Comparison of the Acute Hemodynamic Effect of Right Ventricular Apex, Outflow Tract, and Dual-Site Right Ventricular Pacing

Andrzej Rubaj, M.D., Ph.D.,* Piotr Rucinski, M.D., Ph.D.,*
Tomasz Sodolski, M.D., Ph.D.,* Andrzej Bilan, M.D., Ph.D.,† Marcin Gulaj, M.D.,‡
Alicja Dabrowska-Kugacka, M.D., Ph.D.,§ and Andrzej Kutarski, M.D., Ph.D.*

From the *Department of Cardiology, Medical University of Lublin, Poland; †Department of Internal Medicine, Medical University of Lublin, Poland; ‡Department of Cardiology, Ministry of Interior and Administration Hospital, Bialystok, Poland; and §Department of Cardiology and Electrotherapy, Medical University of Gdansk, Poland

Background: We studied the acute effect of pacing at the right ventricular outflow tract (RVOT), right ventricular apex (RVA) and simultaneous RVA and RVOT—dual-site right ventricular pacing (DuRV) in random order on systolic function using impedance cardiography.

Methods: Seventy-three patients (46 males), aged 52–89 years (mean 71.4 years) subjected to routine dual chamber pacemaker implantation with symptomatic chronic II or atrioventricular block, were included to the study.

Results: DuRV pacing resulted in significantly higher cardiac index (CI) in comparison to RVOT and RVA and CI at RVOT was higher than at RVA pacing (2.46 vs 2.35 vs 2.28; $P < 0.001$). In patients with ejection fraction $>50\%$ significantly higher CI was observed during DuRV pacing when compared to RVOT and RVA pacing and there was no difference of CI between RVOT and RVA pacing (2.53 vs 2.41 vs 2.37; $P < 0.001$). In patients with ejection fraction $<50\%$, DuRV and RVOT pacing resulted in significantly higher CI in comparison to RVA pacing while no difference in CI was observed between RVOT and DuRV pacing (2.28 vs 2.21 vs 2.09; $P < 0.001$).

Conclusion: Dual-site right ventricular pacing in comparison to RVA pacing improved cardiac systolic function. RVOT appeared to be more advantageous than RVA pacing in patients with impaired, but not in those with preserved left ventricular function. No clear hemodynamic benefit of DuRV in comparison to RVOT pacing in patients with impaired systolic function was observed.

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Since almost 50 years, the right ventricular apex (RVA) has been the preferred site of ventricular pacing. This lead location allowed easy implantation, stable function, and low incidence of complications. There are accumulating data indicating that RVA pacing might have detrimental effects on left ventricle (LV) function. Chronic RVA pacing can result in unfavorable LV remodeling: ventricular dilatation,¹ myocardial fiber disarray, regional perfusion defects, and subsequent increased risk of LV dysfunction and death.² These observations have prompted research on alternative to RVA pacing sites. Right ventricular outflow tract (RVOT) pacing seemed to be such an option and some

authors reported significant hemodynamic benefit from pacing at this location in comparison to RVA,³ however results of hemodynamic effects of RVA and RVOT pacing are conflicting and there is still no substantial evidence that RVOT is more beneficial in comparison to RVA pacing in short-term hemodynamic effect^{4,5} as well as long-term survival.⁶ Cardiac resynchronization therapy (CRT) is the preferred method of treatment of selected heart failure patients, however, some patients requiring ventricular pacing even with impaired LV function do not meet indications for CRT. Furthermore, about 6 to 14% of patients with CRT indications encounter problems with LV lead implantation or its

Address for correspondence: Kutarski Andrzej, M.D., Ph.D., Department of Cardiology, Medical University of Lublin, 21-002 Jastków, Marysin 14 Perłowa Street, Poland. Fax +48-81-7428747; E-mail: a_kutarski@yahoo.com

later dysfunction (dislocation, exit block, etc.).⁷⁻⁹ Dual-site right ventricular pacing (DuRV), that means simultaneous RVOT and RVA pacing, could be a promising method that offers some hemodynamic benefits over unifocal RVA or RVOT pacing¹⁰⁻¹² and could be applied in patients where CRT implantation was not successful. However, the beneficial effects of DuRV pacing were reported mostly in studies of small and not homogeneous populations.

Impedance cardiography (ICG) is a simple and reliable noninvasive method for hemodynamic beat-to-beat measurements. It relies upon changes in chest electrical impedance caused mostly by blood flow in aorta. ICG requires four dual sensors placed on the neck and chest to transmit a low-amplitude, high-frequency, alternating electrical signal to the patient's thorax. Pulsatile changes in blood volume and velocity are measured as impedance changes, and then applied to electrocardiogram and blood pressure measurements, automatically calculate hemodynamic parameters such as cardiac output (CO), cardiac index (CI), velocity index (VI), acceleration index (ACI), and electromechanical timing intervals.

ICG is an established method of accurate measurement of CO when compared with invasive methods^{13,14} in patients with preserved LV function as well as in heart failure.¹⁵ Several authors proved usefulness of ICG in optimizing dual-chamber pacemakers^{16,17} and suggested that ICG may supplement or even replace invasive measurements and Doppler echocardiography¹⁸⁻²⁰ in the optimization of implanted pacing systems including CRT devices.

The aim of the study was to compare hemodynamic effects of RVA, RVOT, and DuRV pacing using ICG.

METHODS

Study population was recruited from consecutive patients subjected to routine dual chamber pacemaker implantation in single pacemaker implantation center. Inclusion criteria: symptomatic chronic II or III degree atrioventricular block with class I indication for permanent pacemaker implantation according to the European Society of Cardiology guidelines, sinus rhythm, age >50 years. Exclusion criteria: hemodynamic instability, New York Heart Association (NYHA) Functional Classification IV, unstable angina, acute myocardial in-

Table 1. Basic Characteristics of the Study Group (n = 73)

	Mean (SD) or n (%)
Age	71.4 (9.4)
Male	46 (63.0)
Hypertension	44 (60.3)
Ischemic heart disease	49 (67.1)
Postmyocardial infarct	19 (26.0)
Heart failure symptoms	34 (46.6)
NYHA I	6 (8.2)
NYHA II	8 (11.0)
NYHA III	20 (27.4)
Dilated cardiomyopathy	7 (9.6)
EF (%)	49.4 (13.2)
LVEDd [mm]	54.3 (10.4)
IVSd [mm]	11.5 (2.1)
LVPWD [mm]	9.9 (1.7)
LA [mm]	42.3 (6.9)
Temporary pacing	27 (37.0)
ACE-I	41 (56.2)
ARB	9 (12.3)
Dihydropyridine Ca channel blockers	12 (16.4)
Diuretics	46 (63.0)

ACE-I = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; IVSd = interventricular systolic diameter; LA = left atrium; LVEDd = left ventricular end-diastolic diameter; LVPWD = left ventricular posterior wall diameter.

farction, CRT indications (NYHA $\geq$ III, LV ejection fraction (LVEF) < 35%, and QRS > 130 ms). Local ethical committee approved the study protocol, and all patients gave their written informed consent to pacemaker implantation and participation in the study.

Seventy-three patients were included to the study (46 males), aged 52–89 years (mean 71.4 $\pm$ 9.4 years). Basic characteristics of the study group are shown in Table 1.

The study was performed during the pacemaker implantation procedure, under local anesthesia in the operation room. Measurements of LV systolic function: CI, VI, ACI, and preejection period (PEP) were determined by means of ICG (BioZ ICG Monitor, CardioDynamics, San Diego, CA, USA). Blood pressure was measured noninvasively in 30-second intervals. ECG tracing (50 mm/s, 10 mV/cm) was recorded at each mode.

Study Protocol

Atrial screw-in lead was implanted into right atrial appendage (RAA), one ventricular (passive

fixation) lead was implanted in RVA position and second ventricular (screw-in) lead in RVOT position. Positions of the electrodes were confirmed by fluoroscopy and electrocardiography (ECG) tracing. The RVOT lead was placed approximately three-quarter of distance from the apex to the pulmonary valve in the anterior-posterior view, and toward the septum in the left anterior oblique view. Negative QRS complex morphology in lead I confirmed the appropriate RVOT lead position. External analyzer was used to check the leads' thresholds and afterwards it was used for pacing during the experiment. Each patient was assessed in dual-chamber temporary pacing with the atrium paced from RAA and the right ventricle paced from the RVA, RVOT, or DuRV in random order. Constant overdrive atrioventricular pacing was maintained throughout the protocol at a rate of 90 bpm, or in case of rapid sinus rate, 10 bpm higher than the sinus rate. Atrioventricular delay was programed at 150 ms and was constant throughout the study. The protocol ensured at least 15 minutes of cardiovascular stabilization in supine position as well as at least 5 minutes of ventricular pacing at a rate of 90 bpm, before measurements were started. Pacing was continued at each setting for 2 minutes before parameters were recorded. The data were recorded for 2 minutes at each mode. Ventricular pacing site was changed in the order established during the randomization process.

After the experiment, the RVA lead was removed and a standard dual chamber pacemaker was connected to the atrial and the RVOT lead in order to provide chronic therapy. In two patients, the RVOT pacing threshold was unacceptable (over 2.5 V/0.5 ms) and permanent pacing was achieved through the RVA lead.

Statistical Analysis

Data are presented as mean and standard deviation (SD) or number and percentage. Comparisons of dependent variables in tested pacing modes were performed by means of analysis of variance (ANOVA) for repeated measures and least square difference (LSD) test post hoc analysis. STATISTICA software (version 7.1, StatSoft, Inc., Tulsa, OK, USA) was used to calculate statistics. P-level of 0.05 was considered statistically significant.

RESULTS

Dual-site right ventricular pacing resulted in significantly higher CI in comparison to RVOT and RVA pacing. Also, CI during RVOT pacing was higher than during RVA pacing. The QRS duration was longer during RVA pacing, shorter during RVOT pacing, and the shortest during DuRV pacing. PEP was significantly longer during RVA pacing in comparison to DuRV and RVOT pacing, while no difference in PEP was observed between RVOT and DuRV pacing. VI and ACI were significantly lower during RVA pacing in comparison to DuRV and RVOT pacing. There was no difference of VI and ACI between RVOT and DuRV pacing. There was no difference of blood pressure among investigated methods of pacing (Table 2).

In patients with preserved LV systolic function ($EF > 50\%$), significantly higher CI was observed during DuRV pacing when compared to RVOT and RVA pacing and there was no difference of CI between RVOT and RVA pacing (Table 3). In patients with impaired LV systolic function and ($EF < 50\%$), DuRV and RVOT pacing resulted in significantly

Table 2. Parameters in the Whole Study Population

	RVA		RVOT		DuRV		ANOVA
	Mean	SD	Mean	SD	Mean	SD	P Value
QRS	180.33 ^{a,c}	26.73	167.93 ^{b,c}	22.47	152.60 ^{a,b}	22.22	<0.001
sBP	131.78	24.37	130.09	23.55	131.10	25.40	NS
dBP	78.92	15.08	78.02	15.99	77.85	15.65	NS
mBP	98.04	17.41	98.59	17.18	97.99	18.19	NS
CI	2.28 ^{a,c}	0.56	2.35 ^{b,c}	0.52	2.46 ^{a,b}	0.55	<0.001
PEP	0.175 ^{a,c}	0.028	0.169 ^c	0.029	0.165 ^a	0.023	<0.001
VI	30.24 ^{a,c}	10.24	31.06 ^c	10.16	31.25 ^a	10.76	<0.05
ACI	60.23 ^{a,c}	24.13	63.59 ^c	22.62	64.41 ^a	23.70	<0.01

^{a,b,c}Post hoc LSD test $P < 0.05$.

ACI = acceleration index; CI = cardiac index; dBP = diastolic blood pressure; mBP = mean blood pressure; PEP = preejection period; sBP = systolic blood pressure; VI = velocity index.

Table 3. Parameters in Patients with Preserved LV Systolic Function (EF > 50%)

EF > 50	RVA		RVOT		DuRV		ANOVA
	Mean	SD	Mean	SD	Mean	SD	P Value
QRS	168.93 ^{a,c}	21.99	158.72 ^{b,c}	19.00	145.05 ^{a,b}	19.04	<0.001
CI	2.37 ^c	0.59	2.41 ^a	0.57	2.53 ^{a,c}	0.60	<0.001
PEP	0.174 ^{a,c}	0.030	0.165 ^c	0.028	0.164 ^a	0.023	<0.01
VI	31.96	10.94	32.10	10.65	32.52	11.27	NS
ACI	64.23	26.90	66.60	24.16	67.34	24.97	0.14

^{a,b,c}Post hoc LSD test P < 0.05.

higher CI in comparison to RVA pacing while no difference in CI was observed between RVOT and DuRV pacing. Changes of VI and ACI had the same pattern (Table 4).

DISCUSSION

In this study, using ICG we assessed cardiac systolic function during different right ventricular pacing sites: RVA, RVOT, and DuRV pacing. Our study represents a unique report assessing the differences in hemodynamic response between RVA, RVOT, and DuRV pacing in patients with and without impaired LV function. We confirmed that in an acute experiment, CI was the lowest during RVA pacing, higher during RVOT pacing, and the highest during DuRV pacing. Less frequently used in clinical practice parameters of LV systolic function: PEP, VI, and ACI confirmed the main results. The QRS duration was similarly the longest during RVA pacing, shorter during RVOT pacing, and the shortest during DuRV pacing.

Negative correlation between the ventricular activation time reflected by QRS duration and the acute hemodynamic effect during pacing was found at various pacing sites²¹ and paced QRS duration has been shown to correlate with LVEF during

pacing.^{22,23} However, Lieberman et al. indicated that QRS duration might not be valuable in predicting both ventricular synchrony and LV function.²⁴

The improvement in systolic performance during DuRV pacing when compared to RVA pacing was seen in all patients. The hemodynamic effects of RVA, RVOT, and DuRV pacing were different in the groups of patients with preserved LV systolic function (EF > 50%) in comparison to patients with impaired LV function (EF < 50%). In patients with preserved systolic function, no difference was observed between RVA and RVOT pacing effect; however, DuRV pacing provided better hemodynamic effect than RVA or RVOT pacing. In contrast, in patients with impaired LV function, RVOT pacing resulted in better CI than RVA pacing, but no significant difference was observed between RVOT and DuRV pacing.

Our results are consistent with those obtained by Buckingham et al. who found in acute experiment that DuRV pacing resulted in significantly higher CO than RVA pacing in patients with preserved as well as impaired LV function.¹⁰ This study however comprised only a small group of patients and the pacing site was epicardial. Pachon et al. also proved advantage of DuRV stimulation over RVA in patients with heart failure and Chagas disease.¹¹

Table 4. Parameters in Patients with Impaired LV Systolic Function (EF < 50%)

EF < 50	RVA		RVOT		DuRV		ANOVA
	Mean	SD	Mean	SD	Mean	SD	P Value
QRS	197.72 ^{a,c}	25.24	181.64 ^{b,c}	20.80	164.88 ^{a,b}	22.57	<0.001
CI	2.09 ^{a,c}	0.50	2.21 ^c	0.42	2.28 ^a	0.42	<0.001
PEP	0.179	0.027	0.176	0.030	0.170	0.020	0.11
VI	26.11 ^{a,c}	8.27	27.93 ^c	8.79	27.65 ^a	8.88	<0.01
ACI	50.79 ^{a,c}	15.85	56.15 ^c	16.80	56.50 ^a	17.12	<0.01

^{a,b,c}Post hoc LSD test P < 0.05.

Our results show that the hemodynamic effect of pacing strongly depends on systolic cardiac function. In a general population, RVOT pacing is hemodynamically superior over RVA pacing, but this effect is especially evident in patients with impaired systolic LV function. In the group of patients with preserved systolic function ($EF > 50$), we did not find significant difference in CI between RVOT and RVA pacing. Kolettis et al. similarly could not demonstrate any differences in end-diastolic pressure, maximum positive dP/dt , or CO during short-term atrioventricular sequential pacing from the RVA and the RVOT in patients with no structural heart disease.²⁵

Consistent with the results of our study, Cowell et al. observed that in patients with LV dysfunction, RVOT provided higher CO than RVA pacing.²⁶ Similarly, Giudici and coworkers demonstrated a substantial increase in CI during RVOT in comparison to RVA pacing by about 21% and the improvement was greater in patients with lower baseline CI.³ de Cock et al. also demonstrated an overall increase in CI during RVOT pacing when compared to RVA pacing, also in patients with $EF < 50\%$.²⁷ The analysis of studies comparing the acute effects of pacing at the RVOT with the RVA results in a conclusion that most of them did not prove significant difference with respect to CI or systolic function between these two pacing sites.^{22,28–30} However, the above-mentioned studies were not randomized and the reported pacing site was different in each study, affecting different portion of the RVOT what makes interpretation of the data difficult. Meta-analysis performed by de Cock et al. also suggested that RVOT pacing may offer a modest but significant hemodynamic benefit over RVA in patients with symptomatic brady-arrhythmia.³¹ However, the group of patients was not homogeneous and the exact stimulation site during RVOT pacing was not standardized and may vary among studies.

Taking into consideration the hemodynamic effect of DuRV versus RVOT pacing, we found that in patients with restricted LV function DuRV pacing was not better than RVOT pacing.

Similarly, although in long-term observation, Stambler et al. did not find a clear clinical favor of DuRV pacing compared to RVOT pacing in patients with heart failure ($EF < 40\%$) and chronic atrial fibrillation.⁵ Pachon et al. also did not prove the superiority of DuRV over RVOT pacing with respect to the hemodynamic effect.¹¹

Our results indicate that in patients with impaired LV function, simultaneous RVA and RVOT pacing brings no additional effect in comparison to RVOT pacing alone in an acute hemodynamic experiment. RVA pacing is detrimental in patients with impaired LV function and DuRV is suggested as an alternative pacing site for those patients. These suggestions were mostly based on studies comparing DuRV with no pacing or RVA pacing. Our data may imply that RVOT could be an acceptable pacing site also for patients with impaired LV function, not eligible to CRT and that simultaneous RVA and RVOT pacing provides no additional benefit.

As shown in previous studies, RVA pacing impairs LV systolic function probably by lowering regional myocardial perfusion, inducing asynchronous LV contraction, shortening LV filling time, and augmenting mitral regurgitation. Chronic RVA pacing was proved to be harmful especially in patients with heart failure resulting in symptoms worsening and mortality increase.³² The adverse effects of RVA pacing may take a longer period to manifest in patients with preserved LVEF, as the incidence of new-onset heart failure after RVA pacing in patients with normal LVEF is rather low.^{33–35}

The hemodynamic benefit of RVOT pacing could be attributed to shorter intraventricular conduction times during outflow tract pacing, evidenced by shorter QRS complexes and earlier LV activation compared with apical pacing.³⁶

In BRIGHT, Res et al. showed the clinical benefit of DuRV pacing in comparison to no pacing within 7-month follow-up in patients eligible to CRT.¹² DuRV pacing was considered as an alternative to CRT in cases when the LV lead implantation was impossible.³⁷ There are still no established indications for DuRV pacing. Simultaneous RVA and RVOT pacing may be hemodynamically beneficial in some patients in relation to no pacing and unifocal RVA pacing. Up till now nobody was able to show clear benefit of DuRV pacing over RVOT pacing in patients with impaired LV systolic function. One should consider hemodynamic testing and justify if simultaneous RVA and RVOT pacing would be better over RVOT pacing alone in patients with pacing indications, taking into account the potential side effects of implanting an additional lead.

We conclude that dual-site right ventricular pacing in comparison to RVA pacing improved cardiac systolic function. RVOT pacing appeared to be more advantageous than RVA pacing in patients

with impaired, but not in those with preserved left ventricular function. No clear hemodynamic benefit of DuRV in comparison to RVOT pacing in patients with impaired systolic function was shown.

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