospital Pilsen, Faculty of Medicine in Pilsen, Charles University, Prague, Czech Republic; [2]Department of Cardiology, IKEM, Videnska 1958/9, 14000 Prague 4, Czech Republic; and [3]First Faculty of Medicine, Department of Cardiology and Angiology, Charles University, Prague, Czech Republic

Received 13 November 2012; accepted after revision 4 March 2013

Aims Right ventricular apical pacing has a detrimental effect on left ventricular (LV) function. More optimal pacing site may be found by invasive measurement of LV mechanical performance during pacing from different RV pacing sites. We aimed to investigate the effect of RV pacing lead location on invasive indices of LV mechanical performance.

Methods and results Patients undergoing catheter ablation for persistent atrial fibrillation were enrolled. Single-site endocardial pacing from the lateral LV region was periodically switched to pacing from the mapping catheter navigated to different RV sites within the three-dimensional electroanatomical RV map. SystIndex, DiastIndex, and PPIndex were defined as the ratio of LV dP/dt_{max}, LV dP/dt_{min}, and arterial pulse pressure during RV pacing to corresponding values from adjacent periods of LV pacing. Haemodynamic data were analysed in 18 RV segments created by dividing RV horizontally (basal, mid, and apical portion), vertically (inferior, mid, and superior portion) and frontally (septum and free wall). Eight patients (58 ± 7 years; 2 females; 26 ± 4 RV pacing sites per patient) were enrolled into the study. Compared with LV pacing, the best RV pacing values of SystIndex and DiastIndex were achieved in basal-mid-septal segment (+6.9%, $P = 0.02$ and +3.4%, $P = 0.36$, respectively) while the best PPIndex was obtained in superior-mid-septal segment of RV (+4.5%, $P = 0.02$). All indices were fairly concordant showing significant improvement of haemodynamics during RV pacing in the direction from free wall to septum, from apex to base, and from inferior to superior segments.

Conclusion The best LV mechanical performance was achieved by RV septal pacing in the non-apical mid-to-superior segments.

Keywords Right ventricular pacing • Haemodynamics of pacing • Electroanatomical mapping • Optimal pacing site • Resynchronization

Introduction

Implantation of a pacemaker is the only reliable long-term treatment option in patients with significant bradyarrhythmias. Most pacing systems employ one lead in the right ventricle (RV) usually implanted into the apical region. However, RV apical pacing prolongs QRS complex duration,[1] induces mechanical asynchrony,[2,3] promotes atrial fibrillation (AF) and heart failure.[4–6] Detrimental effect of RV apical pacing could be potentially diminished by the use of alternative RV pacing sites. Several studies demonstrated that septal pacing or pacing from RV outflow tract shows better results than apical pacing.[3,7–11] However, none of them mapped systematically RV endocardium to evaluate haemodynamic impact of pacing from various locations.

We hypothesized that a distinct RV pacing region could be identified which would result in best left ventricular (LV) haemodynamics, irrespective of interindividual heterogeneity in pacing response. To test this hypothesis we investigated acute changes in invasively measured indices of LV mechanical performance by alternating single-site LV pacing with different RV pacing sites under the guidance of the three-dimensional (3D) navigation system. The study was performed in patients with persistent AF in order to avoid possible bias introduced by variable atrioventricular delay.

*Corresponding author. Tel: +420 725023787; fax: +420 377103350, E-mail: vancurav@fnplzen.cz

What's new?

- This is the first study analysing virtually entire right ventricular (RV) endocardial surface for the impact of pacing on left ventricular (LV) mechanical performance.
- Investigational protocol utilized: (i) high-rate ventricular pacing; (ii) three-dimensional navigation to RV pacing sites; (iii) absence of atrioventricular synchrony issues; (iv) invasively measured LV function; (v) reference LV pacing; and (vi) computerized analysis of signals.
- Concordant gradients in improvement of LV mechanical performance were observed when pacing in the direction from free wall to septum, from apex to base, and from inferior to superior RV segments.

Methods

Patients

Patients undergoing catheter ablation for AF were eligible for the study. Exclusion criteria encompassed significant structural heart disease (LV ejection fraction $<40\%$, LV end-diastolic diameter >60 mm, QRS ≥ 0.12), valvular heart disease, and coronary artery disease. Patients in sinus rhythm at the time of the procedure were not eligible. Only patients with strictly controlled ventricular response were enrolled in order to minimize the occurrence of fusion beats during ventricular pacing. The protocol of the study was complied with the Declaration of Helsinki, it was approved by the local Ethics Committee and all patients gave written informed consent before entering the study.

Study protocol

After a double transseptal puncture (8 Fr. Swartz SL1 introducer, 8.5 Fr. Agilis NxT steerable introducer, St Jude Medical, Inc.) under the guidance of intracardiac echocardiography (10 Fr. AcuNav, Siemens Healthcare), two catheters were transseptally inserted into the LV: Millar tipmanometric catheter (Millar Instruments, Inc.) and LV pacing catheter positioned at the lateral, basal-to-mid portion of the LV endocardial surface. A short, 5 Fr. sheath was placed into the left femoral artery and connected to standard blood pressure transducer. Left ventricular pacing with a cycle length of 430 ms (pacing output of 5 V and impulse duration of 1 ms) was used to eliminate the effect of fusion. A 3.5 mm irrigated-tip catheter (Navistar Thermocool, Biosense Webster, Inc.) was inserted through the long sheath (8.5 Fr. Swartz SR0, St Jude Medical, Inc.) into the RV. Electroanatomical RV map was obtained using the CARTO system (Biosense Webster, Inc.) with a minimum of 90 mapping points. In all patients, the location of His bundle was identified during short interruption of pacing and annotated on CARTO map while pacing was resumed to take into account possible spatial shifts associated with fast pacing.

The acquisition of electrocardiogram (ECG) and haemodynamic data was commenced after finalizing the anatomical RV map in sufficient quality. Surface ECG, LV, and femoral arterial pressure were recorded using the PowerLab system (ADInstruments Pty Ltd) at a sampling rate of 4 kHz. During continuous LV pacing, mapping catheter was consecutively positioned to specific RV sites. While maintaining stable endocardial RV contact, LV pacing was periodically switched to unipolar pacing from the mapping catheter. Positive pacing pole for unipolar pacing was connected to a proximal ring of decapolar coronary sinus catheter located at the coronary sinus ostium with negligible ventricular far-field potential in order to prevent anodal ventricular capture. Every RV pacing as well as interleaving LV pacing episodes had minimum duration of 30 s. At the end, study catheters were removed and catheter ablation for AF followed.

Data processing

Digital ECG and pressure recordings were exported and off-line analysed using a purpose-made software. QRS complexes were automatically detected employing a combination of threshold and derivative methods. Both ECG and pressure signals were carefully visually inspected and manually edited to exclude artifacts, irregularities in rhythm and morphology including premature/fusion beats, or non-capture events. Semi-automatic QRS template-matching algorithm was used to exclude all abnormal QRS morphologies. His capture was considered a reason for excluding a pacing site from the analysis because even small fluctuations in catheter position could have substantial effect on haemodynamics and permanent His-bundle pacing in clinical practice is not easy to achieve. Edited signals from individual 30-s LV or RV pacing episodes were signal-averaged. Subsequently, LV dP/dt_{max}, LV dP/dt_{min}, and femoral arterial pulse pressure were calculated (*Figure 1*).

All indices obtained during RV pacing were adjusted for mean reference value from LV pacing periods immediately preceding and following a particular RV pacing episode. Thus for each pacing site, an index of contractility (SystIndex) was calculated as the ratio of LV dP/dt_{max} during RV pacing (LV dP/dt_{maxRVP}) and LV pacing (LV dP/dt_{maxLVP}):

$$\text{SystIndex} = (\text{LV } dP/dt_{maxRVP})/(\text{LV } dP/dt_{maxLVP})$$

Analogically, an index of relaxation (DiastIndex) was derived as the ratio of LV dP/dt_{min} during RV and LV pacing, and PPIndex as the ratio of pulse pressures during RV and LV pacing.

Haemodynamic indices from individual RV pacing sites from all patients were pooled and blindly grouped according to electroanatomically defined RV pacing segments. Both septum and RV free wall were divided horizontally into basal, mid, and apical portion, and vertically into inferior, mid, and superior portion, so that a total of 18 segments were defined (*Figure 2*).

Statistical analysis

Haemodynamic variables were expressed as means with standard deviations and 95% confidence intervals after testing for normality of distribution (Shapiro Wilk's test). Superiority/inferiority of RV pacing in individual segments vs. LV pacing was tested by two-tailed *t*-test for dependent samples, specifically by comparison of indices against unity. One-way analysis of variance (ANOVA) with Newman–Keuls *post hoc* test was used for the analysis of differences among multiple RV pacing segments. Two-tailed *t*-test for independent samples was used for comparison of pairs of RV pacing regions. Pearson's correlation was applied for the analysis of relationship between haemodynamic variables. A P value ≤ 0.05 was considered statistically significant. All analyses were performed using the STATISTICA version 9 software (Statsoft, Inc.).

Results

Eight patients were included into the study (mean age 58.0 ± 6.5 years, two women). The mean LV ejection fraction was $57 \pm 6\%$ and LV end-diastolic diameter 54 ± 4 mm. Recordings from a

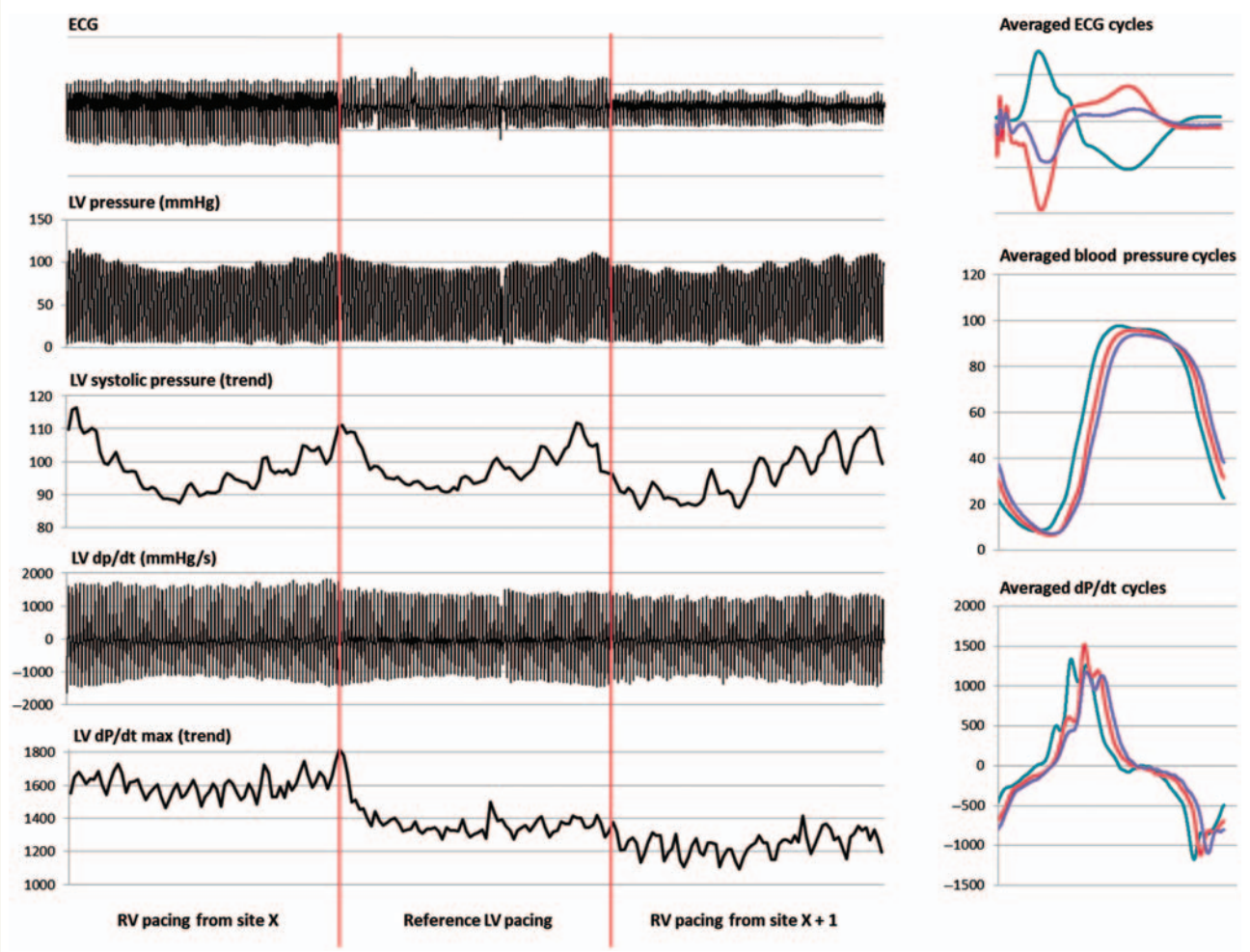

Figure 1 Example of raw data and signal-averaged signals. Left panels (from top to bottom) show ECG, LV pressure, trend in LV systolic pressure, LV d*P*/d*t*, and trend in LV d*P*/dt_{max} during three consecutive 30 s episodes of RV (site X) − LV (reference) − RV (site X + 1) pacing. Two vertical red lines denote the time of switching from RV pacing to LV reference pacing and *vice versa*. Right panel shows (from top to bottom) the corresponding signal-averaged, single-cycle surface ECG channel, LV pressure, and LV d*P*/d*t*. Signal-templates for pacing from RV (site X), LV (reference), and RV (site X + 1) are in red, blue, and green, respectively. Considerable variability of haemodynamic parameters in time can be noted even without changing of pacing site. This underscores the necessity of longer recordings for valid assessment of pacing-induced change in haemodynamics.

total of 209 RV pacing sites (26 ± 4 per patient, range: 21–34) were eligible for the analysis. When assessed by individual RV segments, the highest and the lowest density of pacing sites were 2.8 ± 0.9 at segment #4 (superior midseptum) and 0.6 ± 0.7 at segment #1 (septal superior apex), respectively.

We have not observed fusion beats during postprocessing of signals. Only sporadic ventricular premature complexes induced by catheter irritation and non-capture events required manual editing together with exclusion of several subsequent normal pacing cycles with irregularity-induced transient change in haemodynamics. Data from one pacing site were excluded because of intermittent His bundle capture. The duration of measurement period did not exceed 45 min in any patient. Mean values for measured haemodynamic parameters from all episodes included into analysis are summarized in *Table 1*. There were no major complications related to either study protocol or subsequent left atrial ablation.

Haemodynamic data for individual right ventricular segments

Segment assignment as an independent categorical variable was significantly associated with SystIndex ($r = 0.40$, $P = 0.008$), DiastIndex ($r = 0.47$, $P = 0.00007$) as well as PPIndex ($r = 0.53$, $P < 0.00001$). The mean values of SystIndex, DiastIndex, and PPIndex with 95% confidence intervals for individual RV segments are shown in *Figure 3*. The colour-coded values of haemodynamic indices averaged per segment and projected on electroanatomical map are shown in *Figure 4*.

Figure 2 Definition of RV segments. Right ventricular electroanatomical map. Left panel—free wall view (right anterior oblique projection), right panel—septum view (modified posterior anterior projection). Green and white points are markers for tricuspid and pulmonary valve annulus, respectively. Yellow point denotes the site with His bundle recording. Right ventricular segments are numbered for easier data presentation.

Table 1 Global haemodynamic parameters

	LVP	RVP
LV dP/dt_{max} (mmHg/s)	1245 ± 218	1194 ± 222
LV dP/dt_{min} (mmHg/s)	−1204 ± 354	−1147 ± 309
Systolic BP (mmHg)	112 ± 28	110 ± 26
Diastolic BP (mmHg)	77 ± 15	76 ± 14
Pulse pressure (mmHg)	36 ± 13	34 ± 12

All differences between LVP and RVP were not significant.
BP, blood pressure; LV, left ventricle; LVP, left ventricular pacing; RVP, right ventricular pacing.

The highest SystIndex of 1.07 ($P = 0.019$) was found for segment #8 (septal-basal-mid) while the lowest SystIndex of 0.86 ($P = 0.014$) was found for segment #10 (free wall-apical-superior), both mutually different ($P = 0.013$). There were five more segments (septal-mid-inferior and four others at RV free wall) with significantly lower LV contractility than during LV pacing.

The highest DiastIndex of 1.03 ($P = 0.36$) was found for segment #8 (septal-basal-mid) while the lowest DiastIndex of 0.87 ($P = 0.0004$) was found for segment #18 (free wall-basal-inferior), both mutually different ($P = 0.013$). Superiority of DiastIndex was also found for segment #8 (septal-basal-mid) vs. segment #11 (free wall-apical-mid) ($P = 0.037$) as well as segment #4 (septal-mid-superior) vs. segment #18 (free wall-basal-inferior) ($P = 0.039$). There were six more segments (two at inferior septum and four at RV free wall) with significantly lower LV relaxation when compared to LV pacing.

The highest PPIndex of 1.04 ($P = 0.02$) was found for segment #4 (septal-mid-superior) while the lowest PPIndex of 0.86 ($P = 0.0001$) was found for segment #18 (free wall-basal-inferior), both mutually different ($P = 0.008$). There were six more segments (three at mid/inferior apex and three others at non-superior free wall) with significantly lower LV contractility than during LV pacing.

Table 2 shows pacing segments associated with the highest LV mechanical response (based on limited number of measurements) for individual patients and for individual indices of LV performance. Although the study was not powered to detect the optimum pacing segments in individual patients, it is obvious from the *Table 2* that 88, 100, and 50% patients (depending on SystIndex, DiastIndex, and PPIndex used, respectively) had the maximum haemodynamic response if pacing at septum. On the other hand, pacing in all of six inferior segments was never associated with maximum response according to any of these three indices of LV mechanical performance. The absolute percentage differences in averaged LV haemodynamic indices between the best and the worst RV pacing segments reached 20.7, 16, and 18.9% for SystIndex, DiastIndex, and PPIndex, respectively.

Correlation between SystIndex and DiastIndex analysed per individual pacing segments was significant ($r = 0.53$, $P = 0.02$, *Figure 5*).

Haemodynamic data for right ventricular pacing regions

Aggregation of neighbouring RV segments into clinically meaningful RV pacing regions showed that pacing in inferior regions (not only overall but also when restricted to septal portion) was clearly worse compared to mid/superior regions. Such significant association was consistent across all haemodynamic indices. Favourable effect of pacing in superior region compared to mid/inferior regions (again either overall or restricted to septal portion) was less evident and statistically limited to DiastIndex and PPIndex.

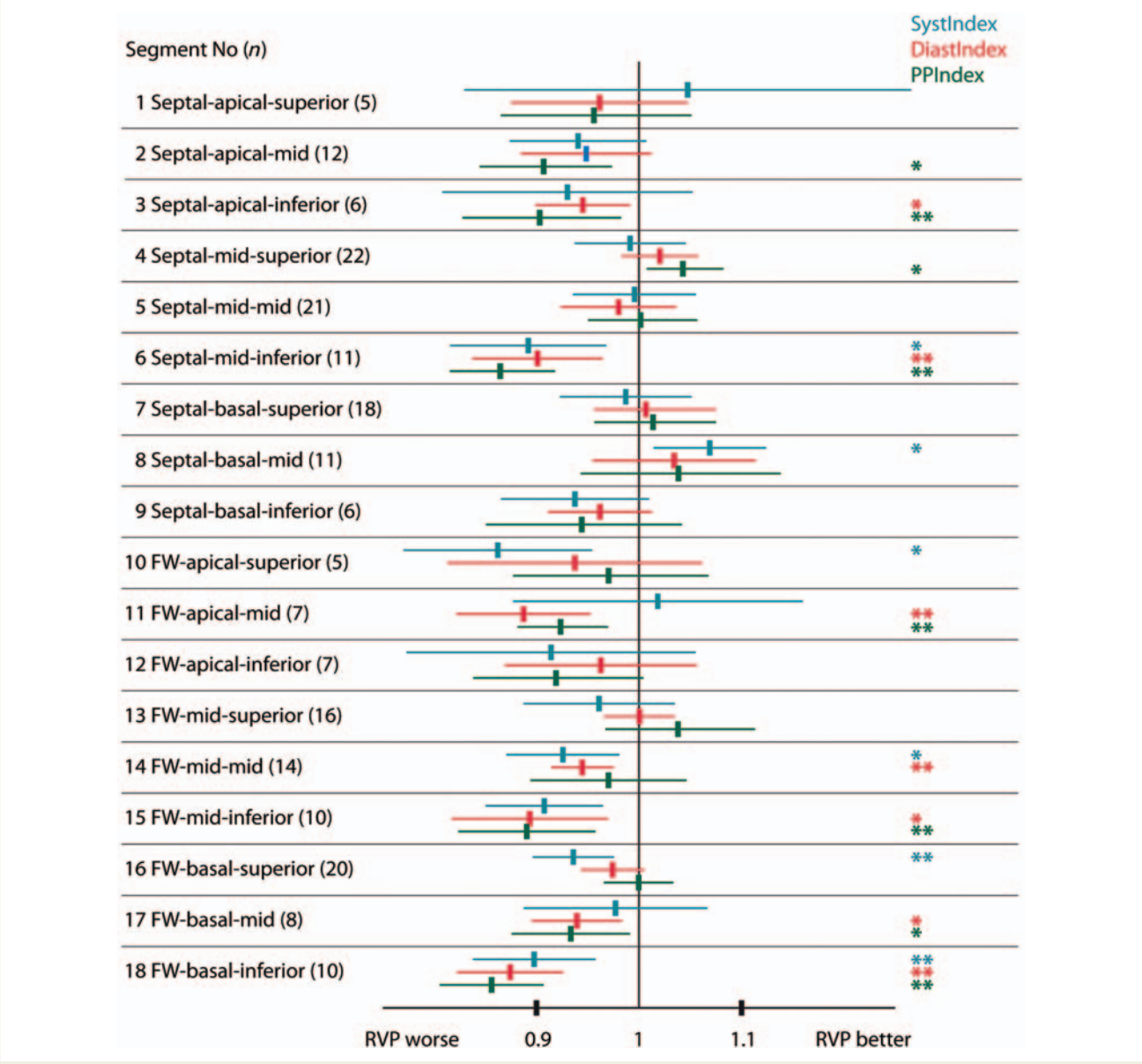

Figure 3 Indices of LV mechanical performance for individual RV pacing segments. Segments numbering is defined in *Figure 2*. Means and 95% confidence intervals are plotted for SystIndex (turquoise), DiastIndex (red), and PPIndex (green); FW—free wall; *n*, number of pacing sites in individual segment; RVP, right ventricular pacing; $*P < 0.05$, $**P < 0.01$ (statistical significance for the difference from unity).

Anticipated superiority of septal vs. free wall pacing was not particularly strong and appeared statistically significant only for SystIndex and DiastIndex. Even less prominent differences were observed in horizontal direction where PPIndex was the only significant variable demonstrating the inferiority of apical pacing while only borderline decrease of DiastIndex was found when pacing from RV apex. Detailed results are shown in *Table 3*.

Discussion

To our knowledge, this is the first study analysing virtually entire RV endocardial surface for the impact of pacing on LV mechanical performance. The study benefited from (i) high-rate ventricular pacing; (ii) 3D navigation to RV pacing sites; (iii) absence of atrioventricular synchrony issues; (iv) invasively measured LV function; (v) reference LV pacing; and (vi) computerized signal analysis. We demonstrated significant variability of impact among RV pacing sites.

Left ventricular haemodynamics

All haemodynamic indices used in this study were moderately concordant across various pacing regions and confirmed the anticipated superiority of RV septal pacing and inferiority of apical pacing. The strongest gradient for improvement of LV

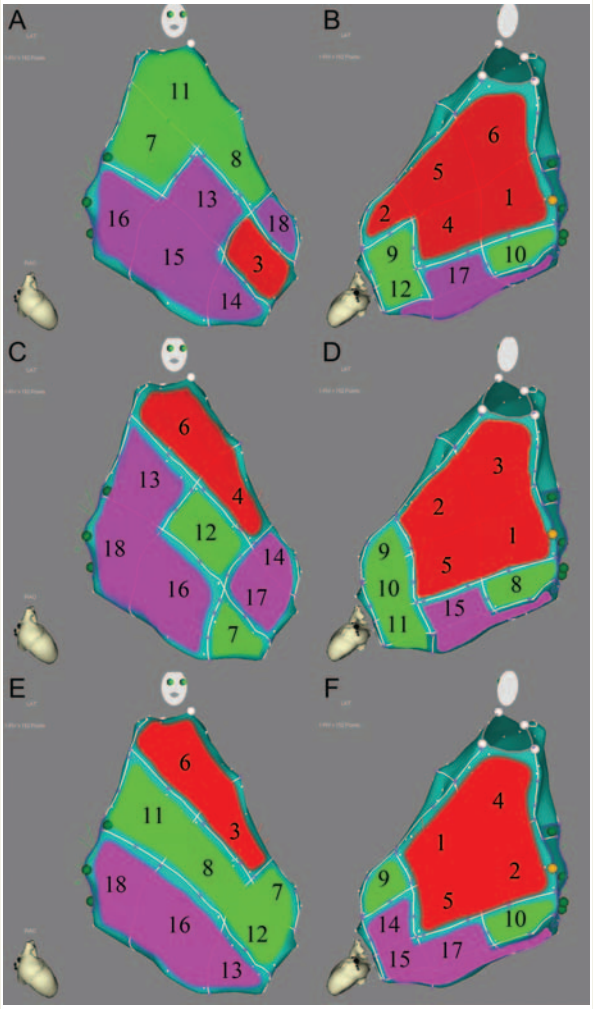

Figure 4 Indices of LV mechanical performance projected on CARTO map. Right ventricular segments are sorted in descendent order by the magnitude of SystIndex (A, B), DiastIndex (C, D) and PPIndex (E, F), numbered accordingly (1 = maximum; 18 = minimum value), and displayed on CARTO map in free wall view (left) and septum view (right). Red, green, and magenta colouring is used for upper, mid, and lower terciles of haemodynamic indices. Tagged points as in *Figure 2*.

Table 2 Right ventricular pacing segments with the highest LV performance for individual patients/indices

Patient #	SystIndex	DiastIndex	PPIndex
1	8 (2)	8 (2)	13 (1)
2	1 (1)	7 (3)	13 (2)
3	4 (2)	5 (4)	13 (2)
4	8 (2)	4 (4)	14 (2)
5	2 (4)	2 (4)	2 (4)
6	11 (1)	8 (1)	5 (5)
7	8 (1)	8 (1)	8 (1)
8	1 (1)	8 (2)	8 (2)

The values are segment # (numbers of corresponding pacing sites). Segments numbering is defined in *Figure 2*. Note that all optimum segments (except the segment #14 with PPIndex maximum in patient #4) belong to mid-to-superior septum or superior free wall area.
LV, left ventricle.

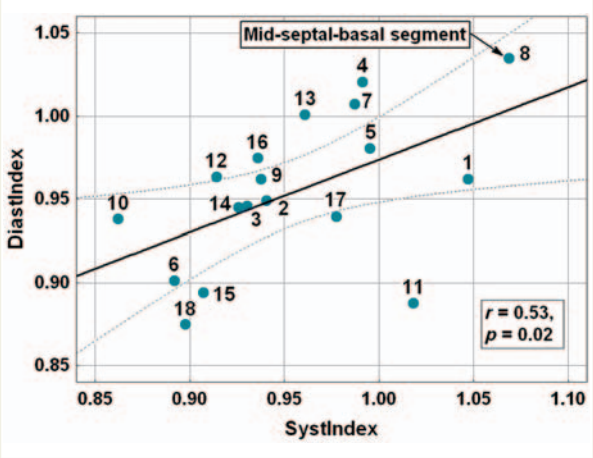

Figure 5 Correlation between SystIndex and DiastIndex. SystIndex vs. DiastIndex were analysed per pacing segments. The best RV pacing site overall was the segment #8 (septal-basal-mid). Regression line with 95% confidence intervals indicates significant positive relationship between both indices.

haemodynamics was unexpectedly found in the direction from inferior to superior segments/regions. Such distinct vertical gradient favouring more superiorly located pacing sites was consistently observed for all three haemodynamic indices and remained significant even when limited only to the septum. In other words, the LV mechanical performance was better during RV pacing at superior segments of the septum but also at superior segments of RV free wall. Consequently, pacing at four septal superior/mid septal segments, specifically basal-mid (#8), basal-superior (#7), mid-mid (#5), and mid-superior (#4) segments, concordantly provided all three LV haemodynamic indices within the upper tercile.

The only RV pacing segment yielding consistently better LV haemodynamics than LV pacing was the septal-basal-mid segment (#8), even if the difference from LV pacing reached statistical significance only for SystIndex based on LV dP/dt_{max}. It should be emphasized that none of the pacing sites in this segment used for calculation demonstrated clear His capture. This finding is even more important when taking into consideration that our reference LV pacing site was within the area considered as the best LV pacing region in heart failure patients for many years[12,13] and that LV endocardial pacing exerts more pronounced positive effect on haemodynamics when compared with epicardial pacing.[14] On the other hand, two recent studies concluded that the best LV pacing area may be individually different and optimization during implant procedure is necessary.[15,16] Moreover, optimum LV pacing site in our study group might substantially differ from

Table 3 Comparison of indices of LV mechanical performance in pre-specified vs. complementary RV pacing regions

Region A	N	SystIndex	DiastIndex	PPIndex	Region B	N	SystIndex	DiastIndex	PPIndex	P (region A vs. B)		
		Mean ± SD					Mean ± SD			SystIndex	DiastIndex	PPIndex
Septal	112	0.98 ± 0.12	0.98 ± 0.10	0.98 ± 0.12	Free wall	97	0.94 ± 0.11	0.94 ± 0.08	0.96 ± 0.11	0.007	0.003	0.11
Superior	86	0.97 ± 0.12	0.99 ± 0.08	1.02 ± 0.10	Non-superior	123	0.95 ± 0.12	0.94 ± 0.10	0.94 ± 0.11	0.42	0.0001	<0.0001
Inferior	50	0.91 ± 0.10	0.92 ± 0.09	0.89 ± 0.08	Non-inferior	159	0.98 ± 0.12	0.98 ± 0.09	1.00 ± 0.11	0.0006	<0.0001	<0.0001
Apical	42	0.95 ± 0.13	0.94 ± 0.09	0.93 ± 0.08	Non-apical	167	0.96 ± 0.12	0.97 ± 0.10	0.98 ± 0.12	0.61	0.07	0.004
Basal	73	0.97 ± 0.11	0.97 ± 0.10	0.98 ± 0.11	Non-basal	136	096 ± 0.13	0.96 ± 0.10	0.97 ± 0.12	0.46	0.38	0.53
Septal superior	45	1.00 ± 0.13	1.01 ± 0.09	1.02 ± 0.10	Septal non-superior	67	0.97 ± 0.12	0.97 ± 0.11	0.96 ± 0.12	0.28	0.03	0.003
Septal inferior	23	0.91 ± 0.10	0.93 ± 0.08	0.90 ± 0.08	Septal non-inferior	89	1.00 ± 0.12	1.00 ± 0.11	1.01 ± 0.12	0.004	0.005	<0.0001
Septal non-inferior basal	29	1.02 ± 0.12	1.02 ± 0.11	1.03 ± 0.13	Septal non-inferior non-basal	60	0.99 ± 0.13	0.99 ± 0.10	1.00 ± 0.11	0.28	0.21	0.27
Septal non-inferior apical	17	0.97 ± 0.13	0.95 ± 0.09	0.92 ± 0.09	Septal non-inferior non-apical	72	1.00 ± 0.12	1.01 ± 0.11	1.02 ± 0.11	0.35	0.054	0.0009

N, number of pacing sites in particular region; *P*, *P* value (*t*-test for independent samples); SD, standard deviation.

candidates of cardiac resynchronization therapy. Conversely, we observed that many segments at inferior aspect of the RV (both RV free wall and inferior septum) were associated with significantly worse LV haemodynamics compared with LV pacing.

The absolute percentage differences in LV haemodynamic indices between the best and the worst RV pacing segments were obviously overestimated by an inherent bias introduced by multiple measurements. However, ANOVA *post hoc* comparison revealed that at least the best and the worst segments differed significantly for all three indices of LV haemodynamics.

Technical aspects

The study was performed in patients with persistent AF undergoing catheter ablation. All patients had safe LV access available because of clinically indicated double transseptal approach. Moreover, measurements during AF excluded the influence of variable mechanical atrioventricular delay due to pacing from different ventricular pacing sites. Higher pacing rate was used in order to augment the differences between better vs. worse pacing configurations[17] and to eliminate potential fusion with intrinsic beats during AF. We also used higher pacing energy to reduce the influence of variable virtual electrode size depending on local pacing thresholds. We found previously that actual pacing energy decreases QRS duration in nonlinear fashion with negligible effect above the quadruple of the threshold value.[18]

Two out of three haemodynamic indices were based on derivatives of the LV pressure wave. The parameter of LV dP/dt_{max} has been widely used as surrogate of contractility. Recently, it has been proven as a predictor of mortality in paced patients with heart failure.[19] Similarly, LV dP/dt_{min} has been found associated with diastolic dysfunction.[20,21] Pulse pressure has been widely used as a surrogate for LV stroke volume.[22–24]

Signal averaging of LV pressure data from 30-s recordings for each pacing site effectively minimized the influence of beat-by-beat variations of haemodynamics of any origin, including the influence of respiration and transients caused by alternation of pacing regimes. For each RV pacing site, the dP/dt data were corrected for corresponding values obtained during immediately preceding and following LV pacing episodes in order to eliminate the influence of low-frequency oscillations or drifts.

Comparison with previous studies

Our results are in agreement with several published papers that compared pacing from the RV outflow tract (RVOT) or high RV septum with the RV apex. In acute studies, pacing from the RVOT or high RV septum induced less LV dyssynchrony than the RV apical pacing.[3,7,8] Several acute haemodynamic studies showed that both the RVOT and RV septal pacing increase cardiac index when compared with the RV apical pacing.[9–11] In one study, better LV diastolic function (LV dP/dt_{min} and isovolumic relaxation time constant) was found with pacing from RVOT compared with RV apex pacing, but unlike similar studies, this study could not find any difference in systolic parameters.[25]

It remains questionable whether acute improvement projects into better long-term results. It has been demonstrated that the pacing site-related difference in dyssynchrony can persist for at least 12 months[26] and that the rate of dyssynchrony after

implantation appears to predict further improvement of LV ejection fraction.[27]

Long-term studies mostly showed that these alternative pacing sites are better than RV apex pacing.[28–32] Some authors tried to analyse the influence on mortality. In one retrospective study, patients with RVOT pacing had better survival[33] whereas another randomized study could not demonstrate any difference.[34]

Limitations

Only patients with AF were included into the study. Such patients may differ from general population of candidates for pacemaker implantation and even more from candidates for cardiac resynchronization therapy. Therefore, the results of the study might only be applicable for single chamber pacing in patients with permanent AF.

The number of patients was low, so that we did not reach statistical significance in LV haemodynamic indices for small intersegment differences. However, estimated sample size for the study with improved resolution power would be unacceptably high in this technically demanding investigation. Similarly, the study was not designed to detect the optimum pacing site in individual patients, so that no inference can be drawn concerning the suitability of the method for individualized optimization in clinical practice.

Our 18 RV pacing segments were defined without knowing exact location of the moderator band and/or the border between the inflow and outflow tract. This information could be obtained through image integration with computed tomography (CT) or magnetic resonance imaging (MRI) angiograms of the RV. However, the disagreement between CT or MRI imaging information obtained before the study and electroanatomical map created during rapid ventricular pacing would substantially interfere with correct anatomical allocation of pacing sites. We consider high-density electroanatomical map of the RV more than sufficient for reliable display of boundaries of true interventricular septum vs. RV free wall.

Finally, it is not known to what extent acutely assessed haemodynamic indices can predict long-term clinical impact in pacemaker candidates. Only limited number of studies investigated this issue. They differed from our study either in measured parameters or in analysed population. None of them exceeded 12 months in duration.[26,27,35]

Conclusion

The best LV mechanical performance was achieved when the RV was paced at the interventricular septum in the non-apical, mid-to-superior segments. Pacing at inferior regions of the RV free wall as well as at inferior regions of the septum exhibited the worst haemodynamic response.

Conflict of interest: J.K. is on the advisory boards of Biosense Webster, Boston Scientific, Siemens, Hansen Medical, and St. Jude Medical. He has received speakers' fees from Biotronik, Biosense Webster, Boston Scientific, Hansen Medical, Medtronic, St. Jude Medical, and Siemens; and his department has received research contracts from Biotronik, Boston Scientific, Endosense, Medtronic, and Rhythmia. All other authors declare no conflict of interest.

Funding

This work was supported by project of Charles University in Prague, Faculty of Medicine in Pilsen SVV 264 807/2012, Charles University Research Project PRVOUK-P35/LF1/5; by the project Ministry of Health, Czech Republic for conceptual development of research organization 00669806—Faculty Hospital in Pilsen, Czech Republic, grant from Ministry of Health Of Czech Republic (MZO 00023001); Grant Agency of Czech Republic (305/09/1390); EU Operational Program Prague—Competitiveness project 'CEVKOON' (CZ.2.16/3.1.00/22126).

References

1. Vassallo JA, Cassidy DM, Miller JM, Buxton AE, Marchlinski FE, Josephson ME. Left ventricular endocardial activation during right ventricular pacing: effect of underlying heart disease. *J Am Coll Cardiol* 1986;**7**:1228–33.
2. Wyman BT, Hunter WC, Prinzen FW, Faris OP, McVeigh ER. Effects of single- and biventricular pacing on temporal and spatial dynamics of ventricular contraction. *Am J Physiol Heart Circ Physiol* 2002;**282**:H372–379.
3. Verma AJ, Lemler MS, Zeltser IJ, Scott WA. Relation of right ventricular pacing site to left ventricular mechanical synchrony. *Am J Cardiol* 2010;**106**:806–9.
4. Sharma AD, Rizo-Patron C, Hallstrom AP, O'Neill GP, Rothbart S, Martins JB *et al.* Percent right ventricular pacing predicts outcomes in the DAVID trial. *Heart Rhythm* 2005;**2**:830–4.
5. Steinberg JS, Fischer A, Wang P, Schuger C, Daubert J, McNitt S *et al.* The clinical implications of cumulative right ventricular pacing in the Multicenter Automatic Defibrillator trial II. *J Cardiovasc Electrophysiol* 2005;**16**:359–65.
6. Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL *et al.* Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation* 2003;**107**:2932–7.
7. Ji L, Hu W, Yao J, Yu J, Chen C, Yong Y *et al.* Acute mechanical effect of right ventricular pacing at different sites using velocity vector imaging. *Echocardiography* 2010;**27**:1219–27.
8. Yoshikawa H, Suzuki M, Tezuka N, Otsuka T, Sugi K. Differences in left ventricular dyssynchrony between high septal pacing and apical pacing in patients with normal left ventricular systolic function. *J Cardiol* 2010;**56**:44–50.
9. de Cock CC, Meyer A, Kamp O, Visser CA. Hemodynamic benefits of right ventricular outflow tract pacing: Comparison with right ventricular apex pacing. *Pacing Clin Electrophysiol* 1998;**21**:536–41.
10. Cowell R, Morris-Thurgood J, Ilsley C, Paul V. Septal short atrioventricular delay pacing: additional hemodynamic improvements in heart failure. *Pacing Clin Electrophysiol* 1994;**17**:1980–3.
11. Giudici MC, Thornburg GA, Buck DL, Coyne EP, Walton MC, Paul DL *et al.* Comparison of right ventricular outflow tract and apical lead permanent pacing on cardiac output. *Am J Cardiol* 1997;**79**:209–12.
12. Butter C, Auricchio A, Stellbrink C, Fleck E, Ding J, Yu Y *et al.* Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. *Circulation* 2001;**104**:3026–9.
13. Gasparini M, Mantica M, Galimberti P, Bocciolone M, Genovese L, Mangiavacchi M *et al.* Is the left ventricular lateral wall the best lead implantation site for cardiac resynchronization therapy? *Pacing Clin Electrophysiol* 2003;**26**:162–8.
14. Garrigue S, Jais P, Espil G, Labeque JN, Hocini M, Shah DC *et al.* Comparison of chronic biventricular pacing between epicardial and endocardial left ventricular stimulation using doppler tissue imaging in patients with heart failure. *Am J Cardiol* 2001;**88**:858–62.
15. Derval N, Steendijk P, Gula LJ, Deplagne A, Laborderie J, Sacher F *et al.* Optimizing hemodynamics in heart failure patients by systematic screening of left ventricular pacing sites: the lateral left ventricular wall and the coronary sinus are rarely the best sites. *J Am Coll Cardiol* 2010;**55**:566–75.
16. Spragg DD, Dong J, Fetics BJ, Helm R, Marine JE, Cheng A *et al.* Optimal left ventricular endocardial pacing sites for cardiac resynchronization therapy in patients with ischemic cardiomyopathy. *J Am Coll Cardiol* 2010;**56**:774–81.
17. Vollmann D, Luthje L, Schott P, Hasenfuss G, Unterberg-Buchwald C. Biventricular pacing improves the blunted force-frequency relation present during univentricular pacing in patients with heart failure and conduction delay. *Circulation* 2006;**113**:953–9.
18. Vancura V, Wichterle D, Brabec M, Bytesnik J, Lefflerova K, Kautzner J. The relationship between right ventricular pacing voltage and qrs complex duration. *Physiol Meas* 2009;**30**:517–27.
19. Suzuki H, Shimano M, Yoshida Y, Inden Y, Muramatsu T, Tsuji Y *et al.* Maximum derivative of left ventricular pressure predicts cardiac mortality after cardiac resynchronization therapy. *Clin Cardiol* 2010;**33**:E18–23.

20. Simantirakis EN, Vardakis KE, Kochiadakis GE, Manios EG, Igoumenidis NE, Brignole M *et al.* Left ventricular mechanics during right ventricular apical or left ventricular-based pacing in patients with chronic atrial fibrillation after atrioventricular junction ablation. *J Am Coll Cardiol* 2004;**43**:1013–8.
21. Buckingham TA, Candinas R, Attenhofer C, Van Hoeven H, Hug R, Hess O *et al.* Systolic and diastolic function with alternate and combined site pacing in the right ventricle. *Pacing Clin Electrophysiol* 1998;**21**:1077–84.
22. Stergiopulos N, Westerhof N. Determinants of pulse pressure. *Hypertension* 1998;**32**:556–9.
23. Kass DA, Chen CH, Curry C, Talbot M, Berger R, Fetics B *et al.* Improved left ventricular mechanics from acute vdd pacing in patients with dilated cardiomyopathy and ventricular conduction delay. *Circulation* 1999;**99**:1567–73.
24. Ather S, Bangalore S, Vemuri S, Cao LB, Bozkurt B, Messerli FH. Trials on the effect of cardiac resynchronization on arterial blood pressure in patients with heart failure. *Am J Cardiol* 2011;**107**:561–8.
25. Kolettis TM, Kyriakides ZS, Tsiapras D, Popov T, Paraskevaides IA, Kremastinos DT. Improved left ventricular relaxation during short-term right ventricular outflow tract compared to apical pacing. *Chest* 2000;**117**:60–4.
26. Gong X, Su Y, Pan W, Cui J, Liu S, Shu X. Is right ventricular outflow tract pacing superior to right ventricular apex pacing in patients with normal cardiac function? *Clin Cardiol* 2009;**32**:695–9.
27. Flevari P, Leftheriotis D, Fountoulaki K, Panou F, Rigopoulos AG, Paraskevaidis I *et al.* Long-term nonoutflow septal versus apical right ventricular pacing: Relation to left ventricular dyssynchrony. *Pacing Clin Electrophysiol* 2009;**32**:354–62.
28. Mera F, DeLurgio DB, Patterson RE, Merlino JD, Wade ME, Leon AR. A comparison of ventricular function during high right ventricular septal and apical pacing after his-bundle ablation for refractory atrial fibrillation. *Pacing Clin Electrophysiol* 1999;**22**:1234–9.
29. Victor F, Mabo P, Mansour H, Pavin D, Kabalu G, de Place C. A randomized comparison of permanent septal versus apical right ventricular pacing: Short-term results. *J Cardiovasc Electrophysiol* 2006;**17**:238–42.
30. Tse HF, Wong KK, Siu CW, Zhang XH, Ho WY, Lau CP. Upgrading pacemaker patients with right ventricular apical pacing to right ventricular septal pacing improves left ventricular performance and functional capacity. *J Cardiovasc Electrophysiol* 2009;**20**:901–5.
31. Tse HF, Yu C, Wong KK, Tsang V, Leung YL, Ho WY *et al.* Functional abnormalities in patients with permanent right ventricular pacing: The effect of sites of electrical stimulation. *J Am Coll Cardiol* 2002;**40**:1451–8.
32. Muto C, Ottaviano L, Canciello M, Carreras G, Calvanese R, Ascione L *et al.* Effect of pacing the right ventricular mid-septum tract in patients with permanent atrial fibrillation and low ejection fraction. *J Cardiovasc Electrophysiol* 2007;**18**:1032–6.
33. Vanerio G, Vidal JL, Fernandez Banizi P, Banina Aguerre D, Viana P, Tejada J. Medium- and long-term survival after pacemaker implant: improved survival with right ventricular outflow tract pacing. *J Interv Card Electrophysiol* 2008;**21**:195–201.
34. Dabrowska-Kugacka A, Lewicka-Nowak E, Tybura S, Wilczek R, Staniewicz J, Zagozdzon P *et al.* Survival analysis in patients with preserved left ventricular function and standard indications for permanent cardiac pacing randomized to right ventricular apical or septal outflow tract pacing. *Circ J* 2009;**73**:1812–9.
35. Steendijk P, Tulner SA, Bax JJ, Oemrawsingh PV, Bleeker GB, van Erven L *et al.* Hemodynamic effects of long-term cardiac resynchronization therapy: analysis by pressure-volume loops. *Circulation* 2006;**113**:1295–304.