Rate-dependent pacing failure after pacemaker implantation:Novel insights into the mechanism of using adenosine

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Abstract

An 82-year-old woman received pacemaker implantation for sick sinus syndrome. Two days after the implantation, electrocardiography showed 2:1 atrial pacing failure, followed by bradycardia-dependent increase in the atrial pacing threshold during a pacemaker examination. However, transient 1:1 atrial pacing capture recovered by adenosine triphosphate (ATP) administration, which was performed to evaluate the bradycardia-dependent pacing failure mechanism. We considered this phenomenon to be caused by phase 4 depolarization and avoided replacing this atrial lead. Three weeks later, the atrial pacing threshold had improved. We report the potential role of phase 4 depolarization in bradycardia-dependent increase in pacing threshold by using ATP.

Introduction

An acute increase in the pacing threshold early after pacemaker implantation is occasionally a problem, even in the era of steroid-eluting leads. In such cases, bradycardia-dependent increase in the pacing threshold without apparent lead dislodgement has been demonstrated to be responsible for micro-dislodgement or phase 4 block and is expected to recover spontaneously[1-2]. However, the mechanism of this phenomenon has not been elucidated.

We herein report a case of a patient who underwent pacemaker implantation for sick sinus syndrome (SSS), in whom the mechanism of bradycardia-dependent increase in the pacing threshold was elucidated using adenosine triphosphate (ATP).

Case report

An 82-year-old woman was referred to our hospital for the management of SSS with lightheadedness. She had a history of lone atrial fibrillation (AF), but was not taking any antiarrhythmic drugs. Holter electrocardiography showed a total heart rate (HR) of about 50,000 beats per day (minimum HR was 29 bpm), 8.3 seconds of cardiac arrest was observed at the termination of AF. Consequently, we decided to implant a dual-chamber pacemaker; a passive-fixation lead (INGEVITY MRI, Boston Scientific, USA) and an active-fixation lead (INGEVITY MRI, Boston Scientific, USA) were implanted in the right atrial appendage and right ventricular mid-septum, respectively. The initial atrial pacing threshold was 0.7 V at 0.4 ms at 60

bpm. The sensing threshold and impedance values of the atrial lead were 2.1 mV and 638 Ω, respectively. The pacemaker was programmed to DDD 60-110 bpm with 3.5 V at a 0.4 ms setting of atrial pacing output.

Two days after the implantation, electrocardiographic monitoring showed 2:1 ventricular pacing following atrial pacing spikes, without atrial capture (Figure 1-A). The chest X-ray showed no apparent dislodgement of either the atrial or ventricular leads. Pacemaker interrogation revealed that atrial pacing capture was dependent on the interval of preceding atrial sensing or captured pacing events (Figure 1-B). Therefore, we evaluated the atrial pacing threshold by changing the pacing rate. The atrial pacing threshold was then increased and was inversely correlated with the pacing rate: 4.0 V at 0.4 ms at 50 bpm, 2.7 V at 0.4 ms at 60 bpm, 1.5 V at 0.4 ms at 70 bpm, and 1.0 V at 0.4 ms at 80 bpm (Figure 2-A). Although there was a slight decrease in the atrial pacing threshold when the pulse width extended from 0.4 ms to 1.0 ms, the rate dependency of the pacing threshold remained unchanged. The sensing and impedance values were slightly decreased, but the decrease was not significant, and it was acceptable. (sensing and impedance values were 1.3 mV and 582 Ω, respectively).

The causes of such a bradycardia-dependent increase in the pacing threshold without apparent lead dislodgement are considered as follows: (1) fluctuation in the contact to the myocardium by lead micro-dislodgement[1], and (2) phase 4 depolarization and block in the injured myocardium[2]. We assumed this phenomenon to be associated with phase 4 depolarization in this patient, because the relationship between the pacing threshold and pacing rate indicated a sigmoid curve, which likely is a physiological phenomenon (Figure 2-A). A pause-dependent paroxysmal atrioventricular block mostly occurs in the presence of an injured His-Purkinje system and is known to be responsible for gradual phase 4 depolarization[3]. On the other hand, Datino et al[4] demonstrated that adenosine could hyperpolarize canine pulmonary vein (PV) cardiomyocytes by increasing the inward rectifier K^+ current (IKAdo) in which the resting membrane potential decreased by radiofrequency (RF) application and this phenomenon could account for the "dormant conduction" in PV isolation for AF. Therefore, we examined whether the administration of ATP could restore the pacing capture in the damaged atrial myocardium by hyperpolarization during phase 4. An intracardiac electrogram (EGM) immediately after the administration of ATP during atrial pacing under the subthreshold voltage, of 2.5 V at 0.4 ms at 50 bpm (the threshold was 3.5 V at 0.4 ms at 50 bpm), is shown in Figure 2-B. Since ATP administration resulted in 1:1 atrial capture transiently, without a change in the pacing rate, we determined that her bradycardia-dependent increase in the pacing threshold was related with phase 4 depolarization. Some authors have already reported bradycardia-dependent increase in the pacing threshold to improve time-dependently[2]; hence, we did not replace her atrial lead and changed the pulse width from 0.4 ms to 1.0 ms, avoiding pacing failure.

No improvement in the atrial pacing threshold was observed at the lower pacing rate at seven days after the pacemaker implantation. However, two more weeks later, the atrial pacing threshold was improved as follows: 1.0 V at 0.4 ms at 50 bpm, 0.7 V at 0.4 ms at 60 bpm, and 0.6 V at 0.4 ms at 70 bpm; this has been maintained for over two years. Informed consent was obtained from the patient for the publication of this case report.

Discussions

Even today, we may encounter patients with varying degrees of transient increase in the pacing threshold after pacemaker implantation. Uehara et al[5] demonstrated an acute and transient, but not persistent, rise in the capture threshold (TRACT) in 6% of patients undergoing dual-chamber pacemaker implantation, which most likely occurred when the damaged atrial myocardium was associated with SSS. Their colleagues also reported three similar TRACT cases of bradycardia-dependent nature in which the involvement of a phase 4 block was suggested[2]. However, to the best of our knowledge, this is the first report in which the potential role of phase 4 depolarization in bradycardia-dependent increase in the pacing threshold was evaluated using ATP.

The resting membrane potential in the normal atrial myocardium is usually at a steady negative level (about -80 mV), whereas in the damaged atrial myocardium, it is expected to be decreased (becomes less negative),

such as in canine PV myocytes injured by RF application. As the resting membrane potential decreases, the voltage-dependent inactivation Na^+ channel gradually closes and inward Na^+ current is reduced to a level at which action potential cannot occur against external stimulations. On the other hand, as described above, ATP could hyperpolarize damaged cardiomyocytes and subsequently facilitate depolarization. Accordingly, we hypothesized that the bradycardia-dependent increase in the pacing threshold observed in the early phase after pacemaker implantation was associated with phase 4 depolarization in the damaged myocardium, cause by factors such as inflammation and edema due to lead-contact and could be improved by the administration of ATP, which increases the resting membrane potential and activates sufficient Na^+ current (Figure 3). Indeed, Blazek et al[6] suggested that pacemaker-lead implantation-induced myocardial micro-damage, either with an active or passive fixation lead, could be monitored by using the high-sensitive troponin T level as an index.

Although further investigations are required, many cases of bradycardia-dependent increase in the pacing threshold early after pacemaker implantation could be due to phase 4 depolarization and ATP could be useful for investigating the mechanism.

Conclusion

ATP injection transiently rectified rate-dependent pacing failure in the acute phase after pacemaker implantation. This observation is concordant with the effect of ATP on phase 4 depolarization. The evaluation of this phenomenon using ATP could help in elucidating the mechanism and making a decision regarding whether to perform re-intervention.

References

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Figure legends

Figure 1. A: Continuous ECG of lead II shows 2:1 wide QRS complexes accompanied by ventricular pacing following the loss of atrial capture. The pacemaker mode was DDD 60-110 bpm with a paced AV interval of 350 ms, 3.5 V at a 0.4 ms setting of atrial pacing output. B: Intracardiac EGM strips during 2:1 atrial pacing failure. The middle portion indicates the atrial EGM channel; the bottom indicates the ventricular EGM channel. Because intrinsic atrial beats (indicated as PAC) were observed after atrial pacing failure, but they were within the post-ventricular atrial refractory period (PVARP), the pacemaker timing cycle was not reset. A shorter coupling period (510 ms and 725 ms) of atrial pacing, followed by the intrinsic atrial beat could capture the atrial myocardium. A longer coupling period (1000 ms was the lower rate interval) of atrial pacing could not capture the atrial myocardium.

Figure 2. A: Pacing threshold during atrial pacing is plotted against each pacing rate. Larger output was required as a lower pacing rate. B: Intracardiac EGM immediately after ATP 20 mg injection. Although

the first, second, fourth and fifth pacing could not capture the atrial myocardium, the sixth, seventh, eighth, and ninth pacing could all capture the atrial myocardium with 2.5 V at 0.4 ms where the threshold before ATP injection was 3.5 V at 0.4 ms at 50 bpm, without changing the pacing rate.

Figure 3. A proposed mechanism of ATP-induced transient improvement of rate-dependent pacing failure. A. The resting membrane potential in the normal atrial myocardium is steady negative and most of Na+ channels are available for generating action potential (D: blue point). B. Bradycardia-dependent pacing failure with myocardial injury after pacing lead implantation can be explained by gradual depolarization during phase 4, in a similar manner to rate-dependent phase 4 block. When pacing with a shorter coupling interval (510 ms) from the preceding depolarization, the Na^+ channel fraction is available enough to capture (D: yellow point). On the other hand, when pacing with a longer coupling interval (1000 ms), a large fraction of the Na^+ channels is inactivated (D: red point), resulting in pacing failure. C. Bolus ATP injection induces hyperpolarization during phase 4 by increasing inward rectifier K^+current (I_{KAdo}). Consequently, Na^+channel availability is restored (D: red point to yellow point) and the myocardium is captured by pacing with a longer coupling interval.

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