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 BiVRVA+LV to BiVHB+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 BiVRVA+LV to BiVHB+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 BiVRVA+LV pacing or HBP alone. Right ventricular apical pacing itself may also impair RV synchrony. An upgrade to BiVHB+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
Learning points

- The upgrade from conventional BiVRVA+LV pacing to BiVHB+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 BiVHB+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) (BiVRVA+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 BiVRVA+LV pacing,1,2 the reasons and mechanisms for better outcomes of HBP alone over BiVRVA+LV pacing in selected patients remain to be clarified.

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

Timeline

| 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) (BiVRVA+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 BiVHB+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      | Ventricular tachycardia (VT) storm occurred                                                                                                                                                             |
| presentation          |                                                                                                                                                                                                        |
| First presentation to  | Catheter ablation was successfully performed for VT storm                                                                                                                                              |
| our institution       | Despite elimination of VT events, heart failure (HF) and pulmonary hypertension continued to worsen (NYHA Class IV)                                                                                     |
|                       | The presence of CAVB was noted                                                                                                                                                                         |
| 90 days later         | He was free from HF and VT (NYHA Class II)                                                                                                                                                             |

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...
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 BiVRA+LV pacing (escape rhythm: 252, BiVRA+LV: 220, and HBP: 213 ms, respectively) (Figure 1B, D, and E), BiVHB+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 BiVHB+LV compared with BiVRA+LV and HBP alone (escape rhythm, 63;
Regarding LV synchrony, although neither BiVRVA+LV nor HBP alone improved LV-SD compared with the escape rhythm, BiVHB+LV did markedly improve it (escape rhythm, 54; BiVRVA+LV, 52; HBP alone, 40; and BiVHB+LV, 13 ms) (Figure 4). Therefore, we programmed BiVHB+LV and DDD mode with a lower rate of 85 b.p.m., AV delay of 50 ms.

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

**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 BiVRVA+LV vs. BiVHB+LV pacing. (D) Analysis of the six segments of the LV. BiV, biventricular; HB, His bundle; LV, left ventricle; RV, right ventricle.
and RV–LV delay of 20 ms with minimized RV pacing output to inactivate RVA pacing. This programming resulted in BiV_{RV,LA+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. 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 valve plasty, tricuspid annuloplasty, and CRT-D implantation with an LV 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_{RV,LA+LV} to BiV_{HB+LV} pacing clearly improved their HF status. One reason for the non-response to BiV_{RV,LA+LV} pacing is RV dysynchrony produced by RVA pacing, especially in patients without intrinsic conduction activating and synchronizing the RV, e.g. CAVB. Varma et al. 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_{RV,LA+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 dysynchrony.

In recent years, HBP alone has become an alternative to BiV_{RV,LA+LV} pacing in patients requiring CRT. 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. 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.\textsuperscript{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 BiVHB\textsubscript{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 BiVHB\textsubscript{LV} than with HBP alone in Patient 1. Taken together, the mechanisms behind the favourable effects of BiVHB\textsubscript{LV} over BiVRV\textsubscript{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.\textsuperscript{18} Starr et al.\textsuperscript{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\%).\textsuperscript{20}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5}
\caption{(Patient 2) Electroanatomical map (CARTO) of the left ventricle during the ablation procedure. The low-voltage area (depicted in red) is defined as sites having local bipolar voltage of $<0.6 \text{ mV}$. Red tags indicate ablation sites, and green tags indicate sites where delayed potentials were observed during mapping. Intracardiac electrograms recorded at the septal scar (fractionated delayed potentials) are shown. All abnormal electrograms within the low-voltage area were ablated. ABL, ablation; d, distal; p, proximal.}
\end{figure}
Finally, configurations of the sensing and pacing system should be discussed. We connected the HBP lead (Model 3830) to the RV pacing port of the CRT-D. However, because the sensing and pacing parameters for the LV lead had...
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.\textsuperscript{16}

**Conclusions**

The upgrade from BiV\textsubscript{RVA}+LV to BiV\textsubscript{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 authors 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.

References

1. Barba-Pichardo R, Manovel Sanche A, Fernandez-Gomez JM, Menniti-Vazquez P, Venegas-Gamero J, Herrera-Carranza M. Ventricular resynchronization therapy by direct His-bundle pacing using an internal cardioverter defibrillator. Europace 2013;15:83–88.
2. Lustgarten DL, Crespo EM, Arkhipova-Jenkins I, Lobel R, Winget J, Koehler J et al. His-bundle pacing versus biventricular pacing in cardiac resynchronization therapy patients: a crossover design comparison. Heart Rhythm 2015;12:1548–1557.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129–2200.
4. Kumar S, Baldinger SH, Gandjikchh E, Maury P, Sellal J-M, Androulakis AFA et al. Long-term arrhythmic and nonarrhythmic outcomes of ICD implantation: a single-center experience. J Am Coll Cardiol 2016;68:2299–2307.
5. Barold SS, Ilercil A, Herweg B. Echocardiographic optimization of the atrioventricular and interventricular intervals during cardiac resynchronization. Europace 2008;10:888–895.
6. Murata M, Tsugur T, Kawakami T, Kataoka M, Minakata Y, Endo J et al. Right ventricular dysynchrony predicts clinical outcomes in patients with pulmonary hypertension. Int J Cardiol 2017;228:912–918.
7. Maruo T, Sato Y, Yamada S, Arita T, Ishizu T, Shiga T et al. The Speckle Tracking Imaging for the Assessment of Cardiac Resynchronization Therapy (START) study. Circ J 2015;79:613–622.
8. Badagliacca R, Reali M, Pescia R, Pecozza B, Papa S, Mezzapesa M et al. Intraventricular dysynchrony in idiopathic, heritable, and anorexigen-induced pulmonary arterial hypertension: clinical impact and reversibility. JACC Cardiovasc Imaging 2015;8:642–652.
9. Burt H, Keene D, Whinnett Z, Zanon F, Vijayaraman P. Device programming for His bundle pacing. Circ Arrhythm Electrophysiol 2019;12:e006816.
10. Yoshida K, Sekiguchi Y, Tanoue K, Endo M, Suzuki A, Kanemoto M et al. Feasibility of targeting catheter ablation to the markedly low-voltage area surrounding infarct scars in patients with post-infarction ventricular tachycardia. Circ J 2008;72:1112–1119.
11. Lee KL, Burnie JE, Mullen TJ, Hettick DA, Tse HF, Lau CP. Avoidance of right ventricular pacing in cardiac resynchronization therapy improves right ventricular hemodynamics in heart failure patients. J Cardivasc Electrophysiol 2007;18:497–504.
12. Varma N, Jia P, Ramanathan C, Rudy Y. RV electrical activation in heart failure during right, left, and biventricular pacing. JACC Cardiovasc Imaging 2010;3:567–575.
13. Sharma PS, Dandamudi G, Herweg B, Wilson D, Singh R, Naperkowski A et al. Permanent His bundle pacing as an alternative to biventricular pacing for cardiac resynchronization therapy: a multicenter experience. Heart Rhythm 2018; 15:413–420.
14. Aijola OA, Upadhyay GA, Macias C, Shivkumar K, Tung R. Permanent His bundle pacing for cardiac resynchronization therapy: Initial feasibility study in lieu of left ventricular lead. Heart Rhythm 2017;14:1353–1361.
15. Vijayaraman P, Dandamudi G, Zanon F, Sharma PS, Tung R, Huang W et al. Permanent His bundle pacing: recommendations from a multicenter His Bundle Pacing Collaborative Working Group for standardization of definitions, implant measurements, and follow-up. Heart Rhythm 2018;15:460–468.
16. Vijayaraman P, Herweg B, Ellenbogen KA, Gajek J. His-optimized cardiac resynchronization therapy to maximize electrical resynchronization. Circ Arrhythm Electrophysiol 2019;12:e006934.
17. Upadhyay GA, Cherian T, Shatz D, Beaser AD, Aziz Z, Ozcan C et al. Intracardiac delineation of septal conduction in left bundle-branch block patterns. Circulation 2019;139:1876–1888.
18. Zhang J, Guo J, Hou X, Wang Y, Qian Z, Li K et al. Comparison of the effects of selective and non-selective His bundle pacing on cardiac electrical and mechanical synchrony. Europace 2018;20:1010–1017.
19. Starr N, Dayal N, Domenichini G, Stettler C, Burri H. Electrical parameters with heart failure and right bundle branch block. Circ Arrhythm Electrophysiol 2018;11:e006613.