Ventricular sense response pacing in cardiac resynchronisation therapy: a potentially effective treatment option for heart failure in patients with atrial fibrillation

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SUMMARY

Cardiac resynchronisation therapy (CRT) for atrial fibrillation (AF) with intraventricular conduction and low cardiac output may not allow high-frequency biventricular pacing (BiVP). To this end, drugs and ablation treatments are commonly used. Ventricular sense response pacing (VSRP) senses self-pulse and can produce a state comparable with BiVP. If found to be effective for cardiac resynchronisation, the benefit of CRT with VSRP is expected to extend to patients with AF. Herein, we describe the case of a man in his early 60s with low cardiac output caused by AF and left bundle branch block. CRT-defibrillator (CRT-D) implantation was performed, and VSRP was applied. We found VSRP to be more effective in improving cardiac function than drug-induced BiVP. VSRP may become an effective treatment option following CRT-D implantation in patients with AF.

BACKGROUND

Cardiac resynchronisation therapy (CRT) has been proven effective in patients with left ventricular systolic dysfunction and intraventricular conduction disorders.[1 2] However, there is still no consensus on the effects of CRT in patients with atrial fibrillation (AF). In cases of AF, atrial-ventricular timing cannot be accurately determined because of irregularities in atrial contraction and conduction, rendering it difficult to obtain high-frequency biventricular pacing (BiVP). High-frequency pacing has been shown to improve prognosis,[3] and -blockers, which can suppress atrioventricular conduction, are used to obtain high-frequency pacing in patients with AF following CRT-device implantation. In cases of low cardiac function, careful administration of these drugs is required because increasing dosages risk exacerbation of heart failure caused by negative inotropic action. Ventricular sense response pacing (VSRP), which is a feature of Medtronic's CRT, creates a state comparable to that created by BiVP by pacing after detecting R waves. The clinical effectiveness of the VSRP approach for AF treatment is promising but requires further real-world substantiation. Herein, we describe a case in which assessment by cardiopulmonary exercise testing (CPX) revealed greater improvement in exercise tolerance and cardiac function following VSRP than following drug-induced high-frequency pacing in a patient with AF and an implanted CRT-defibrillator (CRT-D).

CASE PRESENTATION

The patient was a man in his early 60s who was diagnosed with AF and asymptomatic myocardial ischaemia about 2 years ago, following which a drug-eluting stent was implanted in the right coronary artery. Over the subsequent 5 months, the patient was admitted for congestive heart failure and an additional diagnosis of complete left bundle branch block (CLBBB) was made. He was discharged from the hospital with prescriptions for standard heart failure medications as well as diuretics. However, he was again admitted for congestive heart failure in this case. He was receiving 1.25 mg bisoprolol and 2 mg candesartan on admission. The dose of each drug was carefully increased; however, his heart failure worsened, and he developed symptomatic hypotension. Therefore, 0.125 mg digoxin and 2.5 mg pimobendan were added. However, his heart failure symptoms did not improve. Transthoracic echocardiography (TTE) using the EPIQ 7 ultrasound system (Philips) revealed decreased left ventricular contractility, and his low cardiac function was believed to have been caused by the CLBBB. Consequently, he was transferred to our hospital for ventricular resynchronisation therapy owing to New York Heart Association class IV despite receiving standard heart failure therapies administered at the maximum tolerated doses.

The patient's medical history included hypertension and diabetes, with a Brinkman index of 1600. He smoked 40 cigarettes per day for 40 years but quit smoking 4 years prior to presentation (at approximately 60 years old). He reported drinking approximately 500 mL of beer per day before presentation. His family history was unremarkable. At presentation, the patient was taking 1.25 mg bisoprolol, 15 mg rivaroxaban (standard dosage in Japan), 2 mg candesartan, 60 mg azosemide, 15 mg tolvaptan, 2.5 mg pimobendan, 0.125 mg digoxin, 5 mg linagliptin, 10 mg empagliflozin and 15 mg lansoprazole. On presentation, his blood pressure was 124/60 mm Hg, and his heart rate was 85 bpm. No heart murmur was detected, but his heartbeat was irregular. Physical examination showed no evidence of orthopnoea, but he had severe oedema in his lower legs. Laboratory assessments revealed a B-type natriuretic peptide (BNP) level of 1839 pg/mL (reference range, 0–18.9 pg/mL). Despite implementing conventional drug treatments, the patient's medical history and clinical findings at presentation

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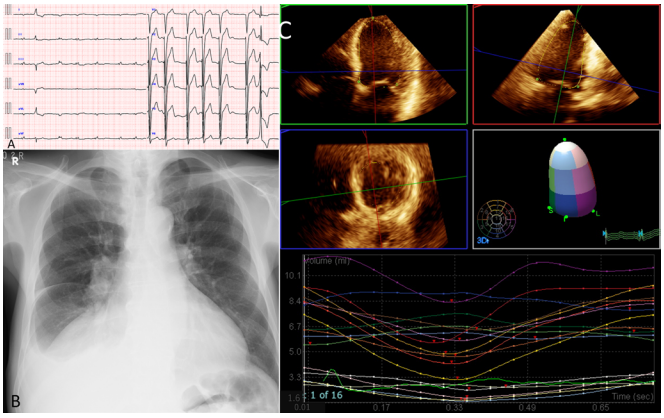

Figure 1 (A) ECG at presentation displaying characteristic features of atrial fibrillation (QRS width, 152 ms). The patient's rhythm was further compromised by complete left bundle branch block. (B) Chest X-ray showing a cardiothoracic ratio of 60% and right pleural effusion. (C) 3D strain analysis performed using the EPIQ 7 ultrasound system and processed using QLAB 10 software (Philips), showing failure of left ventricular synchronisation.

indicated early and recurrent re-exacerbation of heart failure. An alternative approach was needed to improve patient outcome because the treatment of heart failure in this patient was ineffective with drugs alone.

INVESTIGATIONS

The patient's ECG revealed an irregular ventricular rate with a broad QRS complex (QRS width was 152 ms; figure 1A), typical of AF. The cardiothoracic ratio was 60% on the chest radiograph, and the right rib diaphragm angle was dull (figure 1B).

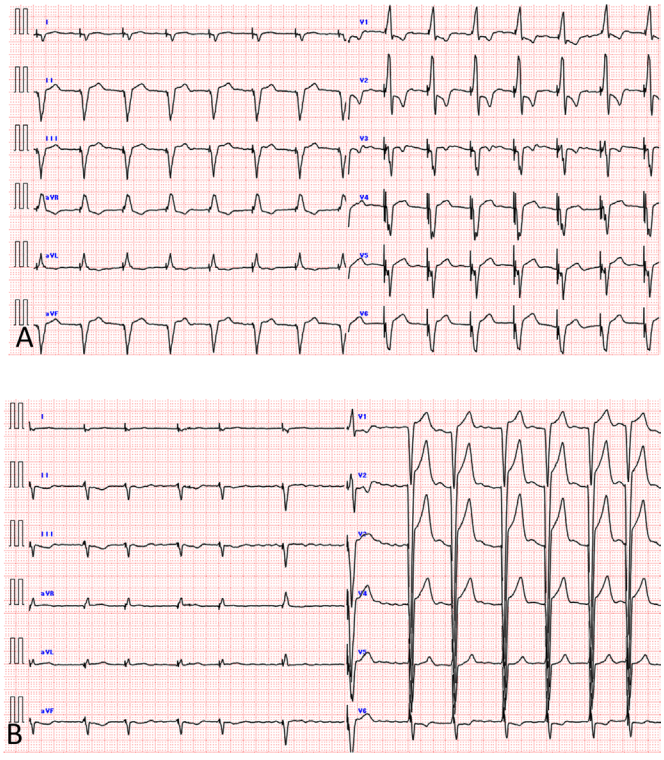

Figure 2 (A) ECG after biventricular pacing (QRS width, 133 ms; HR, 86 bpm). (B) ECG after ventricular sense response pacing (QRS width, 123 ms; HR 77 bpm). HR, heart rate.

Table 1 Comparison of biventricular pacing and ventricular sense response pacing effects on cardiac function after CRT-defibrillator implantation in a patient with atrial fibrillation

	BiVP	VSRP
ECG findings		
QRS width (ms)	133	123
TTE findings; (HR 85 bpm)		
SV (mL)	34	40
SPWMD time (ms)	92	28
EF (%)	36	40
CPX measurements		
AT VO_2 (mL/min/kg)	9.6	10.5
Peak VO_2 (mL/min/kg)	11.2	11.4
Maximum $PETCO_2$	5.60	6.01
Lowest VE/VCO_2 ratio	38.8	38.1
VE/VCO_2 slope	38.1	34.9
$\Delta VO_2/\Delta WR$ ratio	5.37	5.72

AT, anaerobic threshold; BiVP, biventricular pacing; CPX, cardiopulmonary exercise testing; EF, ejection fraction; HR, heart rate; $PETCO_2$, end-tidal carbon dioxide pressure; SPWMD, septal-to-posterior wall motion delay; SV, stroke volume; TTE, transthoracic echocardiography; VCO_2, carbon dioxide output; VE, ventilation; VO_2, peak oxygen uptake; VSRP, ventricular sense response pacing; WR, work rate.

TTE identified a left ventricular end-diastolic diameter (LVDd) of 62 mm and a left ventricular ejection fraction (LVEF) of 20%. The septal-to-posterior wall motion delay (SPWMD) time was 151 ms, and a dyssynchronous pattern was observed by 3D strain analysis (figure 1C) using TTE and QLAB 10 ultrasound quantification software (Philips). Coronary angiography showed no significant stenosis in the coronary arteries, including in the previously treated right coronary artery. In addition, CPX was performed. Oscillatory ventilation was observed; the anaerobic threshold (AT) was 7.8 mL/min/kg, and the peak oxygen uptake (VO_2) was 9.4 mL/min/kg. These findings indicated a high degree of impaired exercise tolerance.

The clinical determination in this case was ventricular synchronisation disorder resulting in drug-refractory low cardiac output. Although such a case would typically be indicated for CRT, the concomitant AF in this patient could potentially preclude attainment of high-frequency BiVP. Since VSRP has previously been reported to be effective in treating heart failure when applied to CRT,4 we decided to include VSPR in our CRT approach. We hypothesised that our patient might therapeutically benefit if we could achieve and sustain a state comparable to that achieved with BiVP.

A CRT-D (Claria MRI Quad CRT-D; Medtronic) was implanted in the left chest. An RV lead was placed in the apical septum of the right ventricle, an LV lead was placed in the left marginal cardiac vein of the left ventricle, and an RA lead was placed in the right atrial appendage. The setting mode applied was VVIR 70–120 ppm+VSR system. The resting heart rate after implantation was 80 bpm, which was mainly accredited to VSRP. ECG, TTE and CPX were used to evaluate the effects of VSRP on cardiac function compared with those of the high-frequency BiVP setting combined with increasing the bisoprolol dose from 1.25 mg to 2.5 mg (table 1). The ECGs (figure 2A and figure 2B), ultrasound images and CPX data showed VSRP to be more effective at restoring cardiac function. Therefore, the bisoprolol dose was set at 1.25 mg, as the standard practice during VSRP. The patient then underwent cardiac rehabilitation and an improvement in cardiac function was observed.

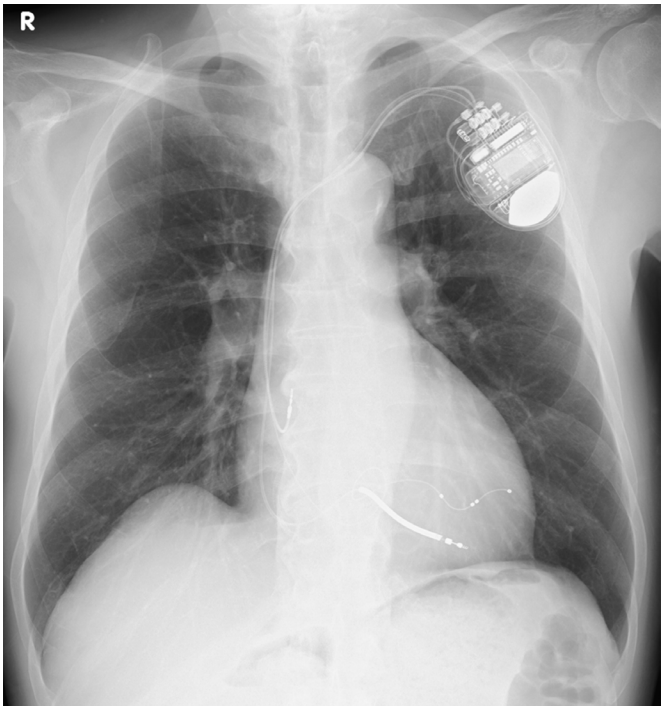

Figure 3 Chest X-ray at the 2-year follow-up showing a cardiothoracic ratio of 49% with no pleural effusion.

Patient's perspective

I was hospitalised for my first heart failure, but shortness of breath during exertion did not improve after discharge. I was readmitted to the hospital with heart failure in less than a few months, despite consideration of drugs and lifestyle. By implanting CRT and performing cardiac rehabilitation continuously this time, shortness of breath was completely eliminated, and I can go about my daily life without any problems. I am very grateful.

Learning points

- The ventricular sense response pacing feature of Medtronic cardiac resynchronisation therapy implantable devices offers an opportunity to imitate high-frequency biventricular pacing in patients with atrial fibrillation.
- In this case, the application of ventricular sense response pacing after cardiac resynchronisation therapy-defibrillator implantation produced a sustained improvement in cardiac function in a patient diagnosed with atrial fibrillation and a complete left bundle branch block.
- By enabling evaluation of cardiac function in the resting state and during exercise, cardiopulmonary exercise testing provided an effective alternative to transthoracic echocardiography for optimising pacing settings for cardiac resynchronisation therapy.
- Application of the cardiopulmonary exercise testing approach successfully guided the decision on optimal drug dosage and personalised pacing settings with notable success in this case.

OUTCOME AND FOLLOW-UP

Two years after CRT-D implantation, the patient's BNP level was 61 pg/mL, and the cardiothoracic ratio was 49% on chest X-ray (figure 3). TTE demonstrated improvements in the LVDd and LVEF (59 mm and 45%, respectively). During CPX, the AT was 11.8 mL/min/kg and the VO_2 was 17.0 mL/min/kg.

DISCUSSION

The present case emphasises the following clinical elements of applying VSRP to CRT in patients with AF: (1) application of VSRP during CRT improves cardiac function compared with application of conventional BiVP and drug enhancement and (2) CPX is an effective alternative to TTE for optimisation of CRT pacing settings and determining final drug dosages.

High-frequency BiVP has been reported to improve prognosis in patients with CRT implants. In cases of normal sinus rhythm, it is possible to optimise the atrial-synchronous ventricular pacing and obtain high-frequency BiVP. However, in cases of AF, atrioventricular timing cannot be accurately determined because of irregular atrial contraction and atrioventricular conduction. Therefore, obtaining high-frequency BiVP in patients with AF is challenging. The VSR system is a feature of Medtronic's CRT technology that uses right and left ventricular leads to affect pacing after autologous pulse detection. In other words, pacing is produced from self-heartbeat sensing. Although there is an associated timing error, VSRP is expected to create a state analogous to BiVP despite the irregular ventricular contraction caused by AF. In the present case, VSRP produced an improved QRS complex on ECG and better SPWMD timing during TTE compared with BiVP. Further, a sustained improvement in LVDd and LVEF was noted after application of VSRP, and the patient did not experience any adverse cardiovascular events between implantation and follow-up (2 years postimplantation). Therefore, the approach was considered successful in countering heart failure and restoring cardiac function in this case. In contrast, the β-blocker dose was not increased in this patient because VSRP was expected to improve cardiac function and exercise tolerance more than BiVP. However, the standard treatment for heart failure is to use the maximum possible drug doses, including β-blockers, and it might have been acceptable to consider increasing the heart failure drug doses during follow-up to reach the maximum possible volume.

We used Medtronic's VSR system. Abbott Vascular's BiV Trigger Mode system, Biotronik's Triggering system and Boston Scientific's Bi Ventricular Trigger system are similar to the Medtronic system; however, MicroPort's CRT does not have the same functionality.

The heart rate is closely associated with cardiac output during exercise. In patients undergoing CRT, it is important to evaluate the cardiac function at rest and during exertion for optimisation of pacing settings. Typically, TTE is used to optimise pacing during CRT[5 6] and can determine stroke volume from a single stable heartbeat, such as in sinus rhythm. However, optimisation of pacing by TTE is less accurate with irregular heartbeats—such as in AF—and evaluation of cardiac function during exertion is impractical using this method. Therefore, we used CPX as an alternative modality for optimising pacing settings. CPX can be used to evaluate the severity of heart failure and the state of cardiac function during exercise by calculating the lowest minute ventilation and carbon dioxide output ratio[7] and end-tidal carbon dioxide pressure,[8] respectively. Therefore, CPX represents an effective alternative to TTE in patients

with AF that offers an added advantage of exercise tolerance assessment.

In patients with AF, β-blocker doses can be increased to achieve high-frequency BiVP. Atrioventricular node ablation can be performed in patients unable to tolerate increased β-blocker doses.[9] However, in some cases, the negative inotropic effect and physiological heart rate response are lost, resulting in reduced cardiac function during exercise. However, it may be possible to optimise drug dosage and pacing settings concurrently using CPX, which would guide an individualised treatment strategy tested during circumstances of exertion. Further, VO_2 recorded during CPX is a measure of exercise tolerance and is a predictor for improved long-term prognosis in patients with compromised cardiac function.[10] CPX-derived measurements may also guide appropriate cardiac rehabilitation by determining the optimum exercise intensity. In our patient, the CLBBB diagnosis presented an additional challenge to conventional CRT. In such a case, preceding LV lead pacing may be more effective in resynchronising ventricular contractions because the CLBBB may re-delay conduction in the left ventricular sidewall. However, VSRP may be an effective alternative, and this is supported by the successful outcome of the patient in this case.

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Future studies are needed to determine whether the approximate BiVP system, including VSRP, is effective in patients with difficulty obtaining high-frequency BiVP.

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