Intracardiac Ventricular Impedance as a Tool for Optimizing Cardiac Resynchronization Therapy

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Summary

Optimizing cardiac resynchronization therapy by utilizing the pacing mode and interventricular delay yields the best hemodynamic benefit, but it requires time-consuming measurements. The aim of this study was to assess whether intracardiac ventricular impedance (IVI) measured by the pacemaker can be used to optimize cardiac resynchronization therapy. Ten severe heart failure patients with chronic atrial fibrillation, left bundle-branch block, and a left ventricular ejection fraction of < 35% were implanted with a dual-chamber pacemaker capable of measuring IVI. The left ventricular lead was connected to the atrial channel. During the study, the pacemaker was programmed in the DDD mode with a 20 ms atrioventricular delay. During follow-up examinations, the interventricular mechanical delay, mitral regurgitation area, and aortic and pulmonary velocity time integral were assessed using Doppler echocardiography during biventricular pacing at the 20 ms and 40 ms interventricular delay, left and right ventricular pacing, and intrinsic sinus rhythm, when it was present. The physician ranked pacing modalities based on assessing the hemodynamic benefits. During the echo procedures, the pacemaker measured the IVI by injecting a sub-threshold, pulsed current and detecting the resulting voltage using a five consecutive electrodes setup. In total, 33 follow-ups were performed (at discharge, 1, 3, 6, and 12 months). The best pacing mode was biventricular pacing at 20 ms in 17 follow-ups, biventricular pacing at 40 ms in eight, left ventricular pacing in five, and an intrinsic sinus rhythm in three follow-ups. The best correlation between physician rank and an IVI parameter was found through the maximum of the second derivative of the intracardiac ventricular impedance curve (Pearson's correlation coefficient $r^2 = 0.74$, p-value < 0.001). The best pacing mode was predicted by the highest value of this parameter in 32 follow-up examinations. An algorithm for the optimization of cardiac resynchronization therapy based on IVI analysis seems to be feasible. If larger studies can confirm these preliminary results, IVI analysis could be used instead of the time-consuming echo assessment.

Key Words

Heart failure, cardiac pacing, cardiac resynchronization, intracardiac impedance

Introduction

Previous studies have shown that cardiac resynchronization using biventricular pacing is an effective therapy for severe heart failure (HF) patients with interventricular conduction disorders [1-7]. Nevertheless, about 25% of selected HF patients do not respond to synchronous biventricular pacing. Therapy optimization in terms of pacing site(s) and interventricular delay is still under discussion. At present, cardiac resynchronization therapy (CRT) optimization requires time and resources using echocardiography measurements. An automatic algorithm for CRT optimization applied in a multisite pacemaker or programmer could improve a patient's quality of life and reduce follow-up costs. The intracardiac impedance has been shown to be related to the blood pressure [8] and blood volume in the cardiac chambers [9,10]. Since this signal reflects cardiovascular hemodynamics and can be measured in vivo, it might be a useful tool for CRT monitoring. The aim of this study was to verify whether intracardiac ventricular impedance measured by a pacemaker can be used to optimize CRT.

Material and Methods

Patients

Ten HF patients (nine male, one female, mean age 71 ± 6 years), were included in this study. The origin of the underlying cardiomyopathy was idiopathic (n = 8) or ischemic (n = 2). All patients had drug-refractory chronic heart failure (eight with an NYHA class III, two with a class IV), left bundle-branch block (mean QRS width 178 ± 36 ms), a left ventricular ejection fraction (LVEF) < 35% (mean 22.7% ± 3.1%), and chronic atrial fibrillation. All patients gave their written informed consent for the procedures.

Device

All patients were implanted with an Inos^{2+} CLS dual-chamber pacemaker (Biotronik, Germany), which implements a closed loop system for rate adaptation based on intracardiac impedance analysis. A unipolar left ventricular (LV) lead passing through the coronary sinus as well as a bipolar passive fixation right ventricular (RV) lead were implanted. The LV lead was connected to the atrial channel of the pacemaker. In the standard operating mode, the intracardiac impedance signal was measured by injecting sub-threshold current pulses (amplitude 200 µA, biphasic pulse width 30.5 µs) between the pacemaker case and ventricular tip electrode that detected the corresponding voltage from the pair of electrodes. A dedicated research software in the device was downloaded through the programmer. It enabled the electrodes to select the impedance measurement, thereby increasing the sampling rate to 128 Hz, facilitating the beat-by-beat impedance and pacemaker flags, and transmitting the information via telemetry.

Study Protocol

At the beginning of the study, drug therapy was optimized to minimize atrioventricular (AV) conduction. At implantation, the device was programmed in the DDD mode and the AV delay was set at the minimum programmable value (20 ms). The same parameters were used throughout the entire study. At the one-month follow-up, if the pacing percentage was still < 95%, the AV node was ablated. During follow-ups (at discharge, 1, 3, 6, and 12 months), the pulmonary to aortic opening delay, mitral regurgitation area, and aortic and pulmonary velocity time integral were assessed using Doppler echo during biventricular pacing at the 20 ms (BiV20) and 40 ms (BiV40) interventricular delay, LV and RV pacing, and intrinsic sinus rhythm, when it was present. Based on the hemodynamic benefit assessed by the echo, the physician ranked the pacing modalities. During echo procedures, the pacemaker measured the intracardiac impedance using five consecutive electrode setups for current injection and voltage detection (Table 1). The impedance signal, pacemaker markers, and flags were downloaded via telemetry and stored for off-line analysis. The intracardiac impedance was averaged in a 50 – 300 ms window after the LV events and was digitally low-pass filtered at 10 Hz in order to remove noise. Parameters calculated from the resulting impedance waveforms (Figure 1) were correlated to the rank of the pacing modalities assigned by the physician.

Results

In total, 33 follow-up examinations were performed. Clinical benefits resulting from biventricular pacing with an interventricular delay of 20 ms are summarized in Table 2. The significant decrease in the QRS width and pulmonary to aortic delay confirm that biventricular pacing improved cardiac synchronization. As a consequence, LVEF increased from 22.7 ± 3.1 to 30.9 ± 7.1. The NYHA class significantly improved from 3.2 ± 0.4 to 1.8 ± 0.6. The best pacing mode was BiV20 in 17, BiV40 in eight, LV in five, and intrinsic activity in three follow-ups. Two out of the three best pacing modes in intrinsic activity were detected in one patient experiencing permanent AF for 1 year before implantation, who was back in sinus rhythm at the 3-month follow-up. It has been shown that in 32 out of 33 follow-ups, the pacing mode with the best rank assigned by the physician based on echo measurements, was the

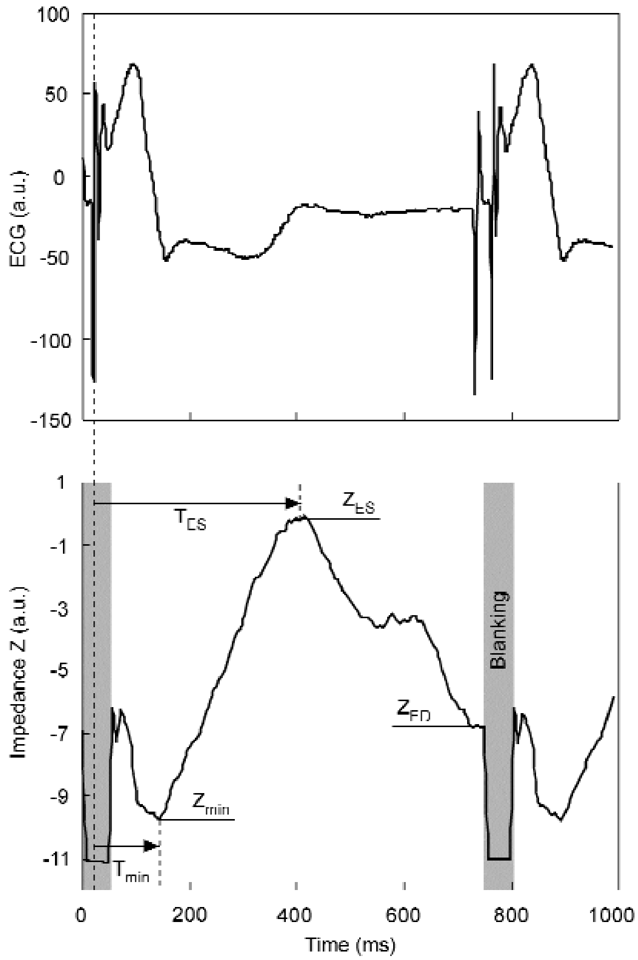

Figure 1. Standard ECG and intracardiac impedance in abitrary units (a.u.) during biventricular pacing with a 20 ms interventricular delay including parameters calculated from the impedance curve. Z_{ES} = maximum during the end of systole; Z_{ED} = baseline during the end of diastole; Z_{min} = minimum; T_{ES} = time interval for left ventricular pacing to the Z_{ES} value; T_{min} = time interval for left ventricular pacing to the Z_{min} value.

Impedance measurement configuration	Current injection	Voltage detection
Bipolar 1	Case – RV tip	Case – RV tip
Bipolar 2	Case – LV tip	Case – LV tip
Tripolar	LV tip – RV ring	LV tip – RV tip
Quadrupolar	Case – RV ring	LV tip – RV tip

Table I. Electrode setups used for intracardiac impedance measurement.

	Baseline	Last FU	Δ	p-value
NYHA class	3.2 ± 0.4	1.8 ± 0.6	-1.4	< 0.001
EF (%)	22.7 ± 3.1	30.9 ± 7.1	8.2	< 0.001
MR area (cm^2)	6.34 ± 4.17	4.17 ± 3.28	-2,17	n.s.
Pulmonary to aortic delay (ms)	48.8 ± 18.7	10.0 ± 11.5	-38.0	< 0.05
Aortic VTI (cm)	23.0 ± 7.9	23.6 ± 7.1	0.6	n.s.
Pulmonary VTI (cm)	15.0 ± 3.0	13.4 ± 4.1	1.57	< 0.05
LVEDD (%)	67.0 ± 8.7	64.3 ± 9.6	2.7	n.s.
LVSED (%)	57.5 ± 10.1	53.9 ± 9.9	3.6	n.s.

Table 2. Clinical results at discharge and the 12-month follow-up of all 10 patients. D = difference; LVEF=left ventricular ejection fraction; MR= mitral regurgitation area (four-chamber apical view) VTI= velocity time integral; LVEDD, LVESD= left ventricular end-systolic and end-diastolic diameter; p-values > 0.05 were considered not significant (n.s.).

same as the one showing the highest maximum of the second derivative (Z''_{max}) of the impedance measured in the quadrupolar configuration. When ranking the pacing mode based on the Z''_{max}, (physician versus the impedance rank correlation), Pearson's correlation coefficient was $r^2 = 0.74$ (corresponding p-value < 0.001).

Discussion

It has been shown that an impaired systolic ventricular function is correlated with a higher risk of death and heart transplantation [11,12]. In this context, the predictive value of the impedance parameter Z''_{max} will be a powerful diagnostic tool for heart failure patients. A hypothesis for the observed correlation between the impedance parameter Z''_{max} and the systolic ventricular function is that the intracardiac impedance measured in a quadrupolar configuration is proportional to blood volume in the left ventricle. In this case, the second derivative Z''_{max} would be a qualitative parameter of blood acceleration and, thus, of contractility and systolic function of the left ventricle. Nevertheless, to prove this rationale, computer modeling or invasive hemodynamic measures are needed.

Conclusion

Preliminary results of this pilot study show that a CRT optimization algorithm, based on intracardiac impedance monitoring, is feasible and can be implemented in a pacemaker or a programmer. A larger number of patients and further hemodynamic measurements are necessary to confirm that this simple and rapid intracardiac impedance monitoring could take the place of echocardiography in evaluating the benefits of resynchronization therapy.

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