

# Cardiac Arrest Due to Pacing Failure From Pilsicainide Poisoning

**Toshiyuki Kishimoto, DDS, PhD;\* Yoshiaki Takitani, DDS, PhD;† Tomoka Ichikawa;‡ Kaho Shiraishi, DDS;§ Hiroki Yamada, DDS;§ Shoko Oya, DDS;§ Makoto Kume, MD, PhD;|| and Satoru Sakurai, DDS, PhD¶**

\*Assistant Professor, Department of Dental Anesthesiology, Division of Oral Pathogenesis and Disease Control, Asahi University School of Dentistry, Mizuho-shi, Gifu, Japan, †Associate Professor, Department of Endodontics, Division of Functional Science and Rehabilitation, Asahi University School of Dentistry, Mizuho-shi, Gifu, Japan, ‡Dental Hygienist, Department of Dental Hygiene, Asahi University Medical & Dental Center, Mizuho-shi, Gifu, Japan, §Clinical Fellow, Department of Dental Anesthesiology, Division of Oral Pathogenesis and Disease Control, Asahi University School of Dentistry, Mizuho-shi, Gifu, Japan, ||Professor, Department of Surgery, Division of General Medicine, Asahi University School of Dentistry, Mizuho-shi, Gifu, Japan, ¶Professor and Chairman, Department of Dental Anesthesiology, Division of Oral Pathogenesis and Disease Control, Asahi University School of Dentistry, Mizuho-shi, Gifu, Japan

**Key Words:** Pilsicainide; Poisoning; Cardiac arrest; Pacing failure; Pacing threshold.

We experienced a case of accidental pilsicainide poisoning suspected as the cause of pacing failure leading to cardiac arrest. The patient was a 36-year-old woman with a history of refractory multifocal supraventricular tachycardia who had previously undergone multiple cardiac ablations requiring placement of a pacemaker. Upon her arrival on the day of dental treatment, the patient's condition deteriorated rapidly, with a heart rate of approximately 30 beats/min, pacing failure, and an idioventricular rhythm upon electrocardiographic examination. During transportation for emergency medical care, the patient experienced clonic convulsions, and ventricular tachycardia was observed. Cardiopulmonary resuscitation, large-volume infusion, and percutaneous cardiopulmonary support were rapidly performed after arrival at a nearby medical hospital. This elicited a pacing response and successful resuscitation of the patient. No abnormalities were found during pacemaker interrogation; however, the patient's serum pilsicainide concentration was 1.46 µg/mL. Accidental ingestion of pilsicainide likely led to an increase in pacing threshold and ultimately to cardiac arrest. In the event of pacing failure, it is important to

judge the degree of urgency, take appropriate emergency measures, and collaborate with other medical colleagues as soon as possible.

Pilsicainide is an antiarrhythmic drug developed and frequently used in Japan and classified as Vaughan-Williams class Ic because of its particularly strong sodium channel blockade effects.<sup>1,2</sup> There have been reports of poisoning associated with increased blood levels of pilsicainide, and cases of pilsicainide-associated mortality exist.<sup>3-13</sup> Here, we report a case of accidental pilsicainide poisoning as the suspected cause of cardiac arrest due to pacing failure.

We have obtained written consent from the patient for the publication of this case report.

## CASE PRESENTATION

The patient was a 36-year-old woman (height 162 cm; weight 47 kg; body mass index 17.9 kg/m<sup>2</sup>) scheduled for restorative dental treatment because of dental caries. Her medical history was significant for refractory multifocal supraventricular tachycardia, and she reported a total of 6 ablation surgeries for atrioventricular (AV) node reentrant tachycardia, inappropriate sinus tachycardia, and junctional tachycardia. No other relevant medical history, medications, or allergies were reported.

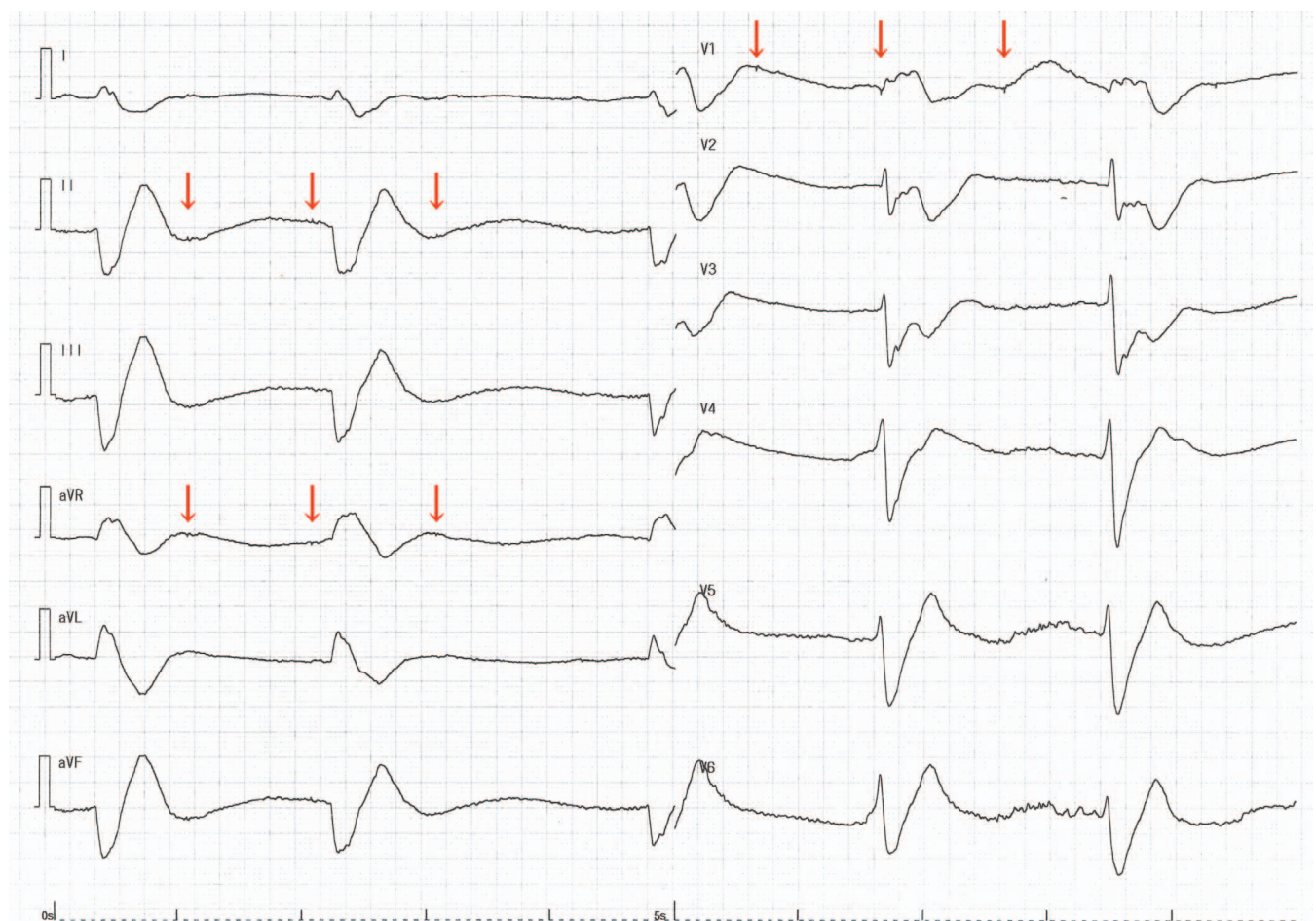
Eight months before the scheduled dental treatment, ablation near the sinus node and superior vena cava isolation was performed, resulting in severe sinus bradycardia with almost no intrinsic automaticity; thus,

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Address correspondence to Dr Toshiyuki Kishimoto, Department of Dental Anesthesiology, Division of Oral Pathogenesis and Disease Control, Asahi University School of Dentistry, 1851-1, Hozumi, Mizuho-shi, Gifu, 501-0296 Japan; kishimototoshiyuki@dent.asahi-u.ac.jp.

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**Figure.** A 12-lead electrocardiogram (ECG) obtained soon after the patient's condition initially deteriorated.



Idioventricular pattern noted on the ECG along with pacing failure. Heart rate was approximately 30 beats/min. Regularly spaced red arrows indicate pacemaker spikes that were occurring despite lack of capture.

a permanent pacemaker was implanted. Two months prior to the dental treatment, AV node ablation was performed because of junctional tachycardia causing cardiac symptoms and impaired exercise tolerance. Post-AV node ablation, the patient was otherwise stable. The pacemaker was programmed as follows: mode, DDDR; lower rate, 60 beats/min; upper rate, 140 beats/min; atrial pacing threshold, 1.0 V (pulse width 0.5 milliseconds); ventricular pacing threshold, 0.3 V (pulse width 0.5 milliseconds); and output, 3.5 V (pulse width 0.4 milliseconds).

The developed plan for her dental care included restorative treatment for dental caries under local anesthesia while she was monitored using a sphygmomanometer, pulse oximeter, and electrocardiogram (ECG) because of the potential for intraoperative vital sign fluctuations. On the day of dental treatment, the patient's condition deteriorated immediately after her arrival on the premises, and she collapsed before

undergoing any dental treatment. Although she was conscious, she had facial pallor and difficulty walking independently. Therefore, she was immediately transferred to the internal medicine department attached to our dental institution, where a sphygmomanometer, pulse oximeter, and ECG were quickly applied. At that time, she exhibited a heart rate of approximately 30 beats/min and pacing failure (Figure). The ECG demonstrated an idioventricular rhythm, with the absence of a QRS complex noted after a pacing impulse (red arrows in Figure). The patient's Glasgow Coma Scale score at this time was 13 points (E3V4M6). Her blood pressure was 67/38 mm Hg, and her radial artery pulse was imperceptible because of low blood pressure. A 22G indwelling catheter was placed in her forearm to secure venous access, and Ringer acetate solution was administered. The patient's oxygen saturation as measured by pulse oximetry (SpO<sub>2</sub>) was 83% on room air; therefore, supplemental oxygen at 2 L/min was admin-

istered via an oxygen mask, after which her SpO<sub>2</sub> recovered to 99%.

Because her pacing failure persisted, we did not provide dental treatment and instead requested emergency transportation to a medical institution where a cardiologist and clinical engineers were on staff. However, the patient repeatedly lost and regained consciousness while she was being transported. Prior to her arrival at the medical hospital approximately 20 minutes later, she lost consciousness, and her radial artery pulse again became imperceptible. Clonic convulsions and ventricular tachycardia were observed upon her arrival to the medical facility. Immediately, cardiopulmonary resuscitation, fluid infusion, defibrillation, and administration of intravenous epinephrine and amiodarone were performed. Possible antiarrhythmic drug poisoning was suspected based on the persistent cardiac arrest and ECG findings of an idioventricular rhythm before the cardiac arrest. Large-volume infusion and percutaneous cardiopulmonary support (PCPS) were performed, which quickly elicited a pacing response and successful resuscitation of the patient. Additionally, no device abnormality was found during evaluation of the patient's pacemaker, which was performed after the start of PCPS.

The day after resuscitation, blood levels of several antiarrhythmic drug possibilities were measured. The concentration of pilsicainide in her blood was found to be as high as 1.46 µg/mL (therapeutic range is 0.2–0.9 µg/mL), suggesting pilsicainide poisoning. After resuscitation, temperature modulation using therapeutic hypothermia was performed for 48 hours to prevent brain damage, followed by withdrawal from PCPS. The patient remained hospitalized for several days, received treatment including physical rehabilitation mainly performed for disuse syndrome, and was later discharged without sequelae.

## DISCUSSION

Pilsicainide is an antiarrhythmic drug classified as Vaughan-Williams class Ic. Because it selectively blocks Na<sup>+</sup> channels and does not affect K<sup>+</sup> and Ca<sup>2+</sup> channels, it inhibits conduction to the atrial muscles, the conduction system tissues below the His bundle, and the ventricular muscles.<sup>14</sup> Pilsicainide has arrhythmogenic and negative inotropic effects and is indicated for ventricular and supraventricular tachyarrhythmias that are not associated with organic heart disease or decreased cardiac function.<sup>2,10,11,15,16</sup>

During the preoperative examination, our patient indicated that there was no immediate history of any oral medication use. However, pilsicainide serum levels

exceeding the therapeutic range were detected in her blood after resuscitation. Upon further investigation, she reported feeling ill on the day of her dental treatment and self-administering oral teprenone. Teprenone increases gastric bicarbonate concentrations and helps heal gastric ulcers. Teprenone and pilsicainide are marketed in different colors; however, both medications are formulated as capsules and are roughly the same size. It is possible that pilsicainide, previously prescribed for the treatment of supraventricular tachycardia and stored by the patient, was mistaken for teprenone and inadvertently ingested.

Some antiarrhythmic agents (eg, procainamide, disopyramide, pilsicainide, and flecainide) raise the pacing threshold and can cause pacing failure.<sup>4,6,17–19</sup> The pacing threshold refers to the minimum voltage required to obtain myocardial excitement after a pacing impulse or “spike.” Pacing failure refers to a state in which voltage-mediated myocardial excitement does not occur even if the pacing threshold voltage is reached. Pilsicainide and flecainide, which belong to the antiarrhythmic class Ic, have particularly strong Na<sup>+</sup> channel blocking effects and therefore cause a large increase in pacing threshold.<sup>19</sup> Moreover, even if the blood concentration of these drugs remains within the therapeutic range, the pacing threshold will increase in proportion to any increases in blood concentration.<sup>20</sup> Pacing failure has been reported, primarily outside of Japan, for both pilsicainide and flecainide poisoning. Therefore, the same level of caution is required when using either of these drugs.<sup>21–23</sup>

In the current case, the patient's blood concentration of pilsicainide was 1.46 µg/mL the day after resuscitation, which far exceeds the therapeutic range. When a healthy adult with a creatinine clearance (CCr) ≥80 mL/min is orally administered 50 mg of pilsicainide, the serum half-life is 3.4 hours.<sup>16</sup> Thus, we surmise that when our patient's condition deteriorated, the pilsicainide level was in fact higher than the later-measured value. In previous reports, pacing failure due to pilsicainide poisoning have occurred at blood levels of at least 2.3 to 2.5 µg/mL, and we surmise that our patient's blood levels at the time of deterioration were close to or higher than this.<sup>6,11</sup> Therefore, it appears that although the patient's pacemaker was delivering pacing impulses, voltage-based excitement of the myocardium did not occur.

Treatment for pilsicainide poisoning includes large-volume infusion, hemodialysis, sodium bicarbonate administration, and PCPS induction, plus cardiac pacing to maintain circulation.<sup>3,10–12</sup> Percutaneous cardiopulmonary support consists of a closed-circuit heart-lung machine that uses a centrifugal pump, a membrane oxygenator, monitors, and a heating system

to provide cardiopulmonary support via the femoral arteriovenous system. In this case, pacemaker capture resumed after large-volume infusion and introduction of PCPS after emergency transportation. It is highly possible that pilsicainide poisoning caused a transient increase in the pacing threshold, ultimately leading to pacing failure and cardiac arrest.<sup>16</sup>

Although the patient in this case had no renal dysfunction, there are many reports of renal dysfunction causing pilsicainide poisoning.<sup>3,5,10,11</sup> Oral administration of 50 mg of pilsicainide to patients with impaired renal function with a  $CCr \leq 20$  mL/min prolongs the serum half-life to 23.7 hours.<sup>16</sup> In patients with impaired renal function, the blood concentration may exceed the therapeutic range and reach toxic levels even if the prescribed dose is taken orally. In addition to concerns about renal dysfunction, caution is warranted for concomitant use of pilsicainide with diuretics and angiotensin receptor blockers, in cases of dehydration, and with elderly patients.<sup>10,13</sup> When the blood concentration of pilsicainide exceeds the therapeutic range and reaches toxic levels, fatal arrhythmias (ie, ventricular tachycardia and ventricular fibrillation) and ECG changes may be observed, as in this case.<sup>7,10,11</sup> Therefore, appropriate dosing and monitoring of drug levels are important considerations for the safe management of patients taking pilsicainide who are undergoing dental treatment.

Causes of pacing failure due to elevated pacing threshold include lead issues, myocardial ischemia, organic changes in the myocardium, metabolic abnormalities, electrolyte abnormalities, and the effects of drugs like antiarrhythmics. Pacing failure due to pacemaker generator or battery insufficiency is rare.<sup>6,18,19,24</sup> In this case, a pacemaker check was performed 12 days before the planned dental treatment and twice after the introduction of PCPS, but no device abnormality was ever observed.

It is difficult for a dentist to identify the causes of pacing failure, given that they are diverse and require specialized knowledge and equipment to identify. In addition, treatments differ depending on the underlying cause of pacing failure. Therefore, it is necessary to verify the relevant medical history, medications, and periodic assessment of the device and its settings prior to treating dental patients with implanted pacemakers.

Although it was difficult to suspect and respond to antiarrhythmic drug poisoning when the patient's condition initially deteriorated, we were able to provide urgent care, applying noninvasive monitors and quickly determining that more definitive medical help was needed. After timely activation of emergency medical services, the patient was expediently transported to a medical hospital, where the likely cause was identified

and appropriately managed. This led to the successful resuscitation of the patient. When pacing failure occurs, it is important to judge the degree of urgency from the patient's vital signs, take appropriate emergency measures, and collaborate with other medical colleagues (eg, a cardiologist or clinical engineer) as soon as possible.

## CONCLUSION

We experienced a case of pilsicainide poisoning suspected to be the cause of pacing failure that led to cardiac arrest. Pilsicainide poisoning is rare and was attributed to accidental ingestion following a possible medication error at home. The patient was expediently transported to a medical hospital, where the likely cause was identified and appropriately managed, leading to a successful resuscitation and discharge.

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