




Upgrade of cardiac resynchronization therapy by utilizing additional His-bundle pacing in patients with inotrope-dependent end-stage heart failure: a case series

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Background

His-bundle pacing (HBP) alone may become an alternative to conventional cardiac resynchronization therapy (CRT) utilizing right ventricular apical (RVA) and left ventricular (LV) pacing (BiV_{RVA+LV}) in selected patients, but the effects of CRT utilizing HBP and LV pacing (BiV_{HB+LV}) on cardiac resynchronization and heart failure (HF) are unclear.

Case summary

We presented two patients with inotrope-dependent end-stage HF in whom the upgrade from conventional BiV_{RVA+LV} to BiV_{HB+LV} pacing by the addition of a lead for HBP improved their HF status. Patient 1 was a 32-year-old man with lamin A/C cardiomyopathy, atrial fibrillation, and complete atrioventricular (AV) block. Patient 2 was a 70-year-old man with ischaemic cardiomyopathy complicated by AV block and worsening of HF resulting from ablation for ventricular tachycardia storm. The HF status of both patients improved dramatically following the upgrade from BiV_{RVA+LV} to BiV_{HB+LV} pacing.

Discussion

End-stage HF patients suffer from diffuse intraventricular conduction defect not only in the LV but also in the right ventricle (RV). The resulting dyssynchrony may not be sufficiently corrected by conventional BiV_{RVA+LV} pacing or HBP alone. Right ventricular apical pacing itself may also impair RV synchrony. An upgrade to BiV_{HB+LV} pacing could be beneficial in patients who become non-responsive to conventional BiV pacing as the His–Purkinje conduction defect progresses.

Keywords

Case report • End-stage • Heart failure • Cardiac resynchronization therapy • Intraventricular conduction defect • His-bundle pacing

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Learning points

- The upgrade from conventional BiV_{RVA+LV} pacing to BiV_{HB+LV} pacing may improve clinical status by more effectively resynchronizing both left ventricle and right ventricle in selected patients with end-stage heart failure (HF).
- Even *non-selective* capture of the His-bundle can be adequately effective when applying BiV_{HB+LV} pacing especially in patients with right bundle branch block or complete atrioventricular block.
- In clinical practice, this method may be a therapeutic option to manage end-stage HF in non-responders to conventional cardiac resynchronization therapy and one bridging therapy to cardiac transplantation.

Introduction

Cardiac resynchronization therapy (CRT) utilizing biventricular pacing of the right ventricular apex (RVA) and left ventricle (LV) (BiV_{RVA+LV}) is an established treatment for patients with reduced left ventricular ejection fraction (LVEF) and a wide QRS with left bundle branch block (BBB) pattern. Although recent studies have shown that His-bundle pacing (HBP) alone may become an alternative to conventional BiV_{RVA+LV} pacing,^{1,2} the reasons and mechanisms for better outcomes of HBP alone over BiV_{RVA+LV} pacing in selected patients remain to be clarified.

We report two patients previously utilizing BiV_{RVA+LV} pacing in whom inotrope-dependent end-stage heart failure (HF) was dramatically improved by upgrading to BiV pacing combining HBP and LV pacing (BiV_{HB+LV}).

Timeline

Case presentation

Patient 1

A 31-year-old man with no past medical history presented to our institution with orthopnoea and systemic oedema. On admission, physical examination found a respiratory rate of 23 b.p.m., regular pulse rate of 45 b.p.m, and blood pressure of 140/95 mmHg. His body height was 173 cm and body weight was 136 kg (30 kg gained in 1 month). No abnormal heart or breath sounds were noted. His brain natriuretic peptide (BNP) level was elevated to 681 pg/mL. The electrocardiogram (ECG) showed complete atrioventricular block (CAVB) with atrial fibrillation (AF) (Figure 1A). The cardiothoracic ratio on chest X-ray was 74%, and echocardiography showed reduced LVEF of 40%. His father died of cardiovascular events at age 45 years, and his grandfather had undergone pacemaker implantation. Because of his family history, co-existence of AF and CAVB, and LV

Time	Events
Patient 1	
26 months before	The patient was hospitalized with orthopnoea and severe systemic oedema [New York Heart Association (NYHA) Class IV] Atrial fibrillation (AF) and complete atrioventricular block (CAVB) with escape ventricular rhythm were observed His left ventricular ejection fraction (LVEF) was 40%
16 months before	Lamin A/C cardiomyopathy was diagnosed by a genetic test Implantation of a cardiac resynchronization therapy-defibrillator (CRT-D) utilizing biventricular pacing of the right ventricular apex (RVA) and left ventricle (LV) (BiV _{RVA+LV} pacing) was performed AF was converted to sinus rhythm by direct current cardioversion He was discharged at NYHA Class III
4 months before	He became inotrope dependent with persistence of AF (NYHA Class IV) LVEF decreased to 19% QRS duration was prolonged at 220 ms
Procedure	An additional lead for His-bundle pacing (HBP) was implanted and an upgrade to BiV _{HB+LV} pacing was performed
1 month later	He was discharged at NYHA Class II
Patient 2	
25 years ago	First anteroseptal myocardial infarction (MI) occurred, and percutaneous coronary intervention was performed
8 years ago	Stent thrombosis causing his second anteroseptal MI occurred He underwent coronary artery bypass grafting, endoventricular circular patch plasty, mitral valve plasty, tricuspid annuloplasty, and implantation of a CRT-D with a surgically implanted LV lead
1 month prior to presentation	Ventricular tachycardia (VT) storm occurred
First presentation to our institution	Catheter ablation was successfully performed for VT storm Despite elimination of VT events, heart failure (HF) and pulmonary hypertension continued to worsen (NYHA Class IV) The presence of CAVB was noted The addition of HBP and upgrade to BiV _{HB+LV} pacing was performed
90 days later	He was free from HF and VT (NYHA Class II)

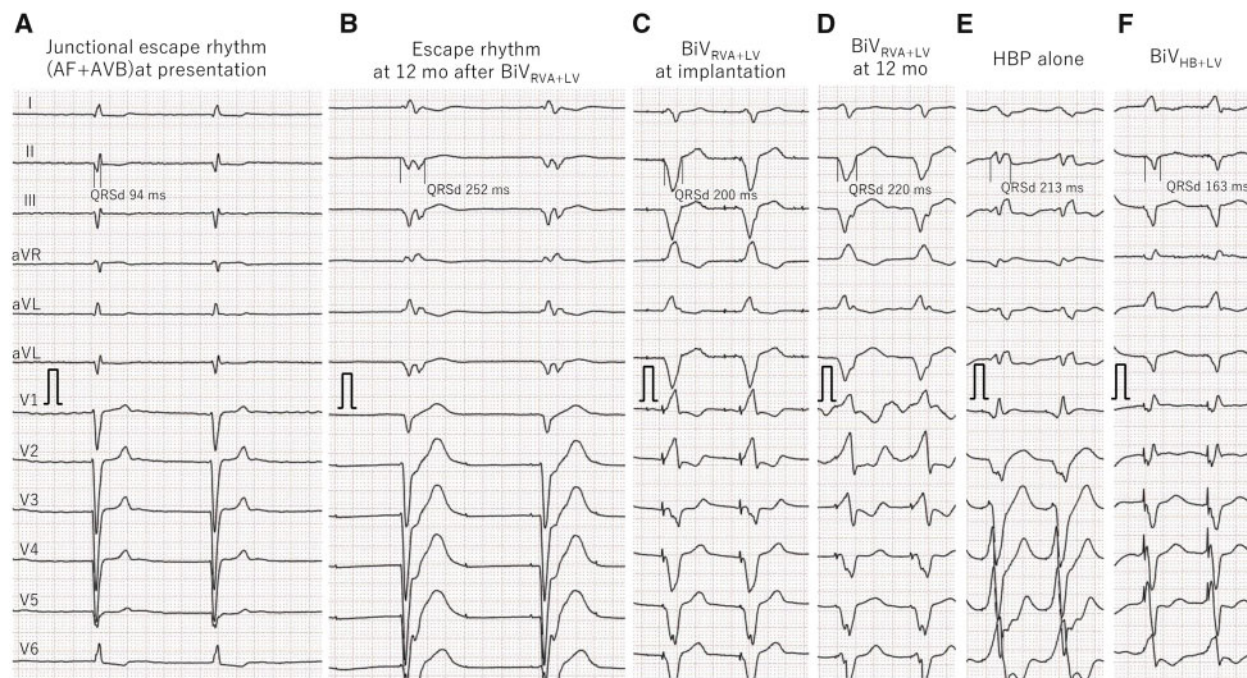


Figure 1 (Patient 1) Twelve-lead electrocardiograms during intrinsic conduction and each of the pacing configurations. See text for details. (A) Junctional escape rhythm at presentation (atrial fibrillation with complete atrioventricular block). (B) Escape rhythm 12 months after BiV_{RVA+LV} implantation. Although this escape rhythm was assumed to be a junctional rhythm, the definite origin was unclear due to the co-presence of complete atrioventricular block, permanent atrial fibrillation, and advanced impairment of the His–Purkinje system. (C) Pacing rhythm at BiV_{RVA+LV} implantation. (D) Pacing rhythm 12 months after BiV_{RVA+LV} implantation. (E) His-bundle pacing alone. (F) BiV_{HB+LV} pacing. AF, atrial fibrillation; BiV, biventricular; CAVB, complete atrioventricular block; HBP, His-bundle pacing; LV, left ventricular; mo., month; QRSd, QRS duration; RVA, right ventricular apical.

dysfunction, we suspected cardiomyopathy due to a lamin A/C (LMNA) gene mutation, and a genetic test subsequently confirmed this.

He underwent implantation of a dual-chamber CRT-defibrillator (CRT-D) for the following three reasons. (i) Optimized medical treatments including oral intake of enalapril maleate of 2.5 mg, bisoprolol of 1.25 mg, spironolactone of 50 mg, furosemide of 40 mg, and tolvaptan of 15 mg and intravenous infusion of dobutamine at 4 µg/min/kg neither reduced his body weight nor improved his HF symptoms. (ii) He was totally pacing-dependent due to CAVB.³ (iii) LVEF <50% may be a predictor of progression to end-stage HF or death among patients with lamin cardiomyopathy.⁴ Subsequently, the atrioventricular (AV) and interventricular (VV) delays were optimized by echocardiographic evaluation,⁵ and AF was converted to sinus rhythm by direct current cardioversion under oral intake of amiodarone of 200 mg daily, resulting in the improvement of New York Heart Association (NYHA) Class from IV to III. However, 12 months after the CRT implantation, AF recurred and persisted, and an echocardiogram showed a reduced LVEF of 19%. A 12-lead ECG showed a change in the paced QRS morphology (Figure 1C and D) suggesting rapid progression of the disease. He had been inotrope dependent but decided against cardiac transplantation due to the expense. We offered the option of additional HBP and upgrade of CRT as a last resort for managing his end-stage HF, to which he consented. Although

we performed mapping of the HB region with a decapolar catheter before placement of the HB lead (Model 3830: Medtronic, Minneapolis, MN, USA), a discrete HB potential could not be recorded, and the pacing threshold in most of the septal region was ≥ 5.0 V/2.0 ms, probably because of the advancement of septal fibrosis and myocardial degeneration in lamin cardiomyopathy, which did not allow evaluation of pacing output-dependent change of the QRS morphology. Furthermore, severe dilation of the right atrium (RA) and right ventricle (RV) made manipulation of the HB lead difficult (Figure 2). After lead fixation, the HBP lead was connected to the atrial port because his AF had already become the permanent form of rhythm. Although the QRS duration did not shorten compared with that of BiV_{RVA+LV} pacing (escape rhythm: 252, BiV_{RVA+LV}: 220, and HBP: 213 ms, respectively) (Figure 1B, D, and E), BiV_{HB+LV} resulted in obvious narrowing of the QRS to 163 ms (Figure 1F). We also assessed ventricular dyssynchrony with speckle-tracking two-dimensional (2D) echocardiography (QLAB11; PHILIPS) and defined the standard deviation of the time to peak strain of six segments of the RV (RV-SD) on the apical four-chamber image and that for the LV (LV-SD) on the short-axis image at the papillary muscle level (Figure 3).^{6–8} Although all pacing configurations caused worsening of RV-SD compared with the escape rhythm (possibly a junctional rhythm), the increase in the RV-SD was the mildest during BiV_{HB+LV} compared with BiV_{RVA+LV} and HBP alone (escape rhythm, 63;

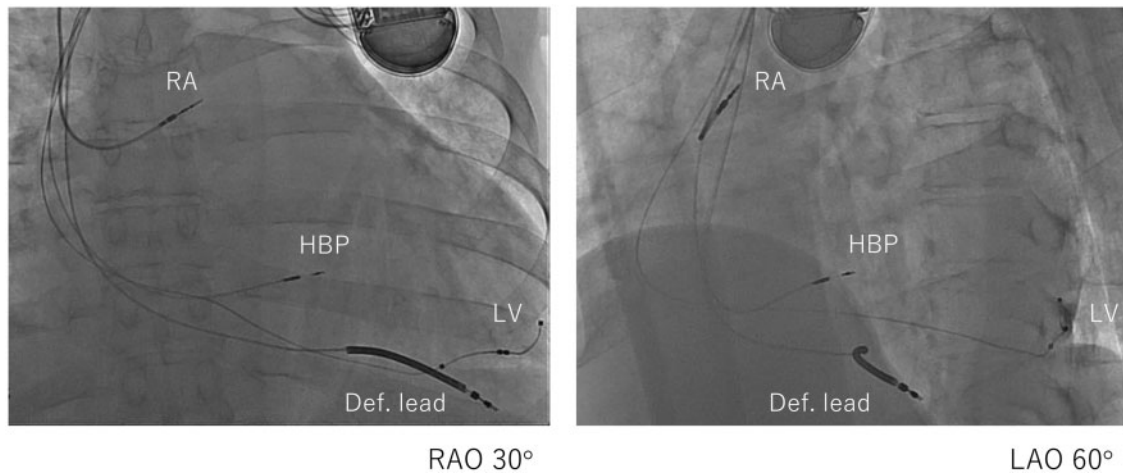
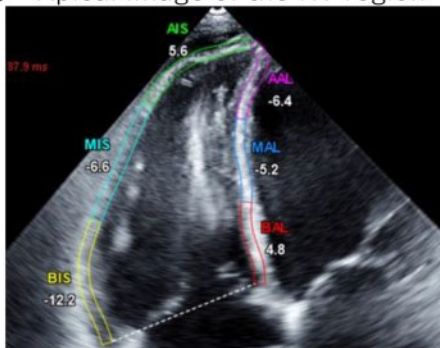
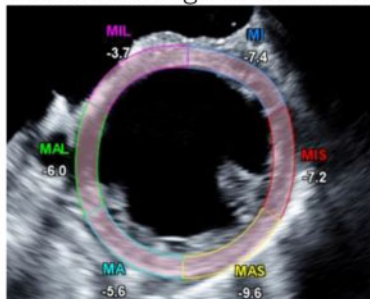


Figure 2 (Patient 1) Fluoroscopic imaging showing BiV_{HB+LV} pacing. Def., defibrillator; HBP, His-bundle pacing; LV, left ventricle; RA, right atrium.

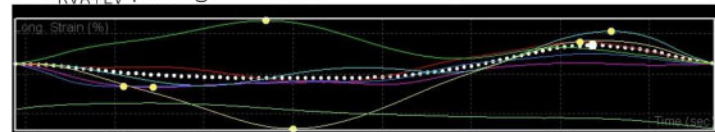
A Apical image of the RV region



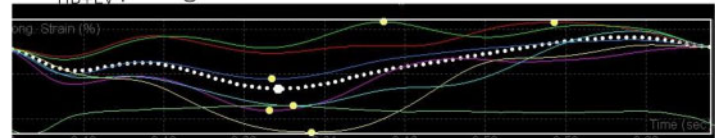
B Short-axial image of the LV region



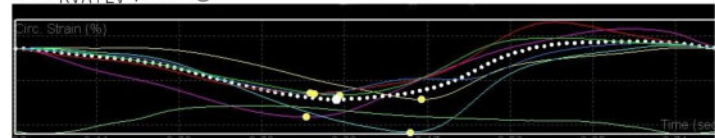
C BiV_{RVA+LV} pacing



BiV_{HB+LV} pacing



D BiV_{RVA+LV} pacing



BiV_{HB+LV} pacing

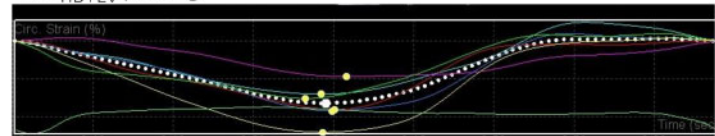


Figure 3 (Patient 1) Speckle-tracking echocardiography. (A) Semi-automatic delineation of endocardial borders and definition of the region of interest of six segments of the RV on the apical four-chamber image. (B) Region of interest of the LV on the short-axis images at the papillary muscle level. (C) Time to peak strain curve of six right ventricle segments throughout the cardiac cycle. Please note the difference in the distribution of the peak time (dots) during BiV_{RVA+LV} vs. BiV_{HB+LV} pacing. (D) Analysis of the six segments of the LV. BiV, biventricular; HB, His bundle; LV, left ventricle; RV, right ventricle.

BiV_{RVA+LV}, 151; HBP alone, 126; and BiV_{HB+LV}, 99 ms). Regarding LV synchrony, although neither BiV_{RVA+LV} nor HBP alone improved LV-SD compared with the escape rhythm, BiV_{HB+LV} did markedly

improve it (escape rhythm, 54; BiV_{RVA+LV}, 52; HBP alone, 40; and BiV_{HB+LV}, 13 ms) (Figure 4). Therefore, we programmed BiV_{HB+LV} and DDD mode with a lower rate of 85 b.p.m., AV delay of 50 ms,

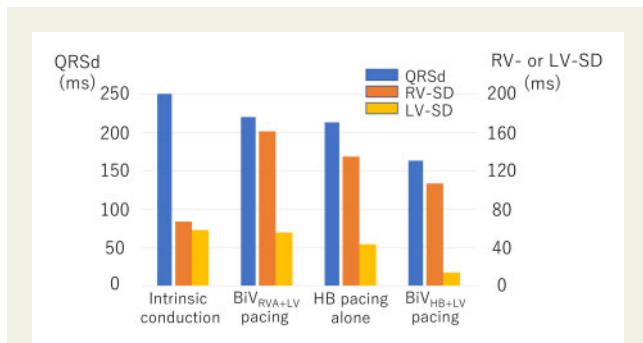


Figure 4 (Patient 1) Alterations in the QRSd, standard deviation of the time to peak strain of six segments of the right ventricle, and standard deviation of the time to peak strain of six segments of the left ventricle during intrinsic conduction, BiV_{RVA+LV} pacing, His-bundle pacing alone, and BiV_{HB+LV} pacing. BiV, biventricular; HB, His-bundle; LV, left ventricular; LV-SD, standard deviation of the time to peak strain of six segments of the left ventricle; QRSd, QRS duration; RV, right ventricular; RV-SD, standard deviation of the time to peak strain of six segments of the right ventricle.

and RV–LV delay of 20 ms with minimized RV pacing output to inactivate RVA pacing. This programming resulted in BiV_{HB+LV} pacing with a VV delay (HB–LV delay) of 70 ms without RVA pacing. Additionally, ventricular arrhythmias were detected based on just their cycle length measured by single-chamber sensing without the sudden onset criterion because of the presence of CAVB and AF in this patient.⁹ Over the week following the pacing upgrade, his haemodynamics improved dramatically, and he was discharged and has remained free from HF (NYHA Class II) for more than 13 months.

Patient 2

A 70-year-old man with ischaemic cardiomyopathy was referred to our institution for catheter ablation of ventricular tachycardia (VT) storm. Eight years prior to his presentation, he had undergone coronary artery bypass grafting, endoventricular circular patch plasty, mitral valve plasty, tricuspid annuloplasty, and CRT-D implantation with an LV lead also surgically implanted for NYHA Class IV HF, reduced LVEF of 24%, and QRS width of 154 ms. He has also suffered from chronic obstructive pulmonary disease and chronic kidney disease (serum creatinine level, 1.99 mg/dL). Physical examination revealed a pansystolic murmur (IV/VI) over the apex and no lower-limb oedema. His BNP level was elevated to 500 pg/mL. Echocardiography revealed an LVEF of 20% and pulmonary hypertension [tricuspid regurgitation pressure gradient (TRPG) of 43 mmHg].

One day after admission, catheter ablation was performed under CARTO guidance (Biosense Webster Inc., Diamond Bar, CA, USA). CARTO mapping revealed a low-voltage area in the anterior and septal walls (Figure 5).¹⁰ After elimination of all abnormal potentials within the low-voltage area, no VT could be induced.

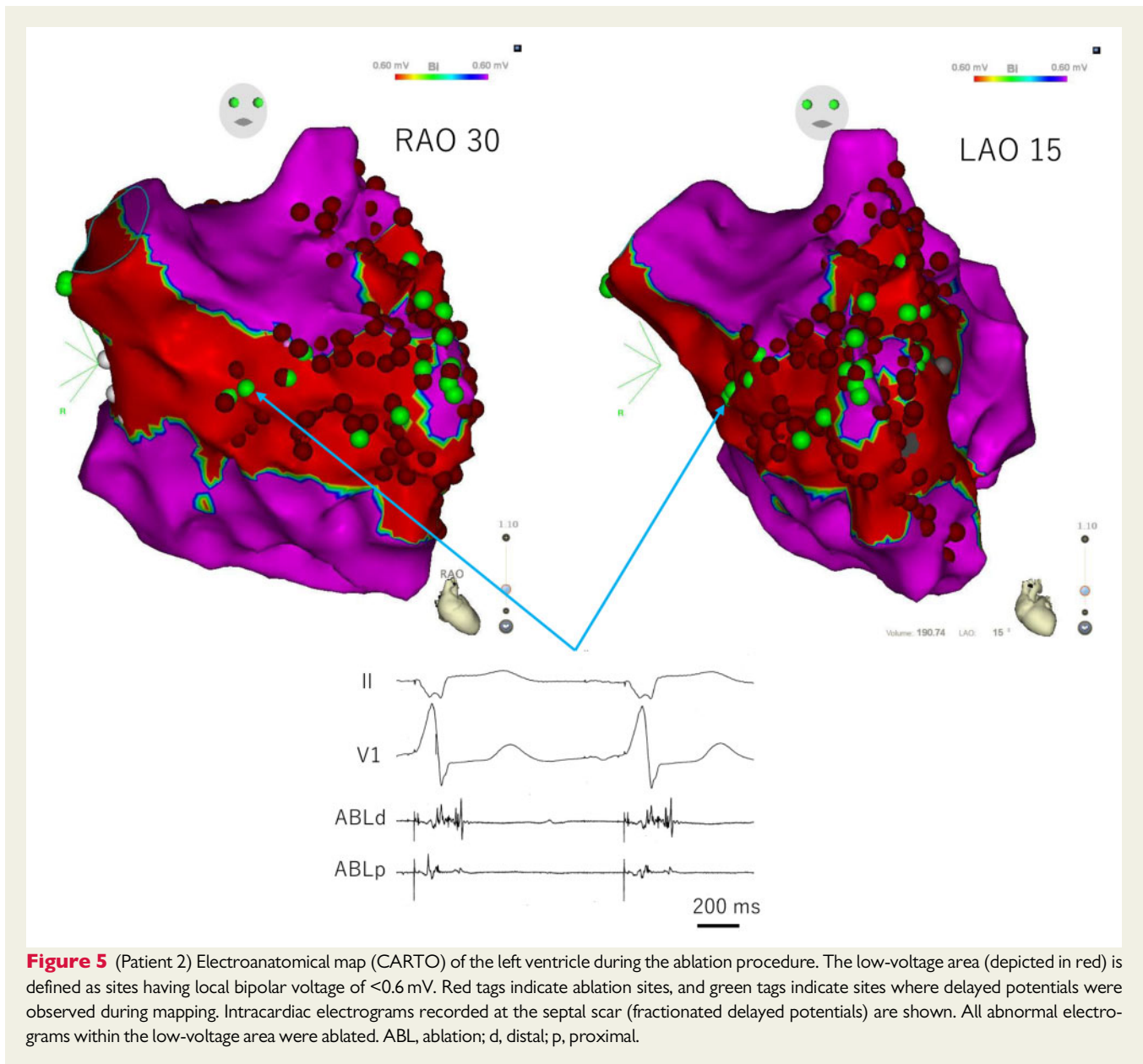
However, the patient developed progressively worsening dyspnoea and hypotension even under optimized medical therapies including oral intake of carvedilol of 10 mg, spironolactone of 50 mg, furosemide of 40 mg, tolvaptan of 15 mg, and amiodarone of 200 mg and intravenous infusion of dobutamine at 5 µg/min/kg. Despite an improved LVEF of 35%, TRPG elevation to 90 mmHg was observed

on echocardiography and respirator support was required. We were aware of the development of CAVB and a change in the QRS morphology during junctional escape rhythm that suggested injury to the left posterior fascicle (Figure 6A). We thought his haemodynamic deterioration was induced by RV and LV dyssynchrony due to CAVB caused by catheter ablation because the VT episodes were completely eliminated. We therefore decided to add a pacing lead (Model 3830, Medtronic, Inc.) at the HB region (Figure 7A). Although we initially placed the lead at the site where a HB potential was recorded, the pacing threshold at that site was too high to obtain stable permanent pacing. Alternatively, the lead was implanted at a more distal (ventricular) site where a possible right bundle branch potential was recorded (Figure 7B). During HBP, the QRS duration was not significantly shortened (186 ms, Figure 6B), so we applied BiV_{HB+LV} pacing. Fortunately, because a DF-1 lead was originally used as a defibrillator lead, we could connect the HBP lead to the RV pacing port. The pin of the original RV pacing lead was covered with a silicon cap and abandoned. Following the application of BiV_{HB+LV} pacing, the QRS narrowed from 167 to 127 ms with an optimized AV delay (atrial–HB delay: 140 ms) and VV delay (HB–LV delay: 40 ms) (Figure 6B). Over the week following the upgrade to BiV_{HB+LV}, his haemodynamics improved dramatically. Although RV-SD and LV-SD had worsened from 52 to 82 ms and 75 to 189 ms after ablation, respectively, BiV_{HB+LV} reversed the RV-SD to 53 ms and LV-SD to 82 ms (Figure 8). Unfortunately, he died from a non-cardiac cause, acute non-occlusive mesenteric infarction, 4 months after the upgrade although he had remained free from HF until that time.

Discussion

We presented two patients with inotrope-dependent end-stage HF in whom upgrade from conventional BiV_{RVA+LV} to BiV_{HB+LV} pacing clearly improved their HF status. One reason for the non-response to BiV_{RVA+LV} pacing is RV dyssynchrony produced by RVA pacing,¹¹ especially in patients without intrinsic conduction activating and synchronizing the RV, e.g. CAVB. Varma *et al.*¹² investigated RV electrical activation in HF patients by using non-invasive mapping. In HF, RVA pacing generated variable areas of slow conduction and prolonged the duration of RV activation. These unfavourable phenomena were never resolved by BiV_{RVA+LV} pacing. In contrast, LV-only pacing reduced the RV activation delay only if AV conduction was intact. In our cases, 2D echocardiographic RV-SD suggested the superiority of HBP over RVA pacing with regard to pacing-induced RV dyssynchrony.

In recent years, HBP alone has become an alternative to BiV_{RVA+LV} pacing in patients requiring CRT.^{1,2,13–15} Furthermore, a small study found that sequential HBP followed by LV pacing resulted in maximized electrical resynchronization and improvement of clinical and echocardiographic outcomes in HF patients.¹⁶ However, its optimal indication and precise mechanisms for favourable outcomes remain to be clarified. A recent interesting study investigated left septal activation in patients with left BBB patterns by using a linear multi-electrode catheter and reported that corrective HBP was observed in patients with proximal complete conduction block by recruitment of latent Purkinje fibres distal to the site of block, whereas HBP did not correct the wide QRS in patients with diffuse injury in the more

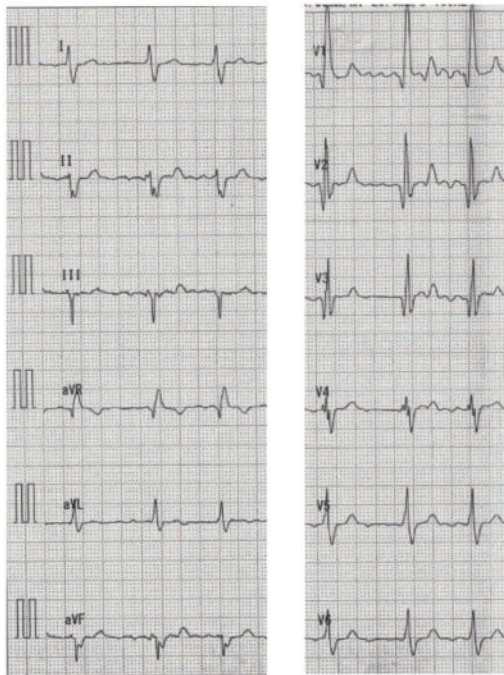


distal Purkinje system.¹⁷ Patient 1 was characterized by lengthening of the QRS duration for a short period, and Patient 2 had broad and diffuse injury of the LV anterior and septal walls (Figure 5), suggesting the presence of septal fibrosis and diffuse intraventricular conduction defect (IVCD), and these may be reasons for the failure of resynchronization by HBP alone and the superiority of $\text{BiV}_{\text{HB}+\text{LV}}$ pacing. Septal activation produced by LV pacing may also contribute to RV synchronization (RV fusion), as was indicated by the lower RV-SD in $\text{BiV}_{\text{HB}+\text{LV}}$ than with HBP alone in Patient 1. Taken together, the mechanisms behind the favourable effects of $\text{BiV}_{\text{HB}+\text{LV}}$ over $\text{BiV}_{\text{RVA}+\text{LV}}$ pacing may involve the avoidance of RVA pacing-induced RV dyssynchrony especially in patients with right BBB or CAVB (as in our two patients), and more effective correction of LV dyssynchrony especially in patients with diffuse and severe IVCD.

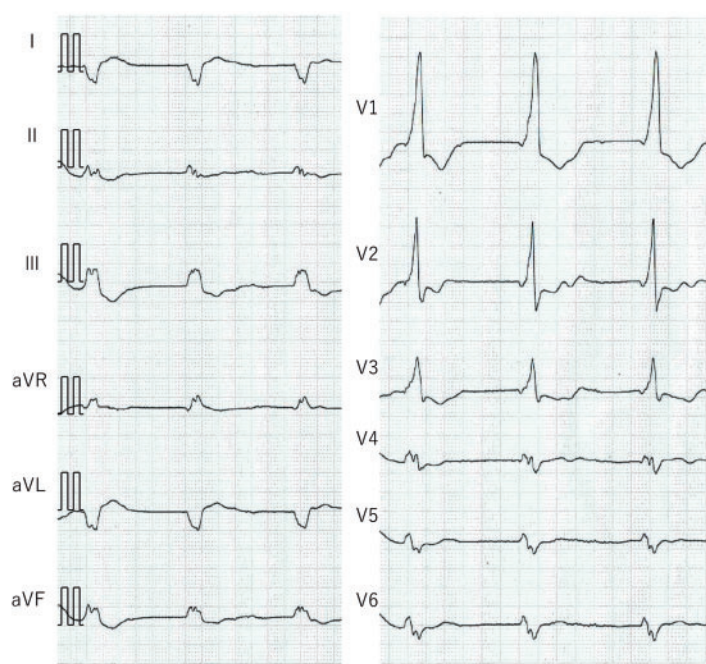
Another important finding was that *non-selective* HBP was actually applied in both patients. Although the initial goal of HBP is local and

direct capture of the HB to normalize the QRS, a completely narrow QRS is commonly difficult to achieve in patients with advanced cardiomyopathy and IVCD. It was difficult to locate the lead at the selective HB region because of anatomical problems of a severely dilated RA and RV and septal fibrosis, which is a characteristic of lamin cardiomyopathy, in Patient 1 and a high capture threshold in Patient 2. A recent study reported that haemodynamic improvement of non-selective HBP was comparable to that of selective HBP.¹⁸ Starr et al.¹⁹ investigated the intervals (in ms) from HBP to RV septal or apical sensing on the lead for back-up pacing in patients with HBP and secondarily implied that RV may be more effectively synchronized by non-selective than selective HBP in the presence of right BBB. Also, it was notable that in a study investigating the effect of HBP in patients with right BBB, QRS narrowing was more frequently achieved in non-selective HBP (19/29, 66%) than in selective HBP (10/29, 34%).²⁰

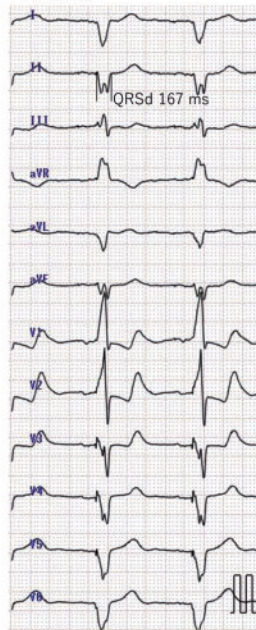
A Intrinsic conduction before ABL



Escape rhythm after ABL



B BiV_{RVA+LV} before ablation



HB pacing alone



BiV_{HB+LV} pacing



Figure 6 (Patient 2) (A) Twelve-lead electrocardiograms during ventricular activation through the intrinsic conduction before and after ablation. Left panel: Atrial fibrillation with QRS morphologies of right bundle branch block and left anterior hemiblock. Right panel: Possible junctional beats with QRS morphologies of right bundle branch block and left posterior hemiblock pattern. Although this escape rhythm was assumed to be a junctional rhythm, the definite origin was unclear due to the co-presence of complete atrioventricular block and advanced impairment of the His–Purkinje system. (B) Twelve-lead electrocardiograms during pacing. Left panel: BiV_{RVA+LV} pacing before ablation. Mid-panel: His-bundle pacing alone. Right panel: BiV_{HB+LV} pacing. ABL, ablation; BiV, biventricular; HB, His bundle; LV, left ventricular; QRSd, QRS duration; RVA, right ventricular apical.

Finally, configurations of the sensing and pacing system : 3830) to the RV pacing port of the CRT-D. However, be-
 should be discussed. We connected the HBP lead (Model : cause the sensing and pacing parameters for the LV lead had

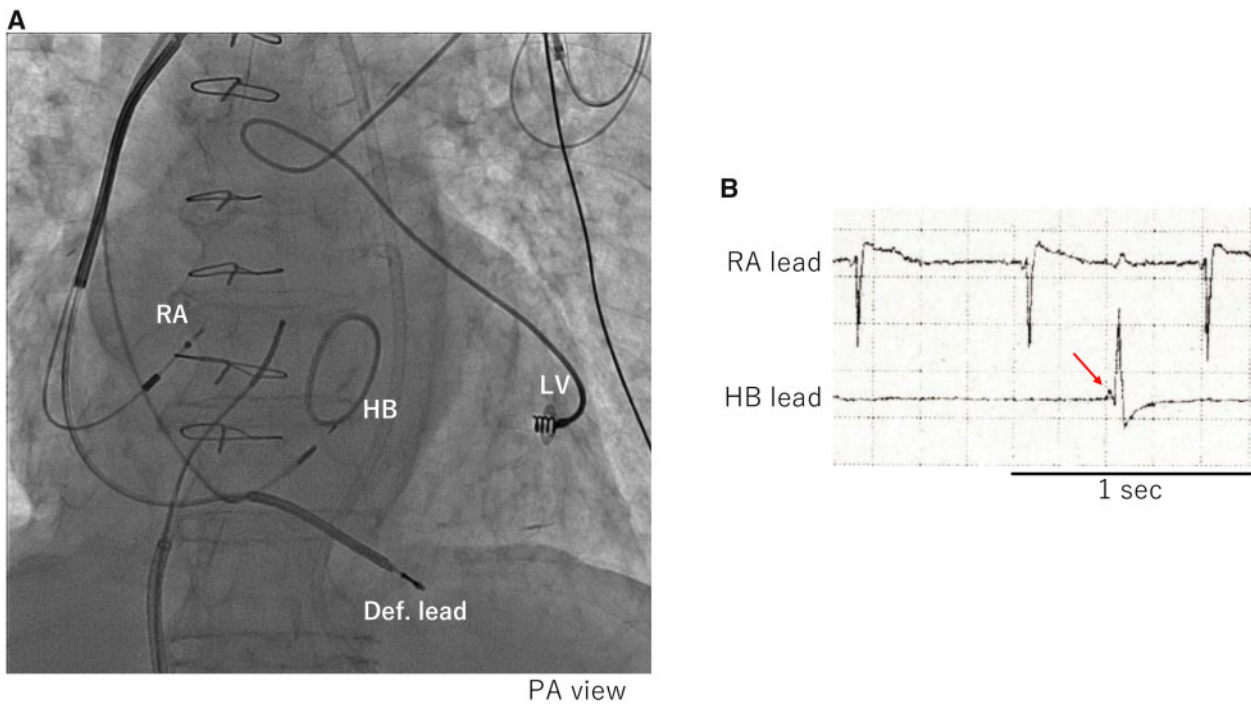


Figure 7 (Patient 2) Fluoroscopic imaging showing BiV_{HB+LV} pacing (A) and intracardiac electrograms recorded at the implantation site (B). The red arrow indicates a possible right bundle branch potential although the co-presence of complete atrioventricular block and the injured His–Purkinje system made its recording and identification difficult. Def., defibrillator; HB, His bundle; LV, left ventricle; PA, posteroanterior; RA, right atrium.

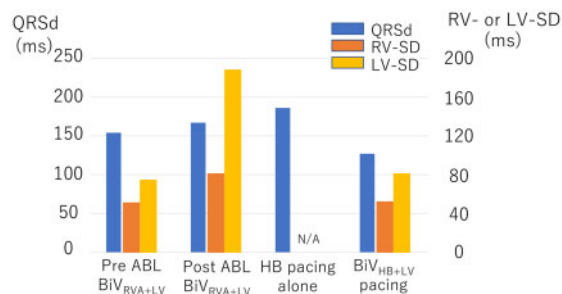


Figure 8 (Patient 2) Alterations in the QRS duration, standard deviation of the time to peak strain of six segments of the right ventricle, and standard deviation of the time to peak strain of six segments of the left ventricle during intrinsic conduction, BiV_{RVA+LV} pacing, His-bundle pacing alone, and BiV_{HB+LV} pacing. ABL, ablation; BiV, biventricular; HB, His bundle; LV-SD, standard deviation of the time to peak strain of six segments of the left ventricle; QRSd, QRS duration; RV-SD, standard deviation of the time to peak strain of six segments of the right ventricle.

been quite stable, this lead should have been connected to the RV port to detect ventricular tachyarrhythmias, and the HBP lead should have been connected to the LV pacing port. We have to consider the possibility that the HBP lead may

not be suitable for VT detection due to unstable sensing performance.¹⁶

Conclusions

The upgrade from BiV_{RVA+LV} to BiV_{HB+LV} pacing contributed to resynchronization of both the RV and LV and improved the haemodynamics and clinical status of these patients with CAVB and inotrope-dependent end-stage HF. In clinical practice, this method may become a therapeutic option or a bridging therapy to cardiac transplantation, although its effects and safety must be evaluated during longer-term follow-up.

Lead author biography



Masako Baba is a general cardiologist at Ibaraki Prefectural Central Hospital and also a graduate student at University of Tsukuba to obtain a PhD. She graduated from Toukai University, Japan. She ultimately wishes to be an expert managing advanced heart failure with cardiac implantable electronic device therapies.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patients in line with COPE guidance.

Conflict of interest: A.N. has received honoraria from Johnson and Johnson and Boehringer-Ingelheim and an endowment from Medtronic Japan and DVx. All other authors declared no conflict of interest.

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