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ORIGINAL ARTICLE

Early Change in Global Longitudinal Strain is an Independent Predictor of Left Ventricular Adverse Remodelling in Patients With Right Ventricular Apical Pacing

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Background Right ventricular apical (RVA) pacing is related to adverse left ventricular (LV) remodelling. This study assessed changes in global longitudinal strain (GLS) after permanent RVA pacing, and investigated whether GLS at one month can predict later LV ejection fraction (LVEF) decline.

Methods The study enrolled 68 patients with normal LVEF ($\geq$50%) who underwent dual chamber pacemaker implantation for third-degree atrioventricular block. Global strains and LVEF were assessed using three-dimensional (3D) speckle tracking strain echocardiography (STE).

Results At one month, GLS was significantly lower in those patients who developed pacing-induced LV dysfunction (PIVD), which was defined as a reduction in LVEF $\geq$5 percentage points at 12 months, than those who did not (-14.9 $\pm$ 1.8 vs -16.1 $\pm$ 1.7, p = 0.014), although GLS was similar at baseline. In patients who developed PIVD, only GLS was significantly reduced at one month compared to baseline (-14.9 $\pm$ 1.8 vs -16.6 $\pm$ 1.2, p = 0.022) whereas LVEF was not. Global longitudinal strain at one month was the only independent predictor for PIVD at 12 months on multivariate analysis (OR, 1.623; 95% CI, 0.986–2.210; p = 0.009). Receiver operating characteristic (ROC) analysis showed that GLS at one month had a high predictive accuracy for the development of PIVD at 12 months, with an area under curve (AUC) of 0.88, 94% sensitivity, and 70% specificity.

Conclusions Global longitudinal strain at one month after pacemaker implantation had high predictive accuracy for identifying subsequent development of PIVD. Global longitudinal strain may be an invaluable parameter to predict LV adverse remodelling following permanent RVA pacing.

Keywords Global longitudinal strain • Right ventricular apical pacing • Three-dimensional echocardiography

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Introduction

Right ventricular apical (RVA) pacing is widely used in bradyarrhythmia therapy around the world. Previous studies have demonstrated that RVA pacing may cause mechanical dyssynchrony and heart failure (HF) [1–3]. Development of HF after RVA pacing seems to be an individual and multifactorial process. Some patients with normal cardiac function prior to pacemaker implantation may also have a reduction in left ventricular (LV) systolic function after RVA pacing [4]. However, cardiologists have major concerns about how to identify patients with normal left ventricular ejection fraction (LVEF) and at risk of developing HF after pacemaker implantation. Early detection of the subtle signs of LV systolic dysfunction can lead to early clinical treatment and better prognosis. A single, easily available, non-invasive test that is able to identify such individuals is most desirable in clinical practice. Three-dimensional (3D) speckle tracking strain echocardiography (STE) has been proven to detect early signs of mild systolic impairment in a range of cardiac diseases before a measurable reduction in LVEF [5,6]. The deterioration of global longitudinal strain (GLS) might be an early manifestation in the development of HF. Patients with abnormal GLS after permanent RVA pacing may benefit from upgrading to biventricular pacing at a very early phase with more intensive clinical follow-up and echocardiographic surveillance.

The current study sought to characterise GLS that might be used to clarify patients with normal LVEF who are more likely to undergo subsequent deterioration of LVEF during permanent RVA pacing for atrioventricular (AV) block.

Methods

Study Subjects

Between January 2012 and December 2014, 105 patients with persistent third-degree AV block were screened for the study. The study only enrolled eligible patients with a normal left ventricular function (LVEF $\geq$50%) and who were scheduled to undergo dual chamber pacemaker implantation. Exclusion criteria were: heart failure, significant ischaemic and valvular heart disease, hypertrophic cardiomyopathy, dilated cardiomyopathy, atrial fibrillation (AF), significant respiratory disease, and renal insufficiency..

Study Design

The investigation protocol was approved by the Institutional Review Board and the Ethic Committee of Huai'an First People's Hospital. Written informed consent was obtained from all study participants. All clinical investigations were conducted in accordance with the Declaration of Helsinki. All patients enrolled into the study received RVA pacing and underwent clinical and echocardiography assessments before pacemaker implantation. Serial pacemaker check-ups, echocardiography and clinical assessments were performed at 1 and 12 months after pacemaker implantation. N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured by Elecsys electrochemiluminescence immunoassay (Roche Diagnostics Corporation, Indianapolis, IN, USA).

The primary objective of the trial was to investigate whether 3D STE can be used to predict the development of pacing-induced LV dysfunction (PIVD) after pacemaker implantation. Pacing-induced LV dysfunction was defined as an absolute decline in LVEF by $\geq$5 percentage points at 12 months. All implantations were performed by experienced operators. The right atrial and right ventricular leads were positioned in the right atrial appendage and RVA, respectively, via a transvenous route. Fluoroscopy and x-ray were used to confirm the anatomical location of the RV lead in each case. The QRS complex in V1-V6 leads showed left bundle branch block and left axis deviation was designated as RVA pacing in the pacing electrocardiography (ECG). Pacemakers were programmed to DDDR mode according to the manufacturers' algorithms.

Echocardiography

Standard transthoracic echocardiography was performed on an iE-33 ultrasound machine (Philips Medical Systems, Bothell, WA, USA). Real-time 3D image was performed using the same ultrasound machine equipped with X3-1 – a fully sampled matrix array transducer. Conventional two-dimensional, M-mode, Doppler measurements were performed according to the American Society of Echocardiography guidelines [7]. End-diastolic volume (EDV), end-systolic volume (ESV), and LVEF were manually measured using the biplane Simpson's method in the 2D mode. Left ventricular mass was calculated using the Devereux formula [8].

Three-dimensional images were taken for all subjects and were then digitally stored for off-line analysis by Qlab 3DQA software (Philips Medical Systems). The software automatically and simultaneously tracked the endocardial and epicardial contours through the entire cardiac cycle in three different vectors. The 3D images of LV walls were automatically divided into 17 segments. Left atrial volume (LAV), EDV, ESV, LVEF were measured. Volume parameters were standardised by body surface area (BSA). The GLS, global circumferential strain (GCS), and global radial strain (GRS) were measured using the speckle tracking method by the software from the single full-volume acquisition. Two consecutive beats data were digitally stored to ensure optimal data quality. The LV dyssynchrony was evaluated by standard deviation index of 3D strain (SDI), which calculated standard deviation of time to the minimum regional volume of 16 segments related to the cardiac cycle. The LV mass index (LVMI) was LV mass indexed to BSA.

Baseline and follow-up echocardiographic examinations were performed using the same machine. All echocardiographic examinations for each patient were performed and evaluated by two independent experienced echocardiographers under blinded conditions.

Reproducibility

Intra-observer and inter-observer variability of both strain measurements and LVEF were examined, by two investigators, in 10 randomly selected patients. The same primary operator analysed selected data twice at intervals of >2 weeks. Both operators were blinded to the results of the first measurement and from each other. Intra-observer and inter-observer variability of 3D STE data were calculated as intra-class correlation coefficients (ICCs). The inter-observer ICCs for LVEF, GLS, and SDI were 0.84, 0.87, and 0.81, respectively. Similarly, intra-observer measurement showed ICCs of 0.86 for LVEF, 0.90 for GLS, and 0.82 for SDI, indicating satisfactory reproducibility of LV measurements by 3D STE.

Statistical Analysis

Continuous data were presented as mean ± standard deviation (SD). Categorical data were summarised as frequencies and percentages. Normally distributed variables were compared using Student's unpaired *t*-test. Non-normally distributed data were compared using the Mann–Whitney U test or Kruskall–Wallis test, as appropriate. Categorical variables were compared by Chi-squared test or Fisher's exact test. The relationships between 3D STE strain parameters and LVEF, SDI, PIVD were assessed using Spearman's correlation. Univariate and multivariate logistic regression analyses were used to explore the independent factors of PIVD. Receiver operating characteristic (ROC) analysis was performed to determine the accuracy of GLS at one month to predict PIVD. A two-sided p-value <0.05 was considered to be statistically significant. Statistical analysis was performed by SPSS 16.0 (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism 6.0 (GraphPad Software, San Diego, CA, USA).

Results

Clinical Characteristics

Seventy (70) patients were recruited into the study. Two (2) patients were excluded because of poor images. No patients were lost during the 1 year of follow-up after implantation. Therefore, 68 patients were finally included in the statistical analysis. At one month, PIVD was observed in 7/68 (10.3%) patients. Pacing-induced LV dysfunction occurred in 16/68 (23.5%) patients at 12 months. Three (3) patients had HF with LVEF <45% at 12 months.

Clinical characteristics for the study participants are summarised in Table 1. There was no significant difference in clinical parameters at 12 months between the two groups of patients who developed PIVD or did not develop PIVD. New-onset AF was observed in six of 68 (8.8%) patients. There was one patient who had new-onset AF in the PIVD group. However, five patients with new-onset AF were observed in the no PIVD group.

Echocardiography Parameters

At one month following pacemaker implantation, the patients who developed PIVD had significantly greater LVEDVI (45.7 ± 6.5 vs 44.5 ± 6.9, p = 0.007), LVESVI (20.3 ± 5.6 vs 17.4 ± 6.0, p = 0.011) and SDI (8.0 ± 1.7 vs

Table 1 Clinical characteristics of patients with and without pacing-induced left ventricular dysfunction.

Variables	Overall (n = 68)	PIVD (n = 16)	No PIVD (n = 52)	P-value
Age	68.9 ± 7.7	70.1 ± 7.9	68.5 ± 7.7	0.493
Male (%)	46 (67.6)	10 (62.5)	36 (69.2)	0.615
Hypertension (%)	32 (47.1)	5 (31.3)	27 (51.9)	0.147
Diabetes mellitus (%)	17 (25.0)	3 (18.8)	14 (26.9)	0.743
Coronary heart disease (%)	14 (20.6)	4 (25.0)	10 (19.2)	0.726
BMI, kg/m^2	24.1 ± 2.3	23.8 ± 2.0	24.1 ± 2.4	0.565
ACE inhibitor/ARB (%)	14 (20.6)	3 (18.8)	11 (21.2)	1.000
Beta blockers (%)	16 (23.5)	4 (25.0)	12 (23.1)	1.000
Calcium channel antagonist (%)	16 (23.5)	3 (18.8)	13 (25%)	0.744
Statins (%)	23 (33.8)	5 (31.3)	18 (34.6)	0.804
Pre-pacing QRS duration, ms	103.9 ± 13.8	105.0 ± 16.3	103.6 ± 13.1	0.718
Paced QRS duration, ms	151.0 ± 13.1	154.0 ± 13.7	150.1 ± 12.9	0.302
Mean Cum%AP at 12 mo	20.3 ± 12.7	22.4 ± 15.8	19.7 ± 11.7	0.465
Mean Cum%VP at 12 mo	90.9 ± 8.6	92.6 ± 6.1	90.4 ± 9.3	0.390
AF during follow-up (%)	6 (8.8)	1 (6.3)	5 (9.6)	1.000
LVEF (%)	61.5 ± 4.8	60.7 ± 5.4	61.8 ± 4.7	0.438
NT-proBNP at baseline (pg/mL)	224 (135,309)	161 (124,281)	230 (148,324)	0.225
NT-proBNP at 12 mo (pg/mL)	246 (160,340)	186 (139,261)	264 (168,374)	0.093

Abbreviations: PIVD, pacing-induced left ventricular dysfunction; BMI, body mass index; LVEF, left ventricular ejection fraction; AF, atrial fibrillation; NT-proBNP, N-terminal pro-brain natriuretic peptide; Cum%AP, cumulative percentage of atrial pacing; Cum%VP, cumulative percentage of ventricular pacing; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker.

Table 2 **Comparison of three dimensional echocardiographic parameters in patients with and without pacing-induced left ventricular dysfunction.**

Variables		PIVD (n = 16)	No PIVD (n = 52)	P-value
LVEDVI (mL/m^2)				
	Baseline	42.4 ± 5.3	43.2 ± 6.2	0.660
	1 month	45.7 ± 6.5	44.5 ± 6.9	0.007
	12 months	50.3 ± 7.8*	46.1 ± 7.4	<0.001
LVESVI (mL/m^2)				
	Baseline	16.6 ± 3.5	16.7 ± 3.1	0.959
	1 month	20.3 ± 5.6	17.4 ± 6.0	0.011
	12 months	24.1 ± 7.5*	18.4 ± 8.4	<0.001
LVEF (%)				
	Baseline	60.7 ± 5.4	61.8 ± 4.7	0.438
	1 month	55.5 ± 6.0	60.9 ± 5.1	0.004
	12 months	52.1 ± 6.6*	60.2 ± 5.2	<0.001
LVMI (g/m^2)				
	Baseline	100.1 ± 18.1	94.7 ± 21.6	0.363
	1 month	108.5 ± 22.3	102.6 ± 25.1	0.467
	12 months	120.6 ± 27.8*	108.5 ± 26.5	0.018
LAVI (mL/m^2)				
	Baseline	24.6 ± 4.0	23.4 ± 5.8	0.472
	1 month	26.2 ± 5.7	24.7 ± 6.0	0.549
	12 months	28.5 ± 7.6*	25.9 ± 6.3	0.006
GLS (%)				
	Baseline	−16.6 ± 1.2	−16.9 ± 1.3	0.373
	1 month	−14.9 ± 1.8*	−16.1 ± 1.7	0.014
	12 months	−12.6 ± 2.2#	−14.9 ± 2.2	<0.001
GRS (%)				
	Baseline	28.6 ± 2.2	29.5 ± 2.7	0.198
	1 month	27.1 ± 2.9	28.0 ± 3.1	0.116
	12 months	24.5 ± 3.4*	27.3 ± 3.5	0.027
GCS (%)				
	Baseline	−22.1 ± 1.5	−22.9 + 2.1	0.139
	1 month	−21.3 ± 2.0	−22.3 ± 2.5	0.332
	12 months	−18.9 ± 2.4*	−21.5 ± 2.8	0.036
SDI (%)				
	Baseline	6.4 ± 1.0	6.2 ± 1.2	0.514
	1 month	8.0 ± 1.7	6.9 ± 1.4	0.041
	12 months	11.4 ± 2.6*	7.8 ± 2.0	<0.001

Abbreviations: PIVD, pacing-induced left ventricular dysfunction; LVEDVI, left ventricular end-diastolic index; LVESVI, left ventricular end-systolic index; LVMI, left ventricular mass index; LAVI, left atrial volume index; GLS, global longitudinal strain; GCS, global circumferential strain; GRS, global radial strain; SDI, standard deviation index of three-dimensional strain.

*$p < 0.05$.

#$p < 0.001$.

6.9 ± 1.4, p = 0.041) compared with those who did not. Both LVEF (55.5 ± 6.0 vs 60.9 ± 5.1%, p = 0.004) and GLS (-14.9 ± 1.8 vs -16.1 ± 1.7, p = 0.014) were significantly reduced in these patients who developed PIVD (Table 2). However, there were no significant between-group differences in LVMI, LAVI, GRS, and GCS.

Further analysis demonstrated that, in patients who developed PIVD, there was a decrease in LVEF (60.7 ± 5.4 vs 52.1 ± 6.6%, p = 0.026) and increase in SDI (6.4 ± 1.0 vs 11.4 ± 2.6, p = 0.015) from baseline to 12 months. Those who had PIVD had a dramatic reduction in GLS from baseline to 12 months (-16.6 ± 1.2 vs -12.6 ± 2.2, p < 0.001). However, only GLS was significantly reduced at one month in patients who developed PIVD compared to baseline (-14.9 ± 1.8 vs -16.6 ± 1.2, p = 0.022). Moreover, from baseline to 12 months, the deterioration of GLS showed high correlation with LVEF reduction ($r = -0.68$, $p < 0.001$) and SDI increase ($r = 0.55$, $p < 0.001$). Change in GLS also had a high correlation with change in log (NT-proBNP) ($r = 0.52$, $p = 0.048$, Figure 1). In the patients without PIVD, GLS, SDI and LVEF were similar from baseline to 12 months.

Predictors of Left Ventricular Dysfunction

Table 3 shows the results of univariate and multivariate logistic regression analyses of predictors of PIVD (defined as reduction in ejection fraction ≥5%) at 12 months in the total study population. On univariate analysis, GLS, LVEF, and SDI at one month correlated with the deterioration of LVEF. By multivariate analysis, one month GLS was the only independent predictor for PIVD at 12 months (OR, 1.623; 95% CI, 0.986-2.210; p = 0.009).

Receiver operating characterstic analysis displayed that one month GLS had a high predictive accuracy for the development of PIVD, with an AUC of 0.88, 94% sensitivity and 70% specificity (Figure 2). A GLS value of less than -14.5 was the optimal cut-off value. At 12 months, LVEF was significantly higher in patients with GLS less than -14.5 (60.3 ± 4.8 vs 50.2 ± 5.3, $p < 0.001$). Additionally, the ROC curves also showed the ability of LVEF and SDI at one month to predict the development of PIVD. The areas under the ROC curves were 0.76 and 0.69, respectively.

Discussion

Chronic RVA pacing may have detrimental effects on LV function [9–11]. However, how to predict which patients with normal LV ejection fraction will have heart failure (HF) remains a big clinical challenge. Global longitudinal strain has emerged as a potentially useful tool for risk stratification of these patients [12–14]. The present study showed that GLS is independently correlated with PIVD in patients with preserved ejection fraction undergoing RVA pacing. Early change in GLS after RVA pacing has been shown to be predictive of later LVEF decline.

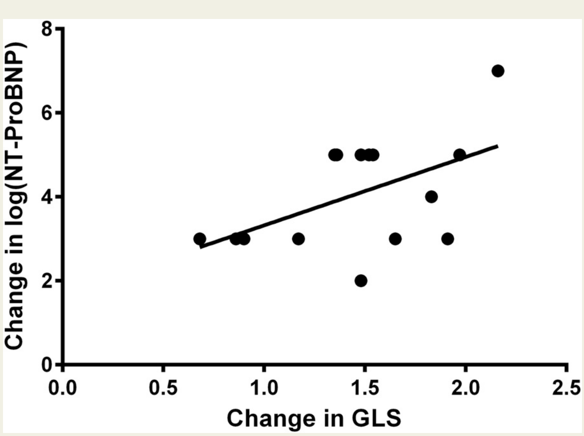

Figure 1 Relation between global longitudinal strain (GLS) and log (HT-proBNP). GLS, global longitudinal strain; NT-proBNP, N-terminal pro-brainnatriuretic peptide.

Accurate quantification of LV function is vital for risk evaluation and management of cardiovascular diseases. Serial assessment of LVEF has become widely used as a research tool for measuring LV mechanical dyssynchrony and systolic function. However, it may be somewhat insufficient in detecting early signs of cardiac dysfunction. In comparison, strain, as a parameter displaying myocardial tissue deformation in any direction within a cardiac cycle, has been clearly demonstrated to be more accurate, reproducible, and sensitive for early detection of myocardial dysfunction than LVEF [5,15,16]. Recently, two-dimensional speckle-tracking echocardiography (2D STE) was validated to be an effective method to quantify myocardial strain. Many previous studies have demonstrated that 2D STE provides incremental prognostic information beyond traditional LVEF in assessment of various cardiac diseases, including heart failure [5,17], chemotherapy [18,19], and ischaemic heart disease [20]. Two-dimensional speckle-tracking imaging may be affected by out-of-plane motion, which may lead to noise and reduced accuracy, which is its main limitation [21]. The newly-developed 3D STE tracks speckle movements of LV endocardial borders through the entire cardiac cycle and relies on 3D data sets, while overcoming the limitations of 2D-based speckle-tracking strain [22–24]. It has also been reported to be able to provide accurate and reproducible ejection fraction and myocardial strain values that are comparable with cardiac magnetic resonance (CMR) [25,26].

Left ventricular strain and function may be altered by RVA pacing [11,12]. The EF is a strong predictor of outcome in patients with clearly reduced myocardial systolic function. However, the measurement of EF may heavily rely on load, heart rate, observer experience, and be relatively insensitive to subtle abnormalities of LV function [27,28]. In the current study, both global strain (GLS, GCS, GRS) and LVEF at 12 months following RVA pacing were significantly lower compared with pre-pacemaker implantation in the group that

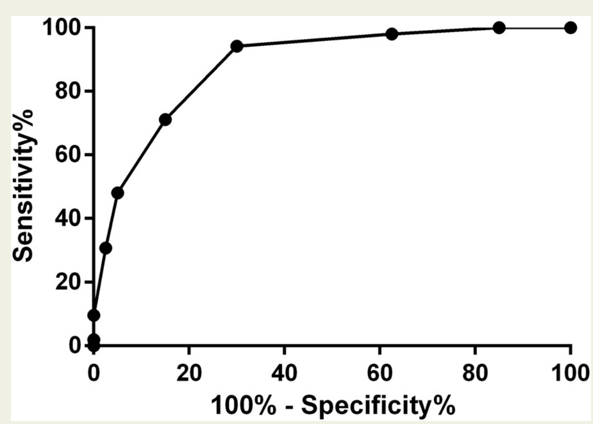

Figure 2 ROC curve of the ability of one-month GLS to predit PIVD. ROC, Receiver operating characteristic; GLS, global longitudinal strain.
Abbreviations: GLS, global longitudinal strain; ROC, receiver operating characteristic; PIVD, pacing-induced LV dysfunction.

Table 3 Univariate and multivariate logistic regression analyses of predictors of pacing-induced left ventricular dysfunction (defined as reduction of ejection fraction ≥5%) at 12 months.

Variables	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	1.005 (0.749–1.462)	0.544	–	–
Male	0.814 (0.478–1.186)	0.709	–	–
History of hypertension	1.023 (0.900–1.165)	0.302	–	–
History of diabetes mellitus	1.136 (0.961–1.343)	0.160	–	–
History of coronary heart disease	1.294 (0.916–1.829)	0.731	–	–
BMI	0.714 (0.446–1.412)	0.160	–	–
NT-proBNP	1.784 (1.003–2.966)	0.128		
Paced QRS duration	1.157 (0.998–1.342)	0.065	–	–
LAVI	1.079 (0.594–1.958)	0.803	–	–
LVMI	0.965 (0.800–1.164)	0.709	–	–
LVEF	0.842 (0.745–1.198)	0.351	–	–
GLS	1.612 (0.966–2.857)	0.141	–	–
GRS	0.652 (0.222–1.917)	0.437	–	–
GCS	1.149 (0.493–3.553)	0.476	–	–
SDI	1.104 (0.278–2.469)	0.415	–	–
One month GLS	2.012 (0.960–3.680)	<0.001	1.623 (0.986–2.210)	0.009
One month LVEF	0.688 (0.556–0.935)	0.008	0.981 (0.960–1.003)	0.087
One month SDI	1.214 (0.906–3.173)	0.012	1.058 (0.379–2.957)	0.109

Abbreviations: BMI, body mass index; LAVI, left atrial volume index; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; GRS, global radial strain; GCS, global circumferential strain; SDI, standard deviation index of three-dimensional strain; NT-proBNP, N-terminal pro-brain natriuretic pep- tide.

went on to develop PIVD. At one month, only GLS was significantly reduced in these patients. The deterioration of GLS showed high correlation with LVEF reduction. Furthermore, on multivariate analysis, GLS at one month was an independent predictor for deterioration of LVEF at 12 months. These data demonstrate that LV GLS at one month has a high predictive accuracy (AUC, 0.88) in patients with PIVD at 12 months following RVA pacing. The optimal threshold for LV GLS at one month to predict development of PIVD was -14.5%, yielding a sensitivity of 94% and a specificity of 70%. Global longitudinal strain has the ability to identify subclinical LV dysfunction. The mechanism of abnormal GLS in HF patients has not been fully clarified. Reduced longitudinal function could identify subclinical LV dysfunction because subendocardial fibres are most susceptible to injury [29]. Another mechanism of subclinical LV impairment is systolic dyssynchrony, which is defined as uncoordinated regional wall motion leading to decreased LVEF. Real-time 3DE is feasible for assessing LV mechanical dyssynchrony [30]. Left ventricular SDI assessed by 3D STE has been reported, in previous studies, as a potentially more reliable index [31]. The current results showed that the patients who developed PIVD had significantly greater SDI compared with those who did not at 12 months.

Consistent with previous studies, the present study found deterioration of GLS after RVA pacing in serial assessment of GLS compared to baseline. Saito et al. evaluated the effects of RVA pacing on synchrony, efficiency, and regional function at 2 years [12]. Global longitudinal strain was significantly impaired by RVA pacing compared to controls. Right ventricular apical pacing was also independently correlated with change in GLS over 2 years. However, this study did not yield information regarding the temporal changes from baseline to 2 years. Ahmed et al. reported that GLS rather than LVEF at one month was significantly reduced compared with baseline in the PIVD group [13]. Global longitudinal strain at one month had high predictive accuracy for determining subsequent development of PIVD, but global strain and LVEF were analysed by semi-automated non-contrast 2D methods. The present study showed a decline in GLS alone at one month in those who developed PIVD at 12 months following RVA pacing using 3D echocardiography. The data further suggest the importance of GLS in identifying this patient group at an early stage of subsequent development of PIVD.

NT-proBNP is an excellent and easy to perform biomarker in patients with established HF, but has limited ability to assess HF in patients with normal EF [32,33]. In another study, 29% of outpatients with HF with preserved ejection fraction (HFpEF) had normal BNP levels [34]. Recent data suggest that LV GLS is abnormal in patients with HFpEF and that impaired LV GLS is associated with higher NT-proBNP values [35]. The present study found a linear correlation between GLS and log-transformed NT-proBNP in PIVD patients.

Limitations

The present study had some limitations. First, it was a single centre study with a small sample size. Three patients had HF, with LVEF <45% at 12 months following RVA pacing. A study with more patients and longer follow-up would be needed to confirm the findings. Furthermore, this study lacked a comparison with cardiac MRI, which is the noninvasive gold standard for LVEF and strain by tagging. However, the results showed that good reproducibility of LV measurements by 3D STE, and 3D STE has already been validated in recent studies. Finally, alternative pacing sites were not examined in the current study. It would be desirable for future studies to show the difference of GLS at one month between RVA and non-RVA pacing sites.

Conclusions

Global longitudinal strain is a significant predictor of LV adverse remodelling following RVA pacing. Global longitudinal strain at one month after pacemaker implantation has high predictive accuracy for identifying subsequent development of PIVD. In patients with preserved EF after permanent RVA pacing, GLS may have the potential to identify subtle LV dysfunction that is not detected by LVEF in the early stages of myocardial dysfunction.

Sources of Funding

None.

Competing Interests

The authors declare that there are no conflict of interests regarding the publication of this paper.

References

[1] Thambo JB, Bordachar P, Garrigue S, Lafitte S, Sanders P, Reuter S, et al. Detrimental ventricular remodeling in patients with congenital complete heart block and chronic right ventricular apical pacing. Circulation 2004;110:3766–72.

[2] Sweeney MO, Hellkamp AS. Heart failure during cardiac pacing. Circulation 2006;113:2082–8.

[3] Ahmed M, Gorcsan 3rd J, Marek J, Ryo K, Haugaa K, Ludwig RD, et al. Right ventricular apical pacing-induced left ventricular dyssynchrony is associated with a subsequent decline in ejection fraction. Heart Rhythm 2014;11:602–8.

[4] Zhang XH, Chen H, Siu CW, Yiu KH, Chan WS, Lee KL, et al. New-onset heart failure after permanent right ventricular apical pacing in patients with acquired high-grade atrioventricular block and normal left ventricular function. J Cardiovasc Electrophysiol 2008;19:136–41.

[5] Kraigher-Krainer E, Shah AM, Gupta DK, Santos A, Claggett B, Pieske B, et al. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. J Am Coll Cardiol 2014;63:447–56.

[6] Li CM, Li C, Bai WJ, Zhang XL, Tang H, Qing Z, et al. Value of three-dimensional speckle-tracking in detecting left ventricular dysfunction in patients with aortic valvular diseases. J Am Soc Echocardiogr 2013;26:1245–52.

[7] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39. e14.

[8] Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man: Anatomic validation of the method. Circulation 1977;55:613–8.

[9] Dreger H, Maethner K, Bondke H, Baumann G, Melzer C. Pacing-induced cardiomyopathy in patients with right ventricular stimulation for >15 years. Europace 2012;14:238–42.

[10] Yu CM, Fang F, Luo XX, Zhang Q, Azlan H, Razali M. Long-term follow-up results of the pacing to avoid cardiac enlargement (PACE) trial. Eur J Heart Fail 2014;16:1016–25.

[11] Algazzar AS, Katta AA, Ahmed KS, Elkenany NM, Ibrahim MA. Changes in left ventricular global and regional longitudinal strain during right ventricular pacing. Cardiol Res 2016;7:17–24.

[12] Saito M, Kaye G, Negishi K, Linker N, Gammage M, Kosmala W, et al. Dyssynchrony, contraction efficiency and regional function with apical and non-apical RV pacing. Heart 2015;101:600–8.

[13] Ahmed FZ, Motwani M, Cunnington C, Kwok CS, Fullwood C, Oceandy D, et al. One-month global longitudinal strain identifies patients who will develop pacing-induced left ventricular dysfunction over time: the Pacing and Ventricular Dysfunction (PAVD) Study. PLoS One 2017;12: e0162072.

[14] Kalam K, Otahal P, Marwick TH. Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. Heart 2014;100:1673–80.

[15] Kamperidis V, Marsan NA, Delgado V, Bax JJ. Left ventricular systolic function assessment in secondary mitral regurgitation: left ventricular ejection fraction vs speckle tracking global longitudinal strain. Eur Heart J 2016;37:811–6.

[16] Smiseth OA, Torp H, Opdahl A, Haugaa KH, Urheim S. Myocardial strain imaging: how useful is it in clinical decision making? Eur Heart J 2016;37:1196–207.

[17] Cho GY, Marwick TH, Kim HS, Kim MK, Hong KS, Oh DJ. Global 2-dimensional strain as a new prognosticator in patients with heart failure. J Am Coll Cardiol 2009;54:618–24.

[18] Pignatelli RH, Ghazi P, Reddy SC, Thompson P, Cui Q, Castro J, et al. Abnormal myocardial strain indices in children receiving anthracycline chemotherapy. Pediatr Cardiol 2015;36:1610–6.

[19] Gunasekaran P, Panaich S, Briasoulis A, Cardozo S, Afonso L. Incremental value of two dimensional speckle tracking echocardiography in the functional assessment and characterization of subclinical left ventricular dysfunction. Curr Cardiol Rev 2017;13:32–40.

[20] Hoogslag GE, Abou R, Joyce E, Boden H, Kamperidis V, Regeer MV, et al. Comparison of changes in global longitudinal peak systolic strain after ST-segment elevation myocardial infarction in patients with versus without diabetes mellitus. Am J Cardiol 2015;116:1334–9.

[21] Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. J Am Soc Echocardiogr 2011;24:277–313.

[22] Luis SA, Yamada A, Khandheria BK, Speranza V, Benjamin A, Ischenko M, et al. Use of three-dimensional speckle-tracking echocardiography for quantitative assessment of global left ventricular function: a comparative study to three-dimensional echocardiography. J Am Soc Echocardiogr 2014;27:285–91.

[23] Luo XX, Fang F, Lee AP, Sun JP, Li S, Zhang ZH, et al. What can three-dimensional speckle-tracking echocardiography contribute to evaluate global left ventricular systolic performance in patients with heart failure? Int J Cardiol 2014;172:132–7.

[24] Cai Q, Ahmad M. Left ventricular dyssynchrony by three-dimensional echocardiography: current understanding and potential future clinical applications. Echocardiography 2015;32:1299–306.

[25] Driessen MM, Kort E, Cramer MJ, Doevendans PA, Angevaare MJ, Leiner T, et al. Assessment of LV ejection fraction using real-time 3D echocardiography in daily practice: direct comparison of the volumetric and speckle tracking methodologies to CMR. Neth Heart J 2014;22:383–90.

[26] Dorosz JL, Lezotte DC, Weitzenkamp DA, Allen LA, Salcedo EE. Performance of 3-dimensional echocardiography in measuring left ventricular volumes and ejection fraction: a systematic review and meta-analysis. J Am Coll Cardiol 2012;59:1799–808.

[27] Aurigemma GP, Zile MR, Gaasch WH. Contractile behavior of the left ventricle in diastolic heart failure: with emphasis on regional systolic function. Circulation 2006;113:296–304.

[28] Marwick TH. Methods used for the assessment of LV systolic function: common currency or tower of Babel? Heart 2013;99:1078–86.

[29] Nesbitt GC, Mankad S, Oh JK. Strain imaging in echocardiography: methods and clinical applications. Int J Cardiovasc Imaging 2009;25 (Suppl 1):9–22.

[30] Kang Y, Sun MM, Cui J, Chen HY, Su YG, Pan CZ, et al. Three-dimensional speckle tracking echocardiography for the assessment of left ventricular function and mechanical dyssynchrony. Acta Cardiol 2012;67:423–30.

[31] Soliman OI, van Dalen BM, Nemes A, Zwaan HB, Vletter WB, ten Cate FJ, et al. Quantification of left ventricular systolic dyssynchrony by real-time three-dimensional echocardiography. J Am Soc Echocardiogr 2009;22:232–9.

[32] Mureddu GF, Tarantini L, Agabiti N, Faggiano P, Masson S, Latini R, et al. Evaluation of different strategies for identifying asymptomatic left ventricular dysfunction and pre-clinical (stage B) heart failure in the elderly results from 'PREDICTOR', a population based-study in central Italy. Eur J Heart Fail 2013;15:1102–12.

[33] Tan YT, Wenzelburger F, Lee E, Heatlie G, Leyva F, Patel K, et al. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. J Am Coll Cardiol 2009;54:36–46.

[34] Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail 2010;3:588–95.

[35] DeVore AD, McNulty S, Alenezi F, Ersboll M, Vader JM, Oh JK, et al. Impaired left ventricular global longitudinal strain in patients with heart failure with preserved ejection fraction: insights from the RELAX trial. Eur J Heart Fail 2017;19:893–900.