CHAPTER 5

EFFECT OF INDUCED LV DYSSYNCHRONY BY RIGHT VENTRICULAR APICAL PACING ON ALL-CAUSE MORTALITY AND HEART FAILURE HOSPITALIZATION RATES AT LONG-TERM FOLLOW-UP

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ABSTRACT

Right ventricular apical (RVA) pacing may induce left ventricular (LV) dyssynchrony. The long-term prognostic implications of induction of LV dyssynchrony were retrospectively evaluated in a cohort of patients who underwent RVA pacing.

A total of 169 patients (62±13 years, 69% male) with high RVA pacing burden were included. Echocardiographic evaluation of LV volumes, ejection fraction and dyssynchrony were performed before and after device implantation. LV dyssynchrony was assessed by 2 dimensional radial strain speckle tracking echocardiography. Based on the median LV dyssynchrony value after RVA pacing, the patient population was dichotomized (induced and non-induced LV dyssynchrony groups) and was followed-up for the occurrence of all-cause mortality and heart failure (HF) hospitalization.

Baseline mean LV ejection fraction was 51±11%. Median LV dyssynchrony value was 40 ms (12-85 ms) before RVA pacing and increased to 91ms (81-138 ms) after a median of 13 months (3-26 months) after RVA pacing. Median follow-up duration was 70 months (interquartile range 42-96 months). Patients with induced LV dyssynchrony defined as LV dyssynchrony value superior to the median at follow-up (≥91ms) showed higher mortality rates (5% and 27% vs. 1% and 3% at 3 and 5 years follow-up; log-rank P=0.003) and HF hospitalization rates (18% and 24% vs. 3% and 4% at 3 and 5 years follow-up; log-rank P<0.001) than patients with LV dyssynchrony <91ms after RVA pacing. A multivariate model was developed to identify independent associates of a combined endpoint of all-cause mortality or HF hospitalization. Induction of LV dyssynchrony was independently associated with increased risk of combined endpoint (HR [95%-CI]: 3.369 [1.732-6.553], P<0.001).

Induction of LV dyssynchrony by RVA pacing is associated with worse long-term mortality and increased HF hospitalization rates.

INTRODUCTION

Right ventricular pacing in symptomatic sinus node disease (SND) and atrioventricular (AV) block is a class I indication.[1] However, recent studies have suggested that right ventricular apical (RVA) pacing might be detrimental to specific subgroups of patients.[2-6] A high burden of RVA pacing has been associated with increased heart failure events in SND patients.[7, 8] Moreover, it has been postulated that RVA pacing has a detrimental impact on myocardial perfusion, oxygen demand and left ventricular (LV) systolic function.[9, 10] Induction of intra-ventricular or LV dyssynchrony by RVA pacing has been demonstrated acutely and at long-term follow-up and might be associated with long-term deterioration of LV systolic function and heart failure (HF).[11] Whether the extent of long-term induction of LV dyssynchrony by RVA pacing is related to a worse outcome is unknown. Furthermore, the characteristics of patients who may experience significant induction of LV dyssynchrony by RVA pacing have not been extensively studied. The present study evaluated the relationship between LV dyssynchrony induced by RVA pacing and long-term outcome, in patients with symptomatic SND or advanced AV block.

METHODS

Patient population and data collection

The present evaluation included patients with indications for RVA pacing who had complete clinical and echocardiographic follow-up data before and after pacemaker device implantation and had high pacing burden. Indications for RVA pacing included symptomatic SND and advanced degree AV block.[1] Particularly, patients with SND who underwent concomitant His bundle ablation were included; 35 patients were included in a previous study.[11] Patients who received an implantable cardioverter defibrillator (ICD) were also included. All patients underwent 2-dimensional (2D) echocardiography before implantation and LV volumes and ejection fraction (LVEF) were assessed.[12] LV dyssynchrony was evaluated with 2D radial speckle strain echocardiography.[9] Baseline RV function was assessed by tricuspid annulus plane systolic excursion (TAPSE) measurement.[13]

After RVA pacemaker implantation, echocardiographic evaluation was repeated to assess the evolution of LV volumes, LVEF and dyssynchrony after RVA pacing. Subsequently, patients were divided into 2 groups

according to the median value of LV dyssynchrony assessed after pacemaker implantation. Patients with LV dyssynchrony equal or superior to the median value formed the induced LV dyssynchrony subgroup.[14] Conversely, patients with an LV dyssynchrony value inferior to the median value formed the non-induced LV dyssynchrony subgroup.[14]

Patients were systematically followed-up in a dedicated outpatient clinic where device function was first controlled 3 months after implantation, and subsequently annually. In particular, the percentage of RVA paced complexes was collected from stored pacemaker data at each patient's visit. In addition, the long-term all-cause mortality and HF hospitalization were recorded.

All clinical and echocardiographic data were prospectively entered into the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, the Netherlands) and retrospectively analyzed.

Echocardiography

All echocardiographic data were obtained with the patient at rest in the left lateral decubitus position using a commercially available system (Vingmed System 7 and E9, GE-Vingmed Ultrasound AS, Horten, Norway) with a 3.5 –MHz transducer. Apical 2- and 4-chamber views were used to calculate LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) and to derive LVEF according to the Simpson's method.[12] LV volumes and LVEF were assessed before RVA pacing and at follow-up. TAPSE was measured in the apical 4-chamber view, as previously described.[13] The maximal displacement of the lateral portion of the tricuspid annulus from end-diastole to end-systole was measured.[13]

LV dyssynchrony was assessed with 2D radial strain speckle tracking.[15] This parameter was evaluated using commercially available software (EchoPac 110.0.0, General Electric/Vingmed Ultrasound) and has been previously described.[15] In brief, the mid LV short-axis view, at the level of the papillary muscles, is first acquired at an optimal frame rate to permit adequate tracking of the speckles (40-80 frames per second). The endocardial border is manually traced at an end-systolic frame. Two concentric regions of interest are then automatically provided by the software. Further adjustment of the region of interest thickness is subsequently performed to optimize the tracking of the myocardium along the cardiac cycle. From the time-strain tracings for each of the 6 mid LV short-axis segments, the time difference between the peak radial strain of the anteroseptal and the posterior segments was calculated to define LV dyssynchrony.[15]

Pacemaker implantation and settings

The attribution of single chamber or dual chamber device implantation was left at the treating physician's discretion. Pacemaker devices were implanted transvenously, with positioning of the right atrial lead in the appendage of the right atrium when applicable, and placement of the RV lead in the apex of the RV. Patients who were additionally eligible for a defibrillator system according to current guidelines for primary or secondary prevention received an appropriate pacemaker-defibrillator device.[1, 16] Implanted systems were manufactured by Biotronik (Berlin, Germany), Boston Scientific (Natick, Massachusetts, formerly CPI, Guidant, St. Paul, Minnesota), Medtronic (Minneapolis, Minnesota), and St. Jude Medical/Ventritex (St. Paul, Minnesota).

Single-chamber permanent pacemakers were set to VVI or VVIR pacing modes and dual-chamber pacemakers to DDD or DDDR pacing modes. The pacemaker settings were based on the cardiac stimulation indication and, with individually customized pacing rates per minute, programmed according to the standard protocol at the time of the implantation. The lower heart rate was 60 beats per minute and the upper rate was 110 beats per minute. Single chamber ICDs were programmed in a pacing mode of VVI 40. However, if ICD recipients were dependent on stimulation or rate responsive pacing, devices were programmed in a mode of VVIR 40-140. To avoid unnecessary RV pacing, the majority of dual-chamber ICDs were programmed in the non-tracking backup mode DDI 40 with sufficiently long AV delay to secure the intrinsic conduction at a lower rate. In stimulation or rate responsive pacing dependent dual-chamber ICD recipients, devices were programmed to DDDR 40-140 with sufficiently long AV delay to secure the intrinsic conduction.

Assessment of RV pacing burden

All patients were followed-up at a dedicated outpatient clinic at 3 and 6 months after RV pacemaker implantation and subsequently yearly to monitor lead impedance, functionality and battery status. Moreover, the percentage of pacemaker stimulations that were delivered in the RV apex was collected at each visit. At the end of the follow-up, the total burden of RV pacing was calculated as the mean percentage of RV paced complexes during the total follow-up period.

Outcome at long-term follow-up

Data on mortality and HF hospitalizations were collected by reviewing medical records and retrieval of survival status through the municipal civil registries. The primary outcome was a combined end point of all-cause mortality or HF hospitalizations. All clinical variables were collected by independent observers blinded to the echocardiographic results. The long-term survival, HF hospitalizations defined as any short- or long-stay admissions that necessitated the intravenous administration of inotropes/diuretics and combined event rates were compared between patients with versus without significant LV dyssynchrony after RVA pacing.

Statistical analysis

Continuous data are expressed as mean ± SD or median and interquartile range, as appropriate, and were compared with the 2-tailed Student's test for paired and unpaired data or a non-parametric test (Mann-Whitney). Categorical variables are shown as number and frequencies and were compared using the chi-square test. The evolution of LV dyssynchrony with RVA pacing was evaluated with the non-parametric Friedman test. Survival curves were derived according to the Kaplan-Meier method. The follow-up onset was set at the RVA pacemaker implantation. Comparisons of cumulative event rates between groups were performed by the log-rank test. Cox proportional hazard analysis was used to determine the association between induction of LV dyssynchrony and long-term occurrence of the combined outcome of all-cause mortality or HF hospitalizations. First, univariate analysis of baseline characteristics was performed using the combined outcome. For each variable, the hazard ratio (HR) and the 95% confidence intervals (CI) were calculated. In the multivariate analysis, the predictive value of LV dyssynchrony induction was corrected for those variables with a P-value <0.20 in the univariate analysis. All statistical analyses were performed with SPSS software (version 18.0, SPSS Inc, Chicago, IL). For all tests, a P-value <0.05 was considered statistically significant.

RESULTS

Patients

A total of 169 patients with complete echocardiographic data (before and after RVA pacemaker implantation) were derived from an ongoing

registry. Baseline characteristics of the patients are displayed in ***Table 1***. The population comprised mostly men (69%), with mean age of 62±13 years. Coronary artery disease (CAD) was recorded in 24% of patients. Mean LVEF was 51±11% and mean QRS duration was 115±28ms.

Table 1. Baseline characteristics of all patients and of the two groups of patients with and without induced LV dyssynchrony after CRT implantation.

Variables at baseline	All patients (n=169)	Induced LV dyssynchrony ≥91 ms (n=85)	Non-induced LV dyssynchrony <91 ms (n=84)	P-value
Age (years)	t	65±12	58±13	<0.001
Gender (male/female)	117/52	57/28	60/24	0.327
ICD, n (%)	15 (9)	2 (2)	13 (15)	0.005
Pacing mode (DDD/VVI)	126/43	68/17	58/26	0.114
Percentage of RVA pacing	100 (99-100)	100 (98-100)	100 (100-100)	0.127
CAD, n (%)	41 (24)	27 (32)	14 (17)	0.019
HF, n (%)	31 (18)	22 (26)	9 (11)	0.009
QRS duration	115±28	119±38	111±26	0.062
QRS morphology, n (%)				0.143
LBBB	18 (11)	11	7	
RBBB	31 (18)	19	12	
LV end-diastolic volume (mL)	124±42	127±42	120±43	0.300
LV end-systolic volume (mL)	66±45	74±56	57±27	0.014
LVEF (%)	51±11	49±13	53±9	0.020
LV dyssynchrony (ms)	40 (12-85)	53 (16-124)	18 (0-72)	0.007
TAPSE (mm)	18 (16-20)	17 (15-20)	19 (17-21)	0.023

Continuous variables are expressed as mean ± SD. % RVA pacing, LV dyssynchrony, and TAPSE are expressed as median and interquartile range. Categorical variables are expressed as n (%).
Abbreviations: AV=auriculoventricular; CAD=coronary artery disease; HF=heart failure; LBBB: left bundle branch block; ICD=implantable cardiovertor-defibrillator; LV=left ventricle; LVEF = Left ventricular ejection fraction; RBBB = Right bundle branch block; RVA=right ventricular apical; SND=sick sinus syndrome; TAPSE=tricuspid annular plane systolic excursion.

Evolution of LV volumes, LVEF and LV dyssynchrony with RVA pacing

Median percentage of RVA pacing burden was 100% (interquartile range 99-100%). Mean QRS duration during RVA pacing was 164±28ms.

After a median of 13 months (3-26 months) of RVA pacing, repeat echocardiography was performed. In overall population, LVEDV increased

from 123±43 mL to 134±49 mL after RVA pacing (P<0.001). Similarly, LVESV increased significantly from 66±45 mL to 77±42 mL after RVA pacing (P<0.001). Consequently, a deterioration in LVEF was noted after RVA pacing (from 51±11% to 44±12% [P<0.001]).

Median LV dyssynchrony assessed by 2D radial strain speckle tracking echocardiography was 40 ms (12–85 ms) before RVA pacing and increased to 91 ms (81–138 ms) after a median time of 13 months (3–26 months) of RVA pacing (P<0.001). An LV dyssynchrony value ≥ to the median LV dyssynchrony value after RVA pacing was defined as significant induced LV dyssynchrony.

Baseline characteristics of patients with and without induction of LV dyssynchrony by RVA pacing

Baseline characteristics of patients with induced LV dyssynchrony after RVA pacing (LV dyssynchrony value after RVA pacing ≥91ms) and of patients without induction of LV dysynchrony after RVA pacing (LV dyssynchrony value after RVA pacing <91ms) are shown in Table 1. Patients with induced LV dyssynchrony were older (65±12 vs. 58±13 years; P<0.001), had more frequently CAD (32% vs. 17%; P=0.019) and heart failure (26% vs. 11%; P=0.009) compared with patients without induced LV dyssynchrony. Interestingly, patients with induced LV dyssynchrony had a lower baseline LVEF (49±13% vs. 53±9%; P=0.020), had a higher degree of LV dyssynchrony (53 ms [16–124 ms] vs. 18 ms [0–72 ms]; P=0.007), and a lower TAPSE value (17 mm [15–20 mm] vs. 19 mm [17–21 mm]; P=0.023) compared with patients without induced LV dyssynchrony.

Long-term outcome of patients with versus without induced LV dyssynchrony

During a median follow-up of 70 months (42–96 months) after RVA pacemaker implantation, a total of 36 (21%) patients died and 29 (16%) patients experienced a HF hospitalization. A total of 56 combined events (all-cause mortality or HF hospitalization) were recorded. After dichotomizing the patient population according to the median LV dyssynchrony assessed after RVA pacemaker implantation (<91 ms versus ≥91 ms), a cumulative 0%, 5% and 27% of patients with LV dyssynchrony ≥91 ms after RVA pacemaker implantation (induced LV dyssynchrony group) died by 1, 3, and 5 years follow-up, respectively. In contrast, the group of patients with LV dyssynchrony <91 ms after RVA pacemaker implantation (non-induced LV dyssynchrony group) experienced a better survival as a respectively 0%, 1% and 3% of patients died during the same time period (log-rank P=0.003) (***Figure 1***). Additionally, a cumulative 6%, 18% and 24% of patients in the induced

LV dyssynchrony group experienced a HF hospitalization compared to 0%, 3% and 4% in the non-induced LV dyssynchrony group at 1, 3 and 5 years follow-up respectively (log-rank P<0.001) (***Figure 2***). Finally, at 1, 3 and 5 years follow-up a respective cumulative 6%, 20% and 36% of patients experienced a combined event in the group of patients with induced LV dyssynchrony whereas in patients with non-induced LV dyssynchrony the cumulative combined event rate was significantly lower (0%, 3%, and 8% at 1, 3 and 5 years follow-up, respectively; log-rank P<0.001) (***Figure 3***).

Figure 1. **Long-term Kaplan Meier estimates of time to all-cause mortality in patients with induced LV dyssynchrony (n=85) and in patients with non-induced LV dyssynchrony (n=84).**

The dotted blue line indicated the median time to follow-up echocardiogram.

Abbreviations: LV = left ventricular.

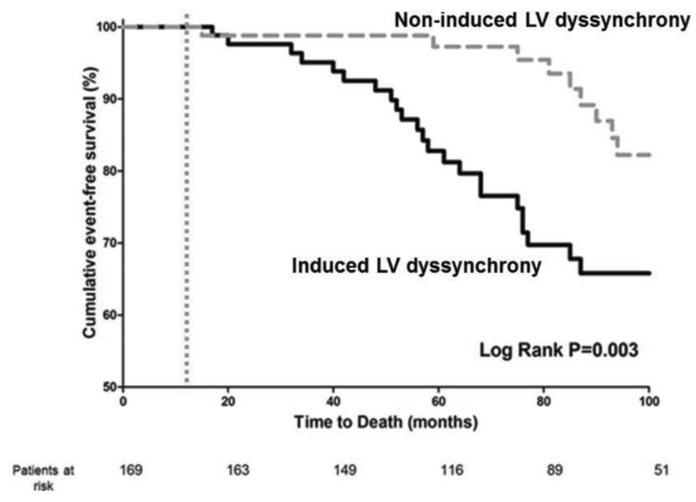


Figure 2. **Long-term Kaplan Meier estimates of time to HF hospitalization in patients with induced LV dyssynchrony (n=85) and in patients with non-induced LV dyssynchrony (n=84).**

The dotted blue line indicated the median time to follow-up echocardiogram.

Abbreviations: HF=heart failure; LV = left ventricular.

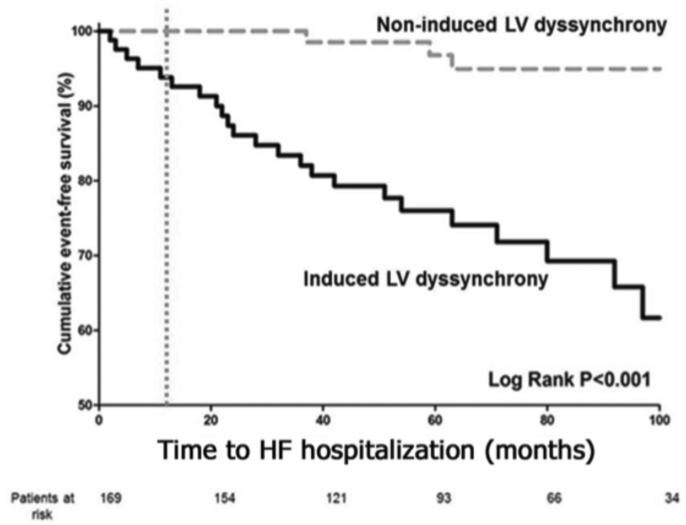
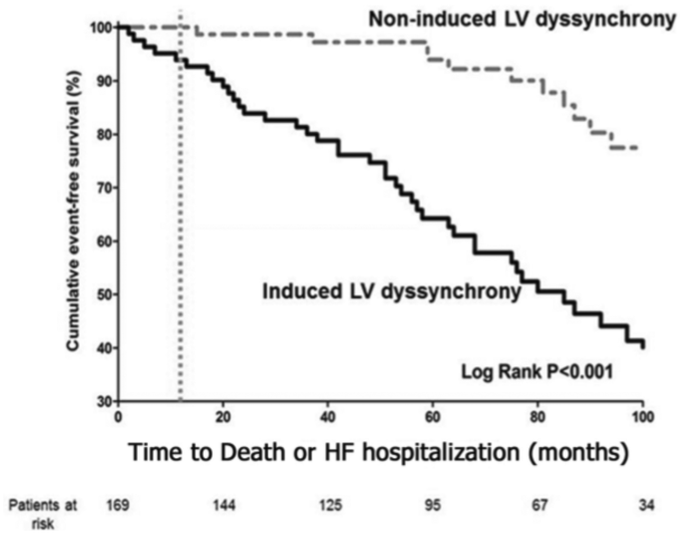


Figure 3. **Long-term Kaplan Meier estimates of time to the combined outcome of all-cause mortality or HF hospitalization in patients with induced LV dyssynchrony (n=85) and in patients with non-induced LV dyssynchrony (n=84).**

The dotted blue line indicated the median time to follow-up echocardiogram.

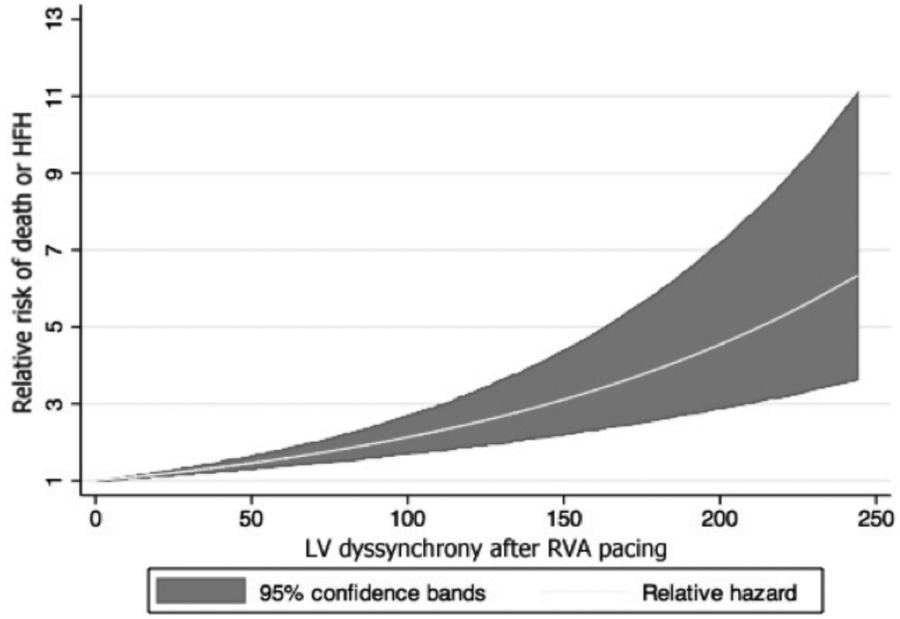
Abbreviations: HF=heart failure; LV = left ventricular.



At univariate Cox regression analysis, each 1ms increase in LV dyssynchrony after RVA pacemaker implantation was associated with increased risk of having the combined outcome of all-cause mortality or HF hospitalization (HR: 1.006; 95% CI 1.003-1.008; P<0.001).The relationship between the univariate relative risk of all-cause mortality or HF hospitalization and the amount of LV dyssynchrony induced after RVA pacemaker implantation is shown in ***Figure 4***. The relative risk for the combined events increased together with the increase in LV dyssynchrony after RVA pacemaker implantation.

Figure 4. **Relationship between the long-term combined outcome of risk of death or HF hospitalization and the extent of LV dyssynchrony post RVA pacemaker implantation. Unadjusted relative risk (yellow curve) with 95% confidence bands (grey shaded zones) of the death or HFH following RVA pacemaker implantation, as a function of LV dysynchrony post RVA pacemaker implantaiton. An increase in LV dysynchrony value after RVA pacemaker implantation is linked to a poorer long-term outcome in this population.**

Abbreviations: HFH=heart failure hospitalization; LV=left ventricular; RVA=right ventricular apical.



Baseline characteristics were evaluated to predict the combined outcome of death or HF hospitalization for patients who underwent RVA pacemaker implantation. In the univariate analysis, age, CAD and induction of LV dyssynchrony were significantly related to the combined outcome (***Table 2***). At the multivariate Cox regression analysis,

induction of LV dyssynchrony (LV dyssynchrony value after RVA pacemaker implantation ≥91 ms) was significantly related to the combined outcome of all-cause death or HF hospitalization with a HR of 3.369 (95% CI: 1.732-6.553, P<0.001) together with age (***Table 2***).

Table 2. Univariate and multivariate Cox regression analysis to identify predictors of long-term mortality or HF hospitalization.

	Univariate		Multivariate	
Variables	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)	1.041 (1.016-1.067)	0.001	1.030 (1.002-1.058)	0.036
CAD	2.414 (1.338-4.197)	0.003	…	…
QRS during RVA pacing (ms)	1.002 (0.991-1.013)	0.727	…	…
Pacing mode (DDD reference)	0.993 (0.525-1.825)	0.997	…	…
Baseline LVEF	0.992 (0.968-1.016)	0.510	…	…
Induction of LV dyssynchrony	4.366 (2.302-8.281)	<0.001	3.369 (1.732-6.553)	<0.001

Abbreviations: CAD=coronary artery disease; HR=hazard ratio; LV=left ventricle; LVEF= left ventricle ejection fraction; RVA=right ventricular apical.

DISCUSSION

The present evaluation showed that in patients with a high burden of ventricular pacing, significant induction of LV dyssynchrony was independently related to worse outcome (all-cause mortality and HF hospitalization). Patients with significant induction of LV dyssynchrony were older, had more frequently CAD, heart failure and lower LVEF before pacemaker implantation and showed a higher degree of LV dyssynchrony and a lower RV longitudinal systolic function than patients without significant LV dyssynchrony induction.

Induction of LV dyssynchrony by RVA pacing

Deleterious effects of RVA pacing on LV performance have been demonstrated in numerous experimental and clinical trials. RVA pacing has shown to acutely induce heterogeneous LV myocardial shortening in experimental models.[17] Interestingly, the LV areas activated earlier exhibited more impaired fiber shortening, showing the association

between asynchronous activation and impaired regional LV mechanics.[17] In addition, clinical trials have shown acute induction of LV dyssynchrony by RVA pacing. For example, Gomes et al. evaluated the acute effect of RVA pacing on the mechanical activation of the septal and lateral LV walls in 12 patients.[18] Importantly, the posterior wall activation occurred substantially later than the septum (posterior activation 116±18 ms vs. septal activation 61±5 ms), leading to an heterogeneous pattern of contraction within the LV.[18] More recently, the acute effects of RV pacing on LV mechanical activation were studied by 2D radial strain imaging.[9] In a group of 25 patients with structural normal heart, worsening of LV dyssynchrony was shown acutely after RVA pacing (from 21 ms [10-53 ms] to 91ms [40-204 ms], P<0.001).[9] Concurrent to the acute changes in LV dyssynchrony values, a significant decrease in LVEF and in myocardial longitudinal mechanics were noted.[9] These experiences show that acutely induced LV dyssynchrony by RVA pacing is associated with significant impairment in LV performance.

The effects of prolonged RVA pacing on LV systolic function have been also studied. Yu et al. observed a significant increase in LVESV and consequent decrease in LVEF one year after RVA pacing for treatment of bradycardia.[2] The present study evaluated LV dyssynchrony and LV volumes at median time of 13 months (3-26 months) after RVA pacing and confirmed these findings. Furthermore, the present study revealed that significant induction of LV dyssynchrony is associated with poor outcome.

Long-term outcome of patients after RVA pacing

The effects of RVA pacing on long-term prognosis have been reported in several trials. In 506 patients with impaired ventricular function, the DAVID (Dual Chamber and VVI Implantable Defibrillator) trial demonstrated that dual chamber rate responsive pacing at 70/min (DDDR-70) was associated with increased mortality and HF hospitalization as compared to ventricular back-up pacing at 40/min.[6] The MOST sub-study further identified substrates of heart failure after RVA pacing. Indeed, in this population of 2010 subjects referred for RVA pacing because of SND, patients with prior myocardial infarction, heart failure, or cardiomyopathy and with a QRS complex width ≥148ms at baseline or ≥185ms after RVA pacing exhibited the highest risk of heart failure development.[8] Furthermore, a high RVA pacing burden appears strongly associated with adverse outcome.[8, 19] It was speculated that desynchronization of LV activation and contraction by RVA pacing was related to the adverse long-term outcome. In the present study, 169 patients

with an echocardiogram performed before and after RVA pacemaker implantation were followed-up for a median duration of 70 months. Induction of LV dyssynchrony (LV dyssynchrony value after RVA pacing ≥91ms) was independently related to increased all-cause mortality or HF hospitalization (HR 3.369 [1.732-6.553], P<0.001) along with age (HR 1.030 [1.002-1.058], P=0.036).

Clinical implications

This study demonstrates the relationship between induction of LV dyssynchrony by RVA pacing and worse long-term outcome. Therefore, close follow-up of RVA paced patients may include monitoring of induction of LV dyssynchrony after device implantation. Particularly, patients with CAD or heart failure exhibiting altered RV longitudinal and LV systolic function and a significantly higher degree LV dyssynchrony at baseline showed a significantly higher risk of significant pacing-induced LV dyssynchrony and consequent development of combined outcome. These findings may potentially help to identify a population of patients with significant conduction disease that should rather receive a biventricular pacing device (i.e. cardiac resynchronization therapy) instead of a conventional pacemaker. The results from the recent BLOCK-HF trial suggest similar implications.[20]

Study limitations

Some limitations to the current study have been identified. First, this is retrospective analysis and only patients with complete echocardiographic follow-up were selected, which may have affected results. Second, all patients had an RV lead implanted in the RV apex, and the impact of RV lead position on induction of LV dyssynchrony and long-term combined outcome could not be determined. Thirdly, in non-pacemaker dependent patients, distinction between fusion or pseudo-fusion and real pacemaker activation was not systematically performed. This may have altered slightly the RVA pacing burden measurement. Finally, 2D radial strain imaging does not reflect the dispersion of the electromechanical activation of the entire LV, but of 6 segments at the mid-ventricular level. This technical limitation may have altered the precision of the presented results.

CONCLUSION

In patients with preserved LV systolic function exhibiting a high RV pacing burden, the incidence of significant induction of LV dyssynchrony by RVA pacing is relatively high. Induction of LV dyssynchrony by RVA pacing is independently related to all-cause mortality and HF hospitalization.

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