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ORIGINAL ARTICLE

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Comparison of heart rate and cardiac output of VVI pacemaker settings in patients with atrial fibrillation with bradycardia

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Abstract

Background: While most VVI pacemakers in bradycardic patients are set to a low limit of 60/min, the optimal lower limit rate for VVI pacemakers in atrial fibrillation has not been established. Although an increase in heart rate within the normal range in the setting of a VVI pacemaker might be expected to lead to an increase in cardiac output with the shortening of the diastolic time, the changes in cardiac output at different pacemaker settings have not been fully clarified.

Methods: We included 11 patients with bradycardic atrial fibrillation who had VVI pacemakers implanted. Stroke volume was measured using the electrical cardiometry method (AESCULON® mini; Osypka Medical) without pacing and at ventricular pacings of 60, 70, 80, and 90/min.

Results: Stroke volume decreased stepwise at ventricular pacing rates of 60, 70, 80, and 90/min (63.6 ± 11.2, 61.9 ± 10.6, 59.3 ± 12.2, and 57.5 ± 12.2 mL, $p < .001$), but cardiac output increased (3.81 ± 0.67, 4.33 ± 0.74, 4.74 ± 0.97, and 5.17 ± 1.09 L/min, $p < .001$). The rate of increase in cardiac output at a pacing rate of 70/min compared to 60/min correlated with left ventricular end-systolic volume ($r = 0.711$, $p = .014$).

Conclusions: Cardiac output increased at a pacing rate of 70 compared to 60 in bradycardic atrial fibrillation patients, and the rate of increase in cardiac output was greater in those with larger left ventricular end-systolic volume.

KEYWORDS
cardiac output, electrical cardiometry, electrical velocimetry, heart failure, pacemaker

1 | INTRODUCTION

Atrial fibrillation with bradycardia is characterized by chronotropic incompetence,[1] which means that the heart rate does not rise sufficiently even when necessary. Permanent pacemakers are used to improve symptoms caused by bradycardia but do not necessarily improve prognosis.[2] According to guidelines, a pacemaker is generally implanted when patients have heart rates <40/min with the

onset of symptoms,[2,3] but there is no clear definition of the heart rate at which treatment is indicated. The guidelines do not describe rate setting when a pacemaker is implanted, and few prospective clinical trials have evaluated outcomes based on the pacing rate in patients with pacemakers.[4] Therefore, the optimal pacing rate in symptomatic pacemaker-implanted patients is unknown.

Although an increase in heart rate within the normal range might be expected to lead to an increase in cardiac output, the impact of stroke volume (SV) and changes in cardiac output at different ventricular pacing rates have not been sufficiently clarified. We investigated the relationship between the rate of increase in cardiac output and cardiac function at different heart rates in patients with bradycardic atrial fibrillation implanted with a ventricular single-chamber pacemaker.

2 | METHODS

2.1 | Study populations

The study included 11 patients with atrial fibrillation who had a new VVI pacemaker implanted or a battery replaced at our hospital from January 2020 to December 2021. All patients' preoperative heart rates averaged less than 60/min. In most cases, the pacing site was the mid-lower ventricular septum of the right ventricle, eliminating any involvement of the His bundle or left bundle branch. Informed consent was obtained from all patients.

2.2 | Measurement of systolic volume with electrical cardiometry

One of the non-invasive methods of measuring SV is electrical cardiometry. We used AESCULON® mini (Osypka Medical, Berlin, Germany) with four surface electrocardiogram (ECG) electrodes connected to the monitor by a cable.[5,6] For this study, surface ECG electrodes were placed on the skin (one pair located side by side in the vertical direction on the left side of the neck and the other pair on the lower thorax along the mid-axillary line, at the level of the xiphoid process).[7] The monitor emits a high-frequency (50 kHz) alternating current of a constant magnitude (2 mA, rms) through a pair of electrodes, inducing a current field.[8] Hemodynamic parameters are measured from the bioimpedance measured over time.[9] Measurements were taken at device implantation, with the patient at rest in the supine position. The patient's SV was measured at baseline and ventricular pacing rates of 60, 70, 80, and 90/min. Cardiac output was defined as SV × pulse/pacing rate.

2.3 | Echocardiography measurement

Transthoracic echocardiography was performed before device implantation. Measurements were taken according to the guidelines of the American Society of Echocardiography.[10] Standard measurements were obtained from parasternal long-axis, apical 4-lumen, and 2-lumen images in conventional two-dimensional B-mode. The left ventricular ejection fraction (LVEF) was estimated using Simpson's biplane method. The left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were calculated from the end-diastolic and end-systolic diameters, respectively, $V = D^3 \times 7.0/(2.4 + D)$ using the Teichhold method.[11] The patient's SV was calculated as LVEDV—LVESV. The maximal volume of the left atrium was measured by Simpson's planimetry; this figure divided by the estimated body surface area was calculated as the left atrial volume index (LAVI).

2.4 | Statistical analysis

Statistical analysis was performed using SPSS (version 26; IBM Inc.). Data are expressed as numbers, percentages, or means ± standard deviations (SD). Comparisons of the two corresponding groups were made using *t*-tests. Repeated measures of one-way analysis of variance were used to evaluate SV and the cardiac output at each pacing rate. Associations of one of the three variables, LVEF, LVEDV, or LVESV, and the rate of increase in cardiac output, were validated using Spearman's correlation coefficient. A difference was considered significant if the probability value was <0.05.

3 | RESULTS

The mean age of the patients was 78.6 ± 8.5 years, and all 11 were male. Eight were new device implantation cases, and the rest were pacemaker battery replacement cases. One of the patients requiring pacemaker battery replacement was pacing-dependent and the patient's SV was not measured at baseline. Patient characteristics at the time of device surgery are shown in Table 1. None had complications of ischemic heart disease. The mean LVEF on echocardiography was maintained at 62.8%, but N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were high, averaging 1390 pg/mL. While most patients had New York Heart Association (NYHA) class I at the time of device implantation, but the dilated cardiac myopathy (DCM) patient had NYHA class IV with LVEF of 30%, and one other patient had a reduced LVEF of 49%. The rest 9 patients had LVEF ≧50%.

When cardiac output was calculated at baseline and VVI pacing rates of 60 and 70/min, the latter exceeded that of the former, except for one patient who had a baseline heart rate of 60/min (VVI 60: 2.82 ± 0.74 vs. 3.70 ± 0.58 L/min, $p = .009$; VVI 70: 2.82 ± 0.74 vs. 4.19 ± 0.61 L/min, $p = .001$). Moreover, as the pacing rate was increased to 80/min and 90/min, cardiac output increased significantly compared to baseline (VVI 80: 2.82 ± 0.74 vs. 4.58 ± 0.85 L/min, $p < 0.001$; VVI 90: 2.82 ± 0.74 vs. 5.01 ± 1.01 L/min, $p < 0.001$) (Figure 1). Comparing the baseline value with VVI at 60, 70, 80, and 90/min, SV decreased progressively (63.6 ± 11.2,

TABLE 1 Clinical characteristics of patients.

Number of patients	11
Age (years)	78.6 ± 8.5
Men (%)	11(100)
Comorbidities, *n* (%)	
Hypertension	9 (82)
Diabetes	1 (9)
Dyslipidemia	4 (36)
Underlying heart disease	
None/DCM/HCM/Valvular disease, *n* (%)	8/1/1/1
History of pacemaker implantation, *n* (%)	3(27)
Medications, *n* (%)	
ACE-I/ARB	8 (73)
β-blocker	2 (18)
Diuretic	5 (45)
NT-pro BNP (pg/ml)	1390 ± 1119
eGFR (ml/min/1.73 m^2)	52.7 ± 21.8
Left ventricular ejection fraction (%)	62.8 ± 13.4
Left ventricular end-systolic volume (mL)	41.0 ± 32.0
Left ventricular end-diastolic volume (mL)	118.2 ± 38.3
Left ventricular stroke volume (mL)	74.9 ± 18.6
Left atrial volume index (mL/m^2)	68.0 ± 43.6

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; DCM, dilated cardiac myopathy; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiac myopathy; NT-proBNP, N-terminal pro-brain natriuretic peptide.

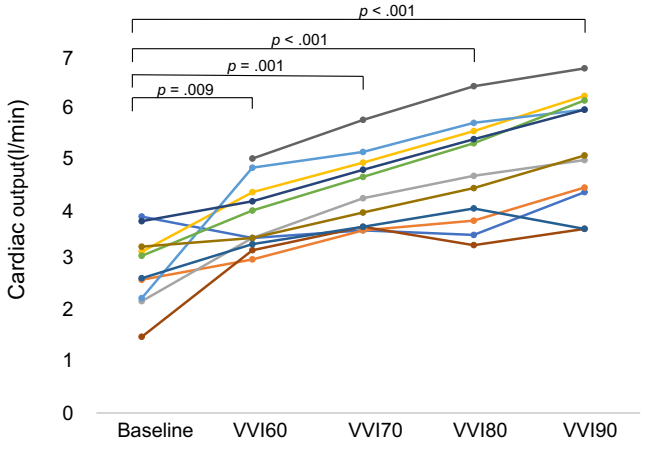


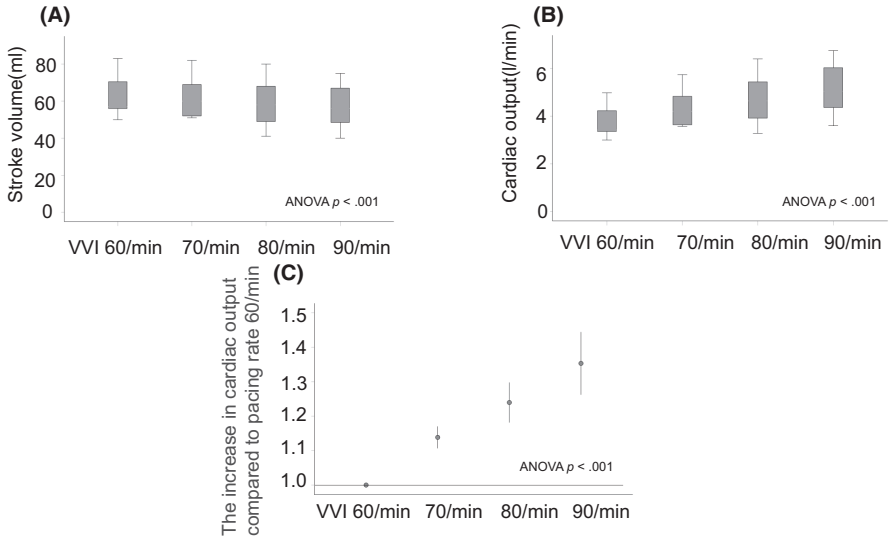
FIGURE 1 Changes in cardiac output at baseline and pacing rate.

61.9 ± 10.6, 59.3 ± 12.2, and 57.5 ± 12.2 mL, $p < 0.001$) (Figure 2A), but cardiac output increased (3.81 ± 0.67, 4.33 ± 0.74, 4.74 ± 0.97, and 5.17 ± 1.09 L/min, $p < 0.001$) (Figure 2B). The increases in cardiac output at VVI 70, 80, and 90 /min compared to VVI 60/min were 1.14 ± 0.05, 1.24 ± 0.10, and 1.35 ± 0.15, respectively, $p < 0.001$ (Figure 2C). The increase in cardiac output at VVI 70/min compared to VVI 60/min did not significantly correlate with baseline LVEF ($r = -0.435$, $p = 0.181$) (Figure 3A) and LVEDV ($r = 0.344$, $p = .301$) (Figure 3C), but it did correlate with LVESV ($r = 0.711$, $p = .014$) (Figure 3B). We divided patients into two groups according to the presence or absence of comorbid hypertension, and the results were compared; the increase in cardiac output at a pacing rate of 70/min compared to a pacing rate of 60/min was significantly different between the two groups (1.12 ± 0.04 vs. 1.21 ± 0.03, $p = .026$). When the patients were divided according to the presence or absence of hyperlipidemia and diabetes mellitus, the results were not significantly different. There were only two patients with LVEF less than 50%; the increase in cardiac output at a pacing rate of 70/min compared to a pacing rate of 60/min in the two groups of patients with LVEF<50% and ≧50% could not be significantly different (1.17 ± 0.03 vs. 1.13 ± 0.06, $p = .356$). Of the 11 patients, only one patient was subsequently readmitted due to heart failure, and two died of cancer.

4 | DISCUSSION

The findings of this study were as follows. (1) When patients with atrial fibrillation have bradycardia, cardiac outputs at ventricular pacing rates of 60, 70, 80, and 90/min are increased compared to that at baseline, (2) The rate of increase in cardiac output at a pacing rate of 70/min compared to 60/min was correlated with LVESV. In particular, those who benefited most from the increased pacing were those with the greatest end-systolic volume.

In this study, cardiac output increased at VVI pacing rates of 60 and 70/min in patients who had bradycardic atrial fibrillation before implantation. Pacemakers are paced primarily from the right ventricular apex, which is a non-physiological contraction site compared to a healthy person's conduction system, making it difficult to achieve efficient cardiac output.[12] Since SV decreases when the heart rate increases with the shortening of the diastolic time, the effect of pacing on cardiac output (=SV × heart rate) is not obvious. In this study, the cardiac output calculated from SV measured by electrical cardiometry increased when the heart rate was increased to more than 60/min by pacing, compared to the baseline bradycardic conduction. In a report by Chiladakis et al.[13] on ventricular pacing in patients with atrial fibrillation, hemodynamics were assessed by echocardiography and ventricular pacing was shown to significantly reduce SV, but the cardiac output was relatively unchanged because of the increased heart rate. In our study, hemodynamics during pacing was assessed by electrical cardiometry rather than echocardiography, but the cardiac output was significantly increased due to increased heart rate for hemodynamic indices (Figure 1). Possible reasons for this discrepancy include; in the study by Chiladakis et al., diltiazem was used in approximately 60% of patients to slow the autologous pulse in order to achieve a regular pacing rhythm. In contrast, our study included patients who originally required pacemakers for bradycardia, only two patients were taking beta-blockers at the time of device implantation, and none were using other antiarrhythmic drugs.



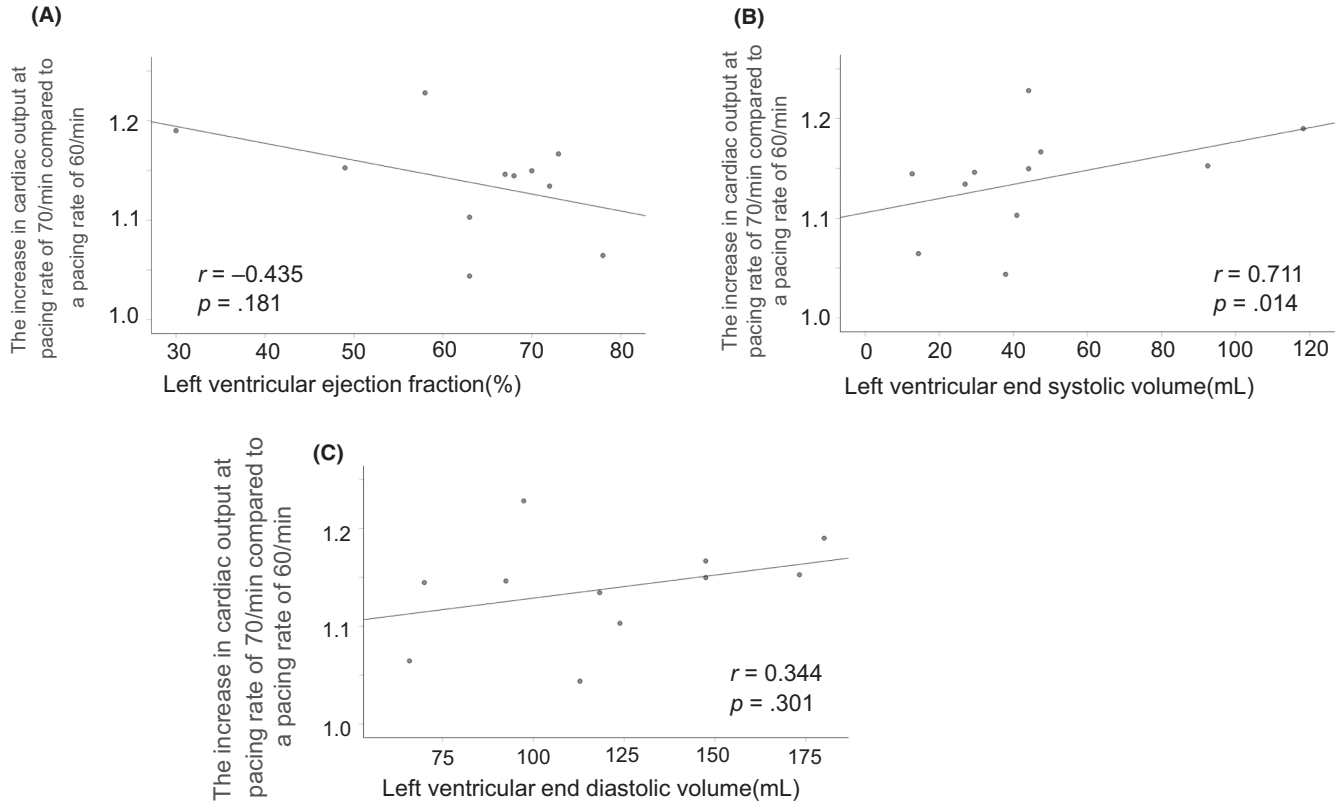


FIGURE 2 Hemodynamic changes at each pacing rate. (A) Stroke volume. (B) Cardiac output. (C) Increase in cardiac output compared to that at VVI 60/min. ANOVA, analysis of variance.

FIGURE 3 The relation between increases in cardiac output and LVEF, LVESV, or LVEDV. (A) The association between LVEF and the increase in cardiac output at VVI 70/min compared to VVI 60/min. (B) The association between LVESV and the increase in cardiac output at VVI 70/min compared to VVI 60/min. (C) The association between LVEDV and the increase in cardiac output at VVI 70/min compared to VVI 60/min. LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume.

Atrial fibrillation is closely associated with heart failure.[14,15] In this study, LVEF was maintained at an average of 62.8%, but NT-proBNP levels were as high as 1390 pg/mL, indicating potential heart failure. Conventionally, the lower rate limit for pacemakers is often set at 50–70/min, and we have little experience with settings above 80/min. In our study, a gradual increase in cardiac output occurred as the lower rate limit was increased, but the long-term prognosis remains unknown. Although a lower survival rate has been reported with higher values of lower rate programming in patients with CRTD implantation,[4] this study excludes patients with persistent atrial fibrillation. Several studies have shown an association between heart rate and survival in patients with atrial fibrillation. In the CHARM trial, a lower heart rate was associated with longer survival in patients with sinus rhythm, but the heart rate in atrial fibrillation

did not predict prognosis.[16] Rate control of atrial fibrillation did not improve prognosis in the strict therapy group of the RACE II study.[17] The results of our study suggest that a lower rate limit of 70/min may improve hemodynamics in pacemaker-dependent patients with cardiac enlargement compared with the lower rate limit of 60/min. In patients with bradycardia in atrial fibrillation, there is potential heart failure, and it may be useful to increase the pacing rate to ensure cardiac output. Whether a higher lower rate limit, such as 80/min or 90/min, is advisable needs to be explored in patients with persistent atrial fibrillation. Moreover, the prognostic impact of pacing rate in atrial fibrillation with bradycardia is not clear from the present study, and a large prospective study comparing the prognostic value of different VVI pacing rate limits in patients with atrial fibrillation is needed.

In this study, only LVESV in parameters of echocardiography was associated with the increase in cardiac output at VVI 70/min compared to VVI 60/min. Although the association among LVEDV, LVEF, and the increase in cardiac output was not significant, the correlation coefficient was around 0.4, and the lack of a significant difference in the association may be due in part to the small number of cases in this study.

There are several limitations to this study. First, there was a small number of patients. In addition, there is no medium- to long-term biomarker follow-up. The second was the failure to measure LVEF and SV on echocardiography when the pacing rate was varied. In the future, it would be useful for hemodynamic evaluation if SVs of both electrical cardiometry and echocardiography could be obtained when the pacing rate is varied. Additional large-scale studies will be needed to examine echocardiographic parameters and the increase in cardiac output when the lower rate limit is increased. Furthermore, only the SV at rest was measured in this study. Hemodynamics during exercise can vary,[18] such that the appropriate setting during exercise may be different. Finally, the prognostic impact of the pacing rate in atrial fibrillation with bradycardia is not clear from this study. Large prospective studies comparing the mid-to-long-term prognosis of different VVI pacing rate limits in patients with atrial fibrillation are needed.

5 | CONCLUSIONS

Cardiac output increased at 70/min compared to 60/min in patients with atrial fibrillation with bradycardia, and the rate of increase in cardiac output was greater in those with dilated left ventricles.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest in the context of this study. TK reports research and education support from Medtronic, Japan Lifeline, and Abbott. KK reports honoraria from Medtronic outside the submitted work.

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