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Original Article

Hemodynamic effects of Purkinje potential pacing in the left ventricular endocardium in patients with advanced heart failure

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ABSTRACT

Background: Various difficulties can occur in patients who undergo cardiac resynchronization therapy for drug-refractory heart failure with respect to placement of the left ventricular (LV) lead, because of anatomical features, pacing thresholds, twitching, or pacing lead anchoring, possibly requiring other pacing sites. The goal of this study was to determine whether Purkinje potential (PP) pacing could provide better hemodynamics in patients with left bundle branch block and heart failure than biventricular (BiV) pacing.

Methods: Eleven patients with New York Heart Association functional class II or III heart failure despite optimal medical therapy were selected for this study. All patients underwent left- and right-sided cardiac catheterization for measurement of LV functional parameters in the control state during BiV and PP pacing.

Results: Maximum dP/dt increased during BiV and PP pacing when compared with control measurements. This study compared parameters measured during BiV pacing with PP pacing and non-paced beats as the control state in each patient (717 ± 171 mmHg/s vs. 917 ± 191 mmHg/s, $p < 0.05$; and 921 ± 199 mmHg/s, $p < 0.005$); however, the difference between PP pacing and BiV pacing was not significant. There was no difference in heart rate, electrocardiographic wave complex duration, minimum dP/dt, left ventricular end-diastolic pressure, left ventricular end-systolic pressure, pulmonary capillary wedge pressure, or cardiac index when comparing BiV pacing and PP pacing to control measurements.

Conclusions: The hemodynamic outcome of PP pacing was comparable to that of BiV pacing in patients with advanced heart failure.

1. Introduction

Cardiac resynchronization therapy (CRT) is an important treatment for drug-refractory heart failure and left ventricular (LV) dyssynchrony. Pacing leads have often been placed at the coronary vein and right ventricle to reduce LV dyssynchrony and to improve hemodynamics in patients with heart failure. In some patients, clinicians encounter difficulties when placing leads; in approximately one-quarter of patients, there is an insufficient response to biventricular (BiV) pacing, primarily because of difficulty in accurately placing the LV lead due to patients' anatomical features, pacing thresholds, twitching, or pacing lead anchoring [1]. Some researchers have described other pacing sites that yield better hemodynamics and less dyssynchrony than BiV pacing. For example, Derval et al. attempted lateral LV wall pacing in patients with left bundle branch block pattern who were referred for CRT device implantation [2]. Van Gelder et al. reported that transseptal lead placement was useful in cases where there was difficulty in placing a coronary sinus (CS) lead [3]. Yoshida et al. reported that triventricular pacing, which uses two right ventricular leads and one LV lead, results in greater improvement in hemodynamics in patients with severe heart failure, when compared with Bi-V pacing [4], Sashida et al. reported improved LV function with His bundle pacing (HBP) in a patient with dilated cardiomyopathy due to atrial fibrillation without intraventricular conduction delay [5], However, whether these or other pacing sites are superior to conventional BiV pacing remains unclear. Some recent studies reported that BiV pacing with LV endocardial stimulation sites yield better hemodynamics and LV synchrony, compared with conventional BiV pacing. These procedures would have the benefit of lead placement in an extended area, regardless of coronary vein location, with better threshold and avoidance of twitching.

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On the other hand, it has been reported that the Purkinje network can survive in patients with ischemic or idiopathic cardiomyopathy [6], and in patients with heart failure and left bundle branch block (LBBB). In addition, idiopathic LV tachycardia that involves the Purkinje network as the circuit is characterized as showing a narrow QRS [7]. Therefore, it is conceivable that direct pacing of the Purkinje fiber or Purkinje network may show a narrow QRS, comparable to conventional BiV pacing in favor of shorter QRS duration, and lead to impulse conduction in the LV endocardium in patients with advanced heart failure. Furthermore, Purkinje fibers are widely distributed in the LV and are easy to detect. We believe that PP pacing is superior to other LV endocardial pacing in reproducibility and ability to detect the Purkinje fiber as the pacing site, even in injured myocardium, but there has been no report of direct pacing of the Purkinje network.

We hypothesized that direct pacing of the peripheral network in patients with LBBB and heart failure might lead to more physiological pacing than conventional pacing. This study was done to verify that Purkinje potential (PP) pacing is a promising strategy for resynchronization and for improving hemodynamics in such patients. The goal of the present study was to compare the effects of PP and BiV pacing on hemodynamics in patients with drug-refractory heart failure.

2. Material and methods

2.1. Study patients

The study population comprised 11 patients (eight men and three women; mean age, 62 ± 14 years) with New York Heart Association functional (NYHA) class II or III heart failure despite optimal medical therapy. The echocardiographic LV ejection fraction, as determined on two-dimensional examination, was $<35\%$, and the QRS duration was >120 ms. These patients were deemed likely to require resynchronization therapy in the near future according to guideline recommendations. Patients with atrioventricular (AV) block were excluded. This study included one patient with atrial fibrillation (AF). All patients were on stable medical therapy for chronic heart failure, including diuretics ($n=10$), spironolactone ($n=7$), β-blockers ($n=11$), angiotensin-converting enzyme (ACE) inhibitors ($n=10$), and amiodarone ($n=1$). The medication regimen was not changed in any patient for at least 3 months prior to the study. Cardiac catheterization was performed to assess the acute hemodynamic effects of BiV pacing as a feasibility study for CRT implantation. This study was approved by the local research ethics committee of Hyogo College of Medicine Hospital, and patients provided written, informed consent to participate.

2.2. Cardiac catheterization

Left- and right-side cardiac catheterization was performed in all patients to assess LV function. A temporary electrode catheter was introduced into the high right atrium (HRA), and ventricular pacing catheters were placed at the right ventricular apex (RVA), coronary sinus, and LV epicardial wall. Another electrode catheter was positioned in the LV endocardium to detect the PP via the aorta. A PP was defined as a sharp, brief, high frequency potential swing in the periphery (Fig. 1). The PP pacing site was defined as the site at which the PP was detected (Fig. 2), most typically at the left posterior fascicle of the left ventricle. The LV lead was positioned mainly in the lateral branch of the coronary vein.

A 5-Fr high-fidelity micromanometer-tipped pigtail angiographic catheter (Millar Instruments Inc., Houston, TX, USA) was placed in the LV cavity via the femoral artery approach in order to determine LV pressure, as previously reported [8,9]. The micromanometer pressure was adjusted to the pressure of the fluid-filled lumen. LV pressure signals were digitized and analyzed on a computer system. Pulmonary capillary wedge pressure (PCWP) and cardiac index (CI) were measured with a Swan-Ganz catheter placed in the proximal pulmonary artery via the femoral vein. Fig. 2 illustrates the placement of the catheters.

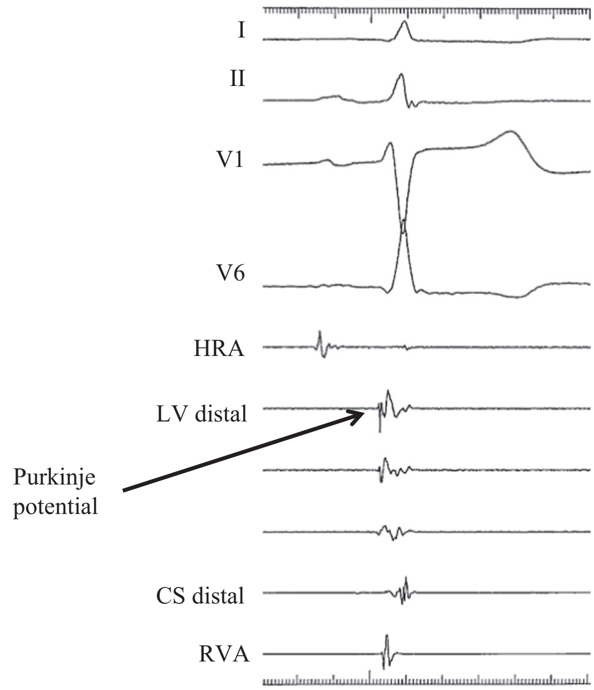

Fig. 1. Purkinje potential (PP pacing) was defined as a sharp, brief, high frequency potential swing in the periphery.

2.3. Study protocol

Six LV functional parameters were measured in the control state and during BiV and PP pacing in each patient: maximum (max) dP/dt (+dP/dt), minimum (min) dP/dt (−dP/dt), LV peak systolic pressure (LVP), LV end-diastolic pressure (LVEDP), PCWP, and CI. All parameters were measured three times in each pacing state. Typical surface electrocardiograms in the control state and during BiV and PP pacing are shown in Fig. 3. After control state measurement, BiV and PP pacing state measurements were done. The order of BiV and PP pacing was switched with each case to avoid confounding factors.

If the sinus rhythm rate was under 75 bpm, the control state was measured under atrial pacing (Ap: sinus rate + 10 to 20 bpm), and the BiV and PP pacing states were measured under the same pacing rate (ApVp: AV sequential pacing).

If the sinus rhythm rate was above 75 bpm, the control state was measured under sinus rhythm, and the BiV and PP pacing states were measured under atrial sensing ventricular pacing (AsVp).

Patients with AF underwent ventricular pacing. Measurements were collected in the non-paced state and at each pacing condition for 5 min, after 3 min of hemodynamic stabilization. AV delay was generally 150 ms in patients with a normal PQ duration, and ventricular pacing was performed with a shorter AV delay (<150 ms) in patients with a short PR duration. There was no adjustment for interventricular (VV) delay because of a limitation of time in this study.

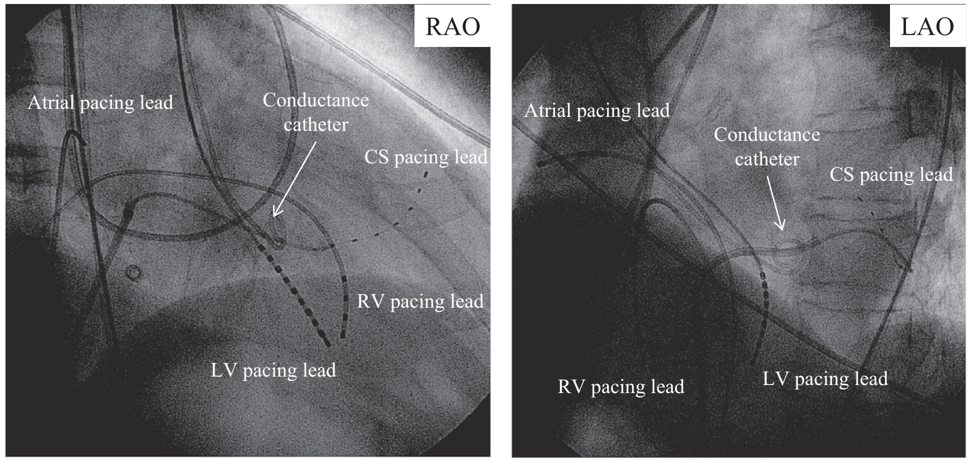

Fig. 2. Fluoroscopic images of catheter placement. RAO = right anterior view; LAO = left anterior view.

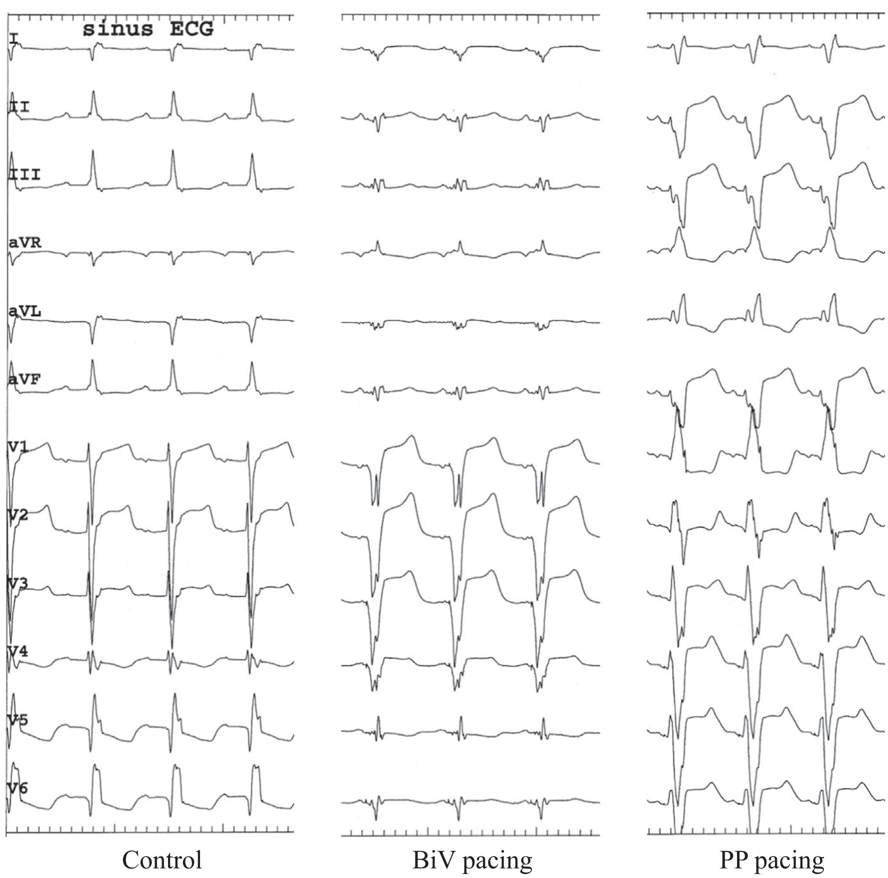

Fig. 3. Twelve-lead electrocardiogram in the control state and during BiV and PP pacing.

2.4. Statistical analysis

Nominal variables were compared between groups using the chi-square test. Parameters fitting a normal distribution, as confirmed by the Shapiro–Wilks test, were analyzed by unpaired *t*-tests and are expressed as means (± standard deviation). Fixed factor analysis of variance (ANOVA) for repeated measures was used for post hoc comparisons. A p value < 0.05 was considered significant. All statistical analyses were performed with EZR (Easy R) (Saitama Medical Center, Jichi Medical University, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) based on R commander (version 1.6-3).

Table 1
Baseline characteristics.

Age (years)	62 ± 14	(35–79)
Sex (male/female)	8/3	
NYHA (II/III)	3/8	
Ischemic/Idiopathic	2/9	
LVEF (%)	28 ± 6	(20–37)
LVDd (mm)	66 ± 9	(49–77)
QRS duration (ms)	142 ± 36	(122–200)
LBBB/intra-ventricular defect	9/2	

NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; LVDd, left ventricular diastolic dimension; LBBB, left bundle branch block.

3. Results

3.1. Baseline characteristics

Baseline characteristics are shown in Table 1. The etiology of heart failure was considered idiopathic cardiomyopathy in nine patients and ischemic cardiomyopathy in two. LV ejection fraction was 35% or lower in all patients (mean, $28 \pm 6\%$). LV end-diastolic diameter (LVDd) was 66 ± 9 mm, and QRS duration was 142 ± 36 ms. Nine (81%) of 11 patients had LBBB, and two had intraventricular conduction delay.

3.2. Effect of PP pacing compared with control and BiV pacing

LV functional measurements are shown in Table 2. Maximum (max) d*P*/d*t* increased during BiV pacing and PP pacing when compared with control (717 ± 171 mmHg/s vs. 917 ± 191 mmHg/s, $p < 0.05$; and 717 ± 171 mmHg/s vs. 921 ± 199 mmHg/s, $p < 0.05$), but the difference between BiV and PP pacing was not significant. There was no difference in HR, QRS duration, min d*P*/d*t*, LVEDP, LVESP, PCWP, or CI when comparing these pacing sites.

After this study, 10 of 11 patients received CRT, and 6 had a satisfactory response. One patient declined CRT for personal reasons.

4. Discussion

4.1. LV endocardial pacing as an alternative, compared with LV epicardial pacing through the coronary sinus

CRT is an important therapeutic strategy for patients with drug-refractory heart failure and LV dyssynchrony. However, limitations to this modality include difficulty in placement of the LV lead and lack of response to BiV pacing.

Some recent studies reported that BiV pacing with LV endocardial stimulation sites yields better hemodynamics and LV synchrony, compared with conventional BiV pacing. Bordachar et al. systematically reviewed efficacy and risk of LV endocardial stimulation [10]. They also assessed the optimal LV pacing site to produce the most satisfactory hemodynamic parameters. These procedures have the benefit of lead placement in an extended area, with better threshold and avoidance of twitching, regardless of coronary vein location.

4.2. Effects of PP pacing

This paper is the first to report on LV endocardial PP pacing. We hypothesized that PP pacing is a good alternative to conventional BiV pacing for patients with LBBB and heart failure. The Purkinje network can remain viable in patients with ischemic or idiopathic cardiomyopathy, and it is detected with relative ease, most typically at the left posterior fascicle of the left ventricle, and is even stable in the injured myocardium. Because PP pacing is single site pacing, we can search for the optimal LV pacing site, without taking the positional relationship between LV and RV pacing sites into consideration.

Therefore, we assessed the efficacy of pacing at the LV left posterior fascicle in patients with advanced heart failure, and showed that stimulation at that site produced hemodynamics comparable to that of BiV pacing. The present study showed that single LV endocardial PP pacing achieved acute hemodynamic effects, and even might be useful in the injured myocardium.

This study compared measures of LV function during BiV and PP pacing in patients with heart failure due to LV systolic dysfunction. Max d*P*/d*t* increased during BiV and PP pacing, when compared with control, but the difference was not significant. The improvements in LV function were similar, when comparing PP and BiV pacing to control.

The mean value of QRS duration did not differ significantly when comparing the three groups. In 4 of 11 cases, the QRS duration during PP pacing was longer than during sinus rhythm and Bi-V pacing. However, in these cases Max d*P*/d*t* also improved, regardless of wide QRS morphology. The cases with long QRS duration during PP pacing often showed right bundle branch block. The potentials during PP pacing, detected by the electrode at the coronary sinus as the terminal branch in the left ventricle, converged earlier than the end of the QRS morphology on the intracardiac electrogram. Therefore, the long QRS duration may not have been caused by the failure of selective PP pacing (i.e., direct capture of the LV endocardium), but rather by delayed right bundle branch potentials.

In the modern era of resynchronization therapy, Alonso et al. reported that better pacing sites in the RV are associated with shorter QRS duration [11]. However, although HBP produces a short QRS duration, it does not always result in improved LV function [12]. Thus, the relationship between LV function and QRS duration would benefit from further study, especially in patients with heart failure.

Purkinje fibers are often still viable in injured myocardium and patients with severe heart failure, and PP pacing in such patients might be effective for maintaining electrical conduction and improving LV function, regardless of QRS duration. Furthermore, Purkinje fibers are widely distributed in the LV and are easy to detect. Consequently, PP pacing might be a good therapeutic strategy in patients with heart failure.

Table 2
Comparison of measurements during control, BiV pacing, and PP pacing.

	Control	Bi-V pacing	PP pacing
HR (bpm)	63 ± 14	74 ± 7	74 ± 8
QRS (ms)	142 ± 36	136 ± 32	151 ± 23
Max d*P*/d*t* (mmHg/s)	717 ± 171	$917 \pm 191^{*}$	$921 \pm 199^{\dagger}$
Min d*P*/d*t* (mmHg/s)	-834 ± 186	-868 ± 189	-860 ± 178
Tau	62 ± 15	62 ± 16	60 ± 14
LVSP (mmHg)	107 ± 31	111 ± 33	110 ± 32
LVEDP (mmHg)	11 ± 10	10 ± 13	10 ± 13
CI (L/min/m^2)	2.7 ± 0.9	2.8 ± 1.0	2.8 ± 0.8
PCWP (mmHg)	12 ± 6	11 ± 5	11 ± 6

LVSP, left ventricular systolic pressure; LVEDP, left ventricular end diastolic pressure; CI, cardiac index; PCWP, pulmonary capillary wedge pressure; HR, heart rate.

* $p < 0.05$; control vs. Bi-V pacing.

† $p < 0.05$; control vs. PP pacing.

4.3. Technical considerations in LV endocardial pacing

Recently, some researchers implanted LV leads transseptally. Van Gelder et al. reported transseptal LV endocardial pacing using standard techniques and equipment, without any dislodgement or thromboembolic events during follow-up [13]. Gamble et al. reported that the intraventricular transseptal approach for implantation of the LV lead would lower the risk of thromboembolism or valvular regurgitation [14]. Other approaches have been reported, such as transseptal, transaortic, or transapical, and further development of reliable and reproducible procedures and instrumentation might lead to safer and more effective LV endocardial pacing. With these procedures, left posterior fascicle permanent pacing has the potential for actual clinical use.

4.4. Limitations of the study

This study has several limitations. The sample size was small, and only hemodynamic changes in the acute phase were assessed. We had estimated the parameters of PP pacing and performed cardiac catheterization to assess the acute hemodynamic effects of BiV pacing before CRT implantation. Therefore we compared parameters among PP pacing, BiV pacing, and controls over a short period. Further studies that include more patients with longer-term follow-up are needed.

Furthermore, despite recently reported developments in LV endocardial pacing, these remain complex procedures, and are also associated with a risk of thromboembolism or valvular regurgitation, compared to conventional BiV pacing.[15] Although some researchers have tried to lower the risks in the placement of LV endocardial pacing leads, the procedure remains challenging, and must be compared with conventional CRT in the long term. Therefore, this treatment should be restricted to those who are not candidates for or did not benefit from BiV pacing.

4.5. Conclusions

The hemodynamic outcome of PP pacing in the LV endocardium was comparable to that of BiV pacing in patients with advanced heart failure.

Conflict of interest

The authors have no conflict of interest to disclose.

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