Benefit of Rate Response with Closed-Loop Stimulation in Patients with Difficult Hemodialysis

Toshiko Nakai, MD, Yukitoshi Ikeya, MD, Naotoshi Tsuchiya, ME, Hiroaki Mano, MD, Sayaka Kurokawa, MD, Koichi Nagashima, MD, Kimie Ohkubo, MD, Ichiro Watanabe, MD and Yasuo Okumura, MD

Summary

Rate-responsive pacing is known to improve quality of life (QOL) in patients with sick sinus syndrome and chronotropic incompetence. However, the sensors for rate response include accelerometers, closed-loop stimulation (CLS), and minute ventilation sensors (MV sensors), each of which has a different mode of action. For this reason, it is important to select appropriate sensors that match the daily habits and behavioral patterns of the patient. For example, young and active patients are expected to have a rate increase when an accelerometer is used, while elderly patients and patients with a physical disability who are only able to move slowly often have a poor response to the accelerometer. MV sensors are therefore better suited to these patients. Furthermore, CLS is considered effective for patients who require an increase in heart rate when at rest, for example, patients undergoing maintenance dialysis.

We describe a representative case, demonstrating the effectiveness of closed-loop stimulation in a patient with hypotension during dialysis.

Key words: Pacemaker, Chronotropic incompetence, Rate response sensor

R
te-responsive pacing is an optional feature that helps improve the QOL in patients who have an insufficient heart rate, due to conditions like sick sinus syndrome (SSS) or chronotropic incompetence (CI). Patients who need a pacemaker have a varied heart rate response to physical or mental activity. Depending on the device manufacturer, there are several different sensors for rate-responsive pacing available. Thus, it is important to understand a patient’s status, lifestyle, habits and activities, and select the right sensor for the patient. Here, we report a case in which we selected a rate-responsive function that uses closed-loop stimulation, and confirmed its effect in a patient on dialysis. Using this case, we would like to emphasize the importance of rate-responsive pacing and device selection in improving patient QOL.

Case Report

The patient is a 74-year-old male who has received maintenance dialysis for nephrosclerosis for over 10 years and has a history of cerebral infarction and angina pectoris. A DDD pacemaker (Adapta DR, Medtronic) was implanted 8 years ago in 2012 for sick sinus syndrome; however, paroxysmal atrial fibrillation became chronic one year after implantation, resulting in VVI mode pacing. In addition, the patient experienced a marked decrease in blood pressure during dialysis, which was accompanied by a feeling of malaise, and the use of a hypertensive agent became unavoidable. About one year after pacemaker implantation, aortic valve replacement and coronary artery bypass grafting were performed due to progression of aortic stenosis and the onset of symptoms of cardiac failure. However, management of the patient’s cardiac failure continued to be difficult after the operation, and cardiac function deteriorated, with dependence on ventricular pacing and an ejection fraction (EF) of 34%. As a result, we decided to upgrade to a cardiac resynchronization therapy-pacemaker (CRT-P). Taking the difficulties encountered during hemodialysis into account, the CRT-P produced by Biotronik (Evia-HF, Biotronik, Berlin, Germany) was selected with the expectation that the rate could be increased by modifying the rate response using CLS. In order to evaluate the rate response as well as changes in blood pressure during dialysis, 24-hour Holter electrocardiogram (ECG) monitoring was performed after setting the accelerometer and CLS parameters to observe the changes in rate.

Upgrade to CRT-P: As a result of coronary sinus (CS) angiography performed prior to implantation, a candidate branch was observed in the posterolateral section. When
the left ventricular (LV) lead was inserted into the posterolateral branch and measurement was performed using a pacing system analyzer (PSA), satisfactory sensing and threshold were observed, and there was no stimulation of the phrenic nerve. For this reason, the LV lead was implanted in this area (Figure 1). An indwelling right ventricular lead had previously been placed in the apex and as there were no signs of problems in relation to lead impedance and threshold its use was continued. On the electrocardiogram, pacing QRS duration was shortened from 198 ms to 154 ms (Figure 2).

**Course of events:** The symptoms of cardiac failure improved after upgrading the pacemaker to CRT. Echocardiography showed an improvement in EF from 34% to 43%, and the left ventricular volume showed a reduction in end diastolic volume/end systolic volume from 141/86 mL to 119/68 mL; the patient was therefore considered to be a responder. We turned on the accelerometer rate response during the initial two months after the upgrade to CRT and only then switched to CLS rate response mode. The results of 24-hour Holter monitoring, which was performed during each period to evaluate the rate response function, showed a higher heart rate in response to the CLS sensor compared to the accelerometer (Table I), with a stable course and no decrease in blood pressure during HD. Determinations of heart rate and blood pressure during dialysis before the upgrade to CRT are shown in the graph (Figure 3). Initially, this patient had to take the hypertensive agent midodrine during every HD session to maintain his blood pressure. Figure 4 shows the values for

---

**Figure 1.** Chest X-ray showing the lead position. Left ventricular lead is placed in the lateral branch of the coronary sinus.

**Figure 2.** Electrocardiogram before and after CRT. Ventricular pacing is shown because of the presence of atrial fibrillation. QRS = 198 ms was observed before CRT, while this was shortened to QRS = 154 ms after CRT.
Table 1. Rate Changes Recorded on 24-Hour Holter Monitor: Comparison Between Different Sensors

| Time, during HD | Accelerometer | Closed Loop Stimulation |
|----------------|---------------|-------------------------|
|                | Max HR (bp/min) | Ave HR (bp/min) | Min HR (bp/min) | Max HR (bp/min) | Ave HR (bp/min) | Min HR (bp/min) |
| 9:00           | 70             | 60                     | 59              | 79              | 68              | 63              |
| 10:00          | 65             | 60                     | 59              | 83              | 71              | 65              |
| 11:00          | 66             | 60                     | 59              | 80              | 69              | 64              |
| 12:00          | 65             | 60                     | 59              | 82              | 70              | 64              |
| 13:00          | 83             | 61                     | 59              | 134             | 85              | 66              |
| Total Heart Beats | 86,459 beats | 103,300 beats |
| Max, Ave, Min in a day | 91, 61, 50 | 134, 71, 58 |

HR indicates heart rate; Max, maximum; Ave, average; and Min, minimum.

Discussion

The use of a rate response function is expected to improve QOL for patients with pacemakers who have sick sinus syndrome or chronotropic incompetence as complications. However, there are several types of rate response sensor among currently available cardiac implantation devices, and a satisfactory rate response may not be obtained for a particular sensor, depending on the case. While an accelerometer is considered beneficial for patients who are able to move around actively, this is not suitable for elderly patients who are only capable of moving slowly, and in particular for certain types of energetic movement such as swimming. In such cases, a minute ventilation (MV) sensor is considered useful. In addition, CLS is capable of responding not only to physical activities but also to the patient’s emotional state, allowing rate responsiveness when an increase in heart rate is required during rest. As described here, sensors have advantages and disadvantages for different activity patterns, and an appropriate model needs to be selected on an individual patient basis.

In this case, an upgrade to CRT and CLS was found to be effective in a patient with cardiac failure who experienced difficulty during dialysis due to the inability to maintain blood pressure and heart rate during HD after the upgrade to CRT. In Table II we compare the average values during HD, obtained over the 5 days that followed the upgrade to CRT with the accelerometer, and similarly following CLS. The average blood pressure and heart rate with CLS were significantly higher than that with the accelerometer. Blood pressure before the CRT upgrade was too low to continue dialysis, however, after the CRT upgrade, blood pressure was high enough to allow dialysis even without CLS function. Blood pressure with CLS was however much higher than with the accelerometer. While the reasons for this could not be fully explained, as the accelerometer was switched on for two months and CLS used thereafter, we might speculate that two months of CRT improved cardiac function, contributing to an increase in blood pressure. The administration of a hypertensive agent was no longer required as subjective symptoms during dialysis had improved and blood pressure was maintained.
Table II. Blood Pressure and Rate Changes: Comparison of Different Sensors

|                  | Accelerometer | Closed-loop Stimulation | P-value |
|------------------|---------------|--------------------------|---------|
| **Systolic BP (mmHg)** |               |                          |         |
| Overall Average   | 117 ± 12      | 152 ± 21                 | < 0.0001|
| HD start          | 114 ± 19      | 165 ± 7                  |         |
| 1 hour            | 114 ± 11      | 176 ± 16                 |         |
| 2 hours           | 105 ± 12      | 164 ± 15                 |         |
| 3 hours           | 116 ± 17      | 136 ± 11                 |         |
| HD End            | 113 ± 5       | 131 ± 12                 |         |
| **Diastolic BP (mmHg)** |     |                          |         |
| Overall Average   | 53 ± 4        | 68 ± 10                  | < 0.0001|
| HD start          | 53 ± 7        | 77 ± 3                   |         |
| 1 hour            | 53 ± 2        | 74 ± 6                   |         |
| 2 hours           | 56 ± 4        | 72 ± 8                   |         |
| 3 hours           | 55 ± 4        | 66 ± 1                   |         |
| HD End            | 52 ± 2        | 62 ± 10                  |         |
| **Heart Rate (/min)** |         |                          |         |
| Overall Average   | 64 ± 9        | 74 ± 4                   | < 0.0001|
| HD start          | 68 ± 2        | 74 ± 7                   |         |
| 1 hour            | 63 ± 5        | 71 ± 2                   |         |
| 2 hours           | 61 ± 4        | 75 ± 5                   |         |
| 3 hours           | 63 ± 1        | 72 ± 0                   |         |
| HD End            | 60 ± 1        | 76 ± 2                   |         |

BP indicates blood pressure. Each value is the average of readings obtained over 5 days. “Overall Average” is average of all values taken during dialysis.

obtain an appropriate rate response. The Japanese Circulation Society guideline recommends that CRT be used for patients, like the one above, who are dependent on pacing and have cardiac hypofunction. Although the upgrade to CRT according to this guideline improved cardiac function, and this contributed somewhat to the stabilization of hemodynamics during dialysis, satisfactory increases in blood pressure and heart rate were not observed from the rate response function provided by the accelerometer. In contrast, the rate response with CLS resulted in a rate increase during dialysis, as well as maintenance of blood pressure and prevention of symptoms such as feeling unwell, and the hypertensive agent was no longer required. Heart rate is reported to change during dialysis, not only due to the extracorporeal circulation of plasma but also due to such factors as changes in electrolytes. Patients with sick sinus syndrome and chronotropic incompetence require a device with a rate response function as they encounter difficulty in changing the rates in response to circumstances. However, as observed for the patient in this report, it is difficult to accommodate rate changes during dialysis with an accelerometer, and possibly also with MV sensors. CLS evaluates cardiac contraction caused by intracardiac impedance and changes the rate in response to changes in the cardiac contraction for each pulse, based on reference values obtained at baseline for each patient. This allows rate responsiveness even in the resting state. Since the mode of operation differs for each type of rate response sensor, it is important to select an appropriate model based on the activity pattern in individual patients.

**Conclusion**

During hemodialysis, heart rate increases due to the movement of blood outside the body and changes in electrolytes. However, patients with sick sinus syndrome may have an inadequate rate response, leading to difficulties in dialysis. CLS is designed to enable adjustment of the heart rate, which responds to both physical activity and the patient’s emotional state. While rate response with an accelerometer is considered difficult during dialysis as the patient is in a resting state, the response function of CLS was found to be beneficial. Further studies will be needed to confirm these effects of CLS.
Disclosure

Conflicts of interest: Dr. Nakai is affiliated with the Department of Medicine, Division of Advanced Therapeutics for Cardiac Arrhythmias established using funds from Abbott Medical, Biotronik Japan, Medtronic Japan, Japan Lifeline; and Boston Scientific Japan. Dr. Nakai has received lecture fees from Abbott Medical, Biotronik Japan, and Medtronic Japan. All of the other authors have no conflict of interest to report.

References

1. Lamas GA, Knight JD, Sweeney MO, et al. Impact of rate-modulated pacing on quality of life and exercise capacity—Evidence from the Advanced Elements of Pacing Randomized Controlled Trial (ADEPT). Heart Rhythm 2007; 4: 1125-32.
2. Bogert LW, Erol-Yilmaz A, Tukkie R, Van Lieshout JJ. Varying the heart rate response to dynamic exercise in pacemaker-dependent subjects: effects on cardiac output and cerebral blood velocity. Clin Sci (Lond) 2005; 109: 493-501.
3. Slade AK, Pee S, Jones S, Granle L, Fei L, Camm AJ. New algorithms to increase the initial rate response in a minute volume rate adaptive pacemaker. Pacing Clin Electrophysiol 1994; 17: 1960-5.
4. Lau CP, Mehta D, Toff WD, Stott RJ, Ward DE, Camm AJ. Limitations of rate response of an activity-sensing rate-responsive pacemaker to different forms of activity. Pacing Clin Electrophysiol 1988; 11: 141-50.
5. Cao Y, Zhang Y, Su Y, Bai J, Wang W, Ge J. Assessment of adaptive rate response provided by accelerometer, minute ventilation and dual sensor compared with normal sinus rhythm during exercise; a self-controlled study in chronotropically competent subjects. Chin Med J (Engl) 2015; 128: 25-31.
6. Cron TA, Pouskoulas CD, Keller DI, et al. Rate response of a closed-loop stimulation pacing system to changing preload and afterload conditions. Pacing Clin Electrophysiol 2003; 26: 1504-10.
7. JCS 2017/JHFS 2017 Guideline on Diagnosis and Treatment of Acute and Chronic Heart Failure - Digest Version. Circ J 2019; 83: 2084-184.
8. Chen K, Su H, Xie C, Wang Q, et al. Prognostic implications of QRS duration in third-degree atrioventricular block patients with heart failure treated with cardiac resynchronization therapy. Int Heart J 2018; 59: 1320-6.
9. Severi S, Cavalcanti S, Mancini E, Santoro A. Heart rate response to hemodialysis-induced changes in potassium and calcium levels. J Nephrol 2001; 14: 488-96.