


## CASE REPORT

# Suppression of amiodarone-induced torsade de pointes by landiolol in a patient with atrial fibrillation-mediated cardiomyopathy

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## Abstract

An elderly Japanese woman developed acute decompensated heart failure caused by persistent atrial fibrillation (AF) and left ventricular systolic dysfunction. Approximately 6 days after starting intravenous administration of amiodarone (600 mg/day) for maintaining sinus rhythm after cardioversion of AF, electrocardiograms revealed a prolonged QT interval associated with torsade de pointes (TdP). The amiodarone-induced TdP disappeared after intravenous administration of landiolol plus magnesium and potassium, without discontinuation of amiodarone or overdrive cardiac pacing, although the prolonged QT interval persisted. To the best of our knowledge, this is the first report that landiolol could be effective for amiodarone-induced TdP.

## KEYWORDS

amiodarone, atrial fibrillation, heart failure, landiolol, long QT syndrome, torsade de pointes

## 1 | INTRODUCTION

Torsade de pointes (TdP) is a potentially lethal form of ventricular tachycardia (Drew et al., 2010). An increased risk of TdP is associated with a prolonged heart rate-corrected QT interval on electrocardiogram (ECG), which represents a pathophysiological substrate for long QT syndrome (LQTS) classified into genetic and acquired forms. Therapeutic drugs are a major cause of acquired LQTS, including class IA and III antiarrhythmic agents and many non-antiarrhythmic agents. Treatment of drug-induced TdP should involve (a) discontinuation of the culprit drug, (b) intravenous administration of magnesium

and potassium, and (c) intravenous administration of isoproterenol or temporary cardiac pacing.

This report describes a case of acute decompensated heart failure (ADHF) caused by atrial fibrillation (AF)-mediated cardiomyopathy (Qin et al., 2019) and subsequently complicated with TdP induced by amiodarone intravenously administered to prevent AF. Although the prolonged QT interval persisted, the amiodarone-induced TdP disappeared after intravenous administration of landiolol hydrochloride, an ultra-short-acting  $\beta_1$ -superselective  $\beta$ -adrenergic blocker (Ikeda et al., 2019), plus magnesium and potassium, without discontinuation of amiodarone hydrochloride or overdrive cardiac pacing.

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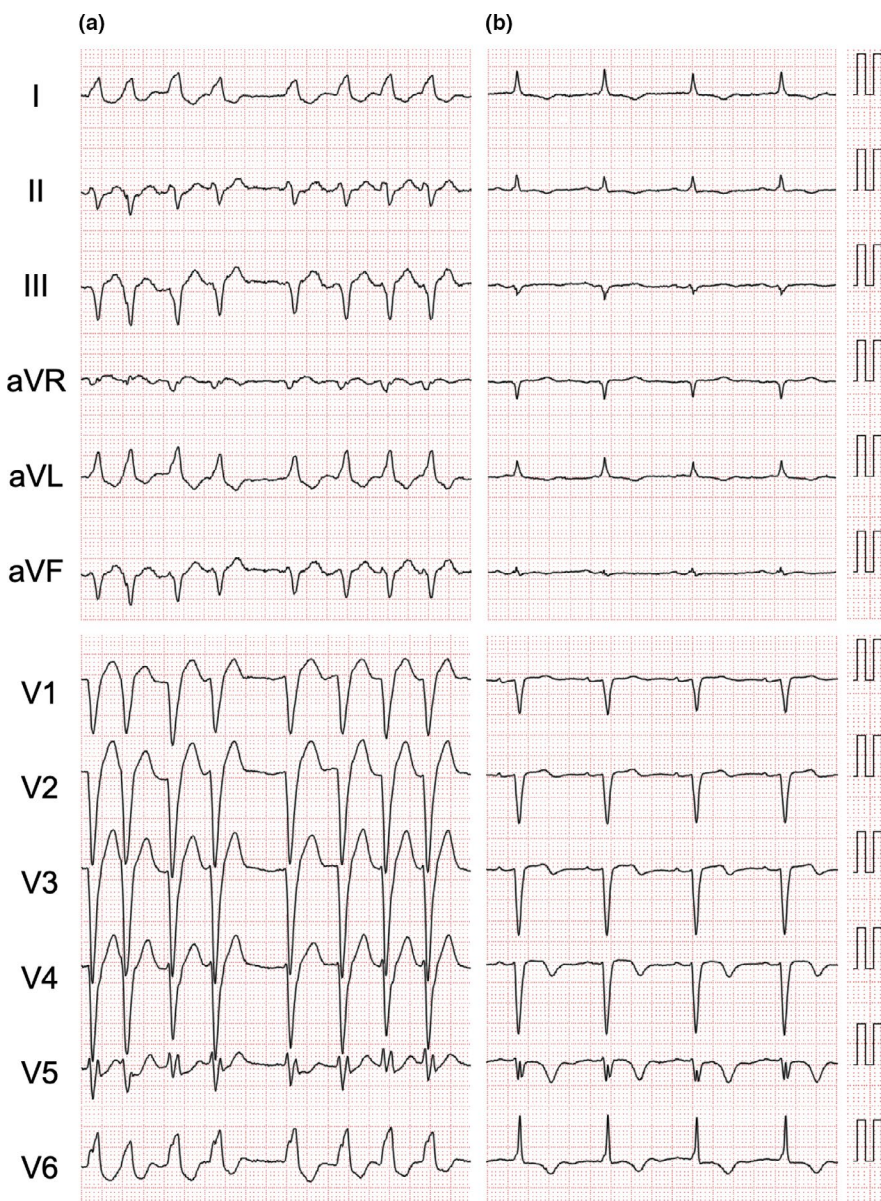
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## 2 | CASE PRESENTATION

An 83-year-old Japanese woman was admitted to our hospital with a 3-day history of exertional dyspnea and anorexia. She had no history of smoking or consuming alcohol. Her medical history included long-standing hypertension and dyslipidemia, and she had been prescribed valsartan (40 mg/day), amlodipine besylate (10 mg/day), trichlormethiazide (1 mg/day), and atorvastatin calcium hydrate (5 mg/day) at another clinic.

On admission, physical examination revealed a body temperature of 36.4°C, a pulse rate of 142 beats/min with irregular rhythm, a systemic blood pressure of 103/82 mm Hg, and 97% oxygen saturation on room air measured using a pulse oximeter. Her body weight was 61 kg. No heart murmurs were audible upon auscultation, although we observed a gallop in the third heart sound and wet rales in the lung fields. The liver was palpable for one finger width along the right midclavicular line below the costal margin, and mild pretibial edema was observed.

Blood tests revealed elevated concentrations of high-sensitivity cardiac troponin I (27.4 pg/ml, reference  $\leq 16.0$  pg/ml) and brain natriuretic peptide (605.3 pg/ml, reference  $\leq 18.4$  pg/ml). Her liver function was normal, but her renal function was depressed (estimated glomerular filtration rate, 38 ml/min/1.73 m<sup>2</sup>). Chest radiography revealed cardiomegaly with a cardiothoracic ratio of 0.54 and pulmonary congestion. An ECG revealed tachycardiac AF with a mean heart rate of 139 beats/min, which had not been detected until that point, and complete left bundle branch block (Figure 1a). Furthermore, echocardiography revealed diffusely hypokinetic wall motions in the left ventricle with an ejection fraction of 30%, mild left ventricular dilation (left ventricular end-diastolic diameter, 48.0 mm), and left atrial dilation (volume of 66.3 ml/m<sup>2</sup>). Thus, the diagnosis was ADHF caused by left ventricular systolic dysfunction with tachycardiac AF. The treatments were oral edoxaban tosylate hydrate (30 mg/day) to prevent cardiogenic thromboembolism, daily intravenous injections of furosemide (20 mg/day) for the ADHF, and continuous intravenous infusion of



**FIGURE 1** Electrocardiograms recorded at admission (a) and on day 11 of hospitalization, which was 2 days after electrical cardioversion from atrial fibrillation to sinus rhythm and 3 days after starting intravenous administration of amiodarone hydrochloride (b). Panel (a) shows tachycardiac atrial fibrillation and complete left bundle branch block. Panel (b) shows sinus rhythm (69 beats/min); poor R-wave progression in the precordial leads; ST-T abnormalities in leads I, II, aVL, and V3-V6; shallow negative U wave in leads V5 and V6; heart rate-corrected QT intervals (QTc) of 475 ms; and T<sub>peak</sub>-T<sub>end</sub> interval of 105 ms. The QTc was calculated using the Bazett formula to adjust the measured QT interval for cycle length by dividing the observed uncorrected QT interval by the square root of the R-R interval

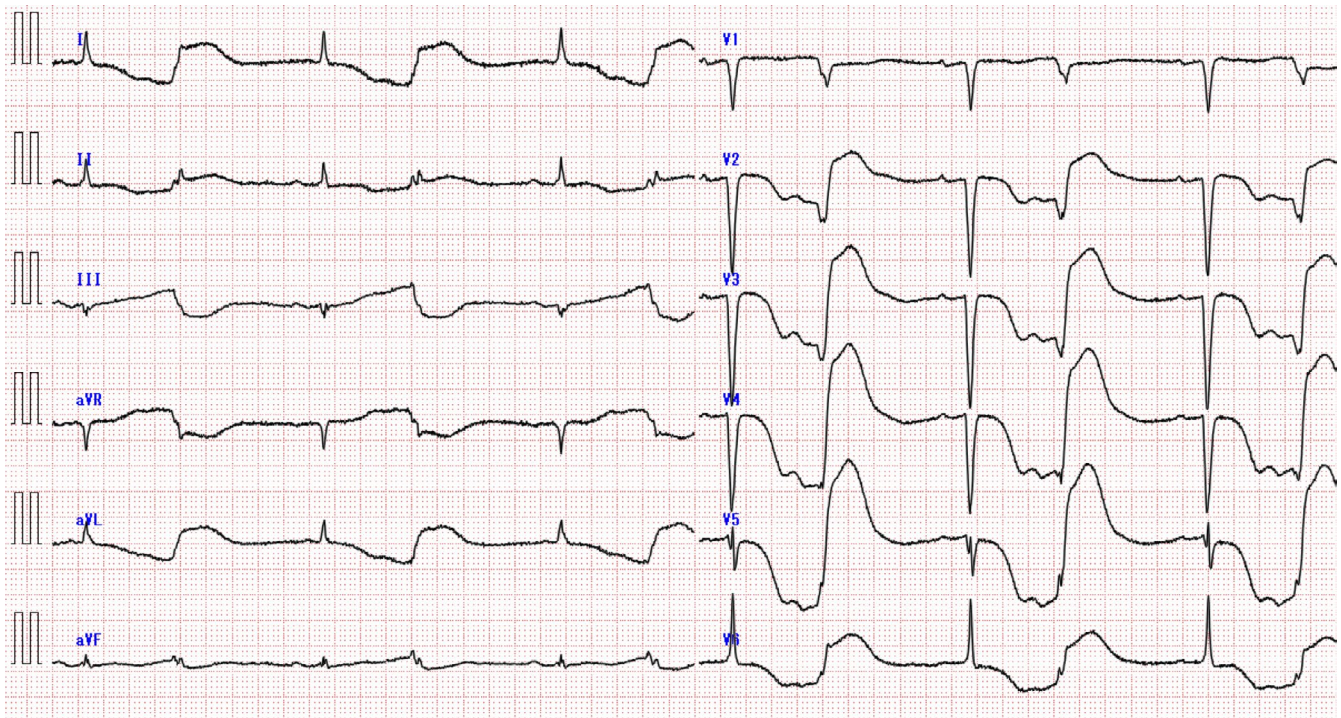
landiolol hydrochloride (starting at  $1 \mu\text{g kg}^{-1} \text{min}^{-1}$  and increasing to  $5 \mu\text{g kg}^{-1} \text{min}^{-1}$ ) to control the rate of AF. The patient also received oxygen via a mask.

On day 4 of hospitalization, the tachycardiac AF continued and her pulmonary congestion worsened. The intravenous doses of furosemide and landiolol hydrochloride were increased to 60 mg/day and  $10 \mu\text{g kg}^{-1} \text{min}^{-1}$ , respectively. In addition, oral potassium gluconate was started because of hypokalemia (serum potassium concentration, 3.2 mmol/L). However, on day 8 of hospitalization, the left ventricular ejection fraction decreased to 18% and her respiratory status worsened. Thus, we started continuous intravenous infusion of dobutamine hydrochloride ( $5 \mu\text{g kg}^{-1} \text{min}^{-1}$ ) and mechanical ventilatory support with nasal biphasic positive airway pressure. Continuous intravenous infusion of amiodarone hydrochloride was started (600 mg/day) without loading infusion.

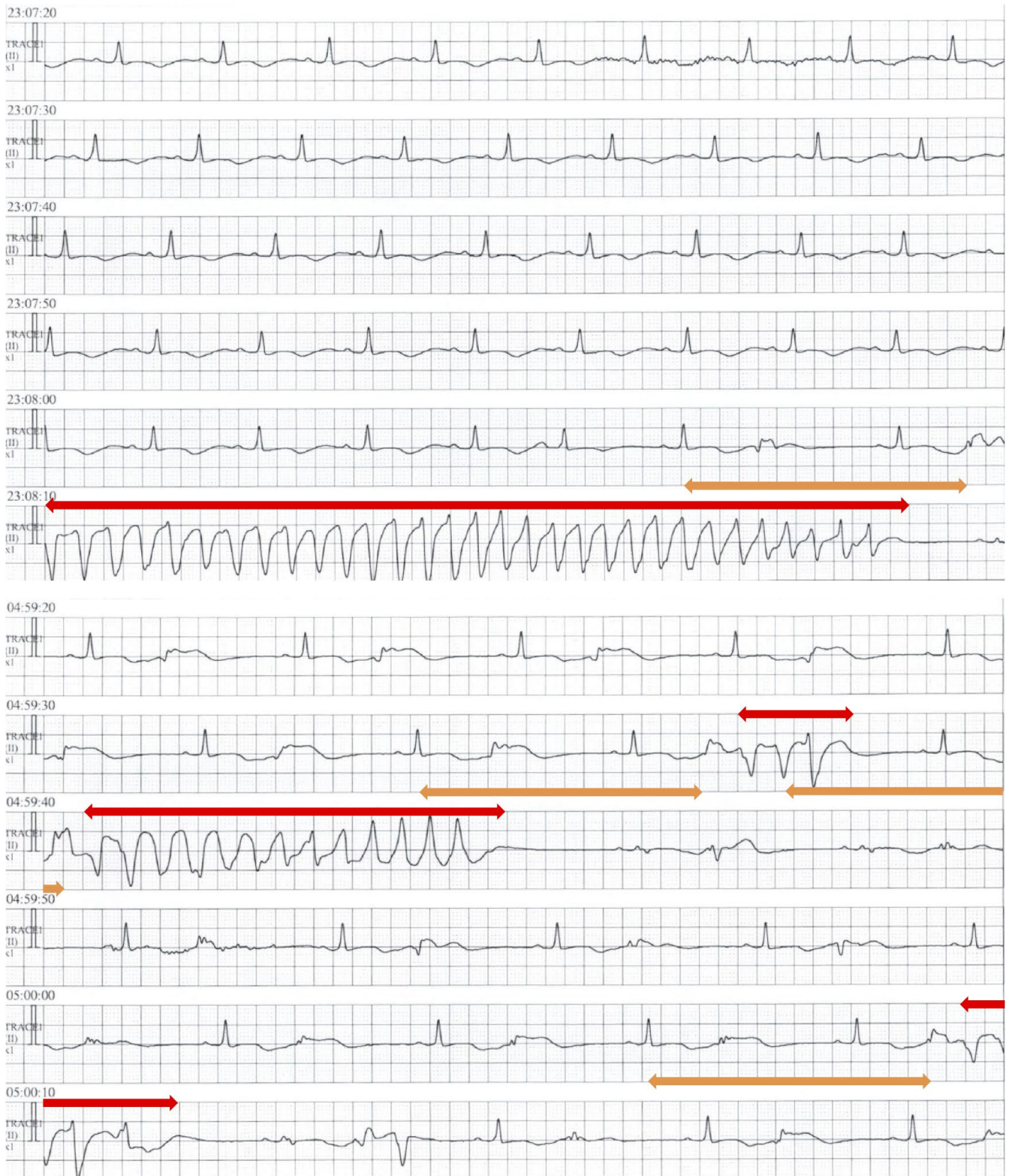
On day 9 of hospitalization, electrical cardioversion of AF was performed via a synchronous direct current discharge, although the possibility of left atrial thrombi was not investigated using transthoracic echocardiography. We observed that sinus rhythm was restored (Figure 1b). Step-wise dose reductions were implemented for the infusions of landiolol hydrochloride and dobutamine hydrochloride, which were eventually stopped, and the patient was also weaned off the mechanical ventilator. Oral carvedilol (5 mg/day) was started for the left ventricular systolic dysfunction, and continuous intravenous infusion of amiodarone hydrochloride was continued at 600 mg/day.

Approximately 6 days after starting the amiodarone hydrochloride infusion (on day 14 of hospitalization), we observed marked prolongation of the QT interval and multiple supraventricular extrasystoles with various deformed QRS-ST-T configurations (Figures 2 and 3). Subsequent ventricular short runs or TdP non-sustained ventricular tachycardia was also documented. Echocardiography revealed that the left ventricular ejection fraction had improved to 41%, and blood tests revealed a serum potassium concentration of 3.9 mmol/L. The magnesium concentration was not investigated. Thus, the diagnosis was amiodarone-induced QT interval prolongation associated with TdP non-sustained ventricular tachycardia, although serum concentrations of N-desethylamiodarone and amiodarone were not measured.

The patient received intravenous administration of potassium and magnesium as well as continuous intravenous infusion of landiolol hydrochloride (starting at  $1.5 \mu\text{g kg}^{-1} \text{min}^{-1}$  which increases by  $1.5 \mu\text{g kg}^{-1} \text{min}^{-1}$  every 30 min to a maximum of  $10 \mu\text{g kg}^{-1} \text{min}^{-1}$ ). The extrasystoles disappeared approximately 2 hr after starting the landiolol hydrochloride infusion, although the QT interval and  $T_{\text{peak}}-T_{\text{end}}$  interval were still prolonged (Figure 4a). We considered amiodarone hydrochloride essential to prevent AF in the patient, and thus, we continued amiodarone hydrochloride as an oral treatment with a dose reduction from 600 mg/day to 200 mg/day. Based on her heart rate, oral carvedilol prescribed with an initial dose of 5 mg/day for week 1 was increased to 10 mg/day for week 2 and then to a maximum dose of 15 mg/day. The dose of landiolol hydrochloride

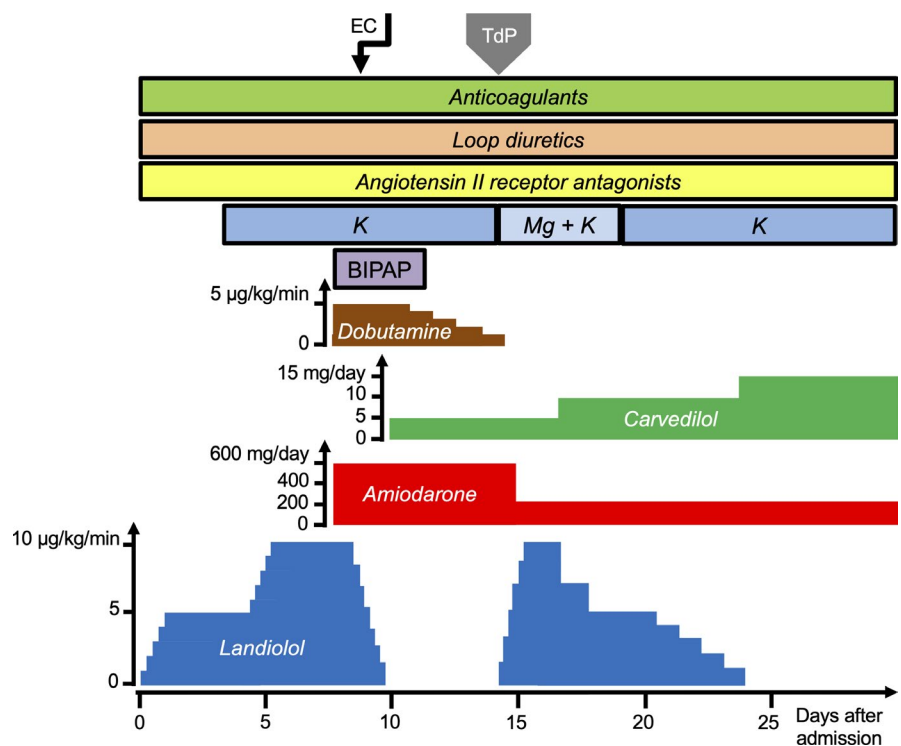
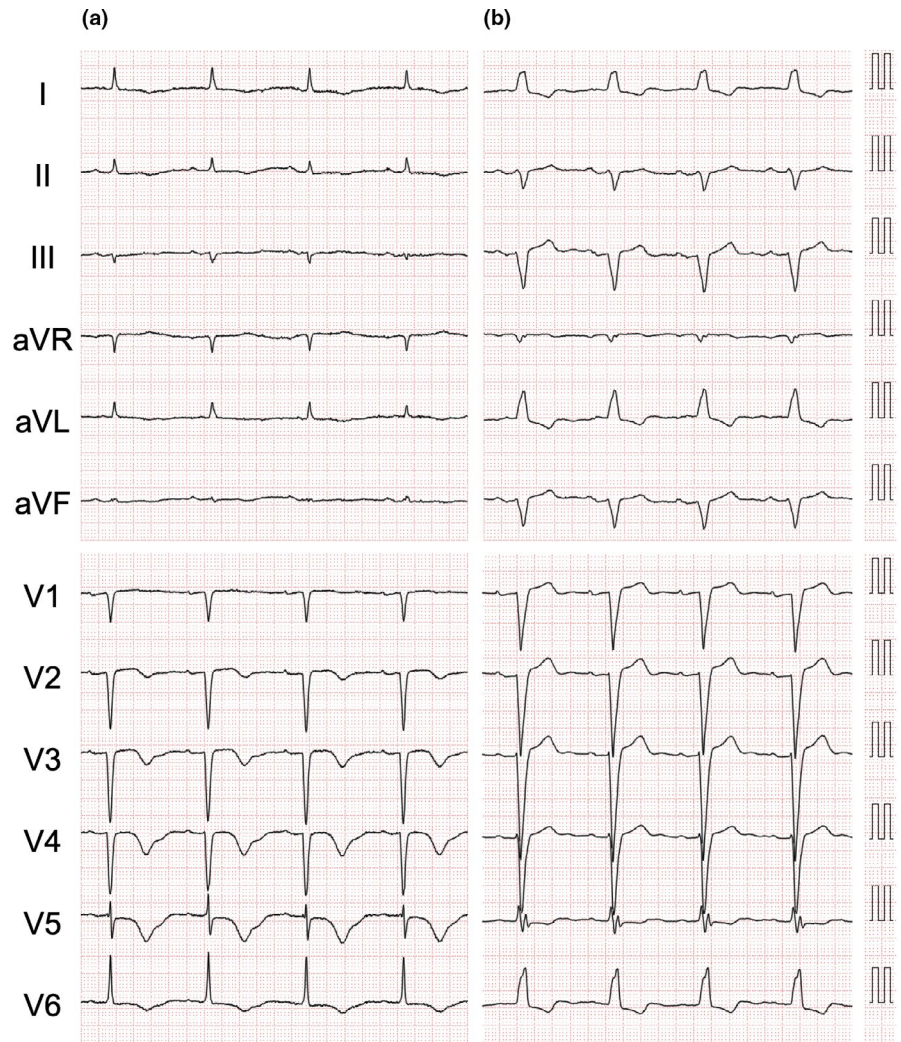


**FIGURE 2** Electrocardiogram recorded on day 14 of hospitalization, approximately 6 days after starting continuous intravenous infusion of amiodarone hydrochloride. Marked QT interval prolongation with upward deflections in the giant negative T waves, so-called giant (negative) T-U waves, and bigeminy of supraventricular extrasystoles (SVE) are observed. The QRS-ST configuration of SVE has a massive ST-segment elevation and undefinable limits of the QRS complex and the T wave, thought to be related to transmurular conduction delay or block



**FIGURE 3** Rhythm strips of continuous electrocardiograms (ECG) from the bedside cardiac monitors approximately 6 days after starting continuous intravenous infusion of amiodarone hydrochloride. Marked prolongation of the QT interval and multiple supraventricular extrasystoles (SVE) with various QRS-ST-T configurations were thought to be related to transmural conduction delay or block, although some of those extrasystoles might be premature ventricular complexes, given the difficulty of determining whether QRS-ST-T complexes have preceding P waves during ECG monitoring. Subsequent ventricular short runs or torsade de pointes (TdP) non-sustained ventricular tachycardias are observed. All TdP events were initiated with a short-long-short R-R cycle sequence (typically extrasystole-compensatory pause-extrasystole) and terminated spontaneously. SVE could be the first beats of TdP. The double-headed orange arrow indicates short-long-short R-R cycle sequence, and the double-headed red arrow indicates the TdP

**FIGURE 4** Electrocardiograms recorded 2 hr after intravenous administration of landiolol hydrochloride (a) and 1 month after discharge (b). Panel (a) shows sinus rhythm (54 beats/min), poor R-wave progression in the precordial leads, and ST-T abnormalities in leads I, II, aVL, and V3–V6. The QTc and a  $T_{\text{peak}}-T_{\text{end}}$  interval are 673 ms and 290 ms, respectively. Panel (b) shows sinus rhythm (57 beats/min) and complete left bundle branch block, with a QTc of 492 ms and a  $T_{\text{peak}}-T_{\text{end}}$  interval of 119 ms. The QTc was calculated using the Bazett formula to adjust the measured QT interval for cycle length by dividing the observed uncorrected QT interval by the square root of the R-R interval



**FIGURE 5** The patient's clinical course with main treatments. BIPAP, biphasic positive airway pressure ventilation; EC, electrical cardioversion; K, oral potassium supplementation; Mg + K, intravenous administration of magnesium and potassium; TdP, torsade de pointes

was initially reduced from  $10 \mu\text{g kg}^{-1} \text{min}^{-1}$  to  $7 \mu\text{g kg}^{-1} \text{min}^{-1}$ , from  $7 \mu\text{g kg}^{-1} \text{min}^{-1}$  to  $5 \mu\text{g kg}^{-1} \text{min}^{-1}$ , and then by  $1 \mu\text{g kg}^{-1} \text{min}^{-1}$  increments every 24 hr. Ultimately, landiolol hydrochloride treatment was stopped without recurrent supraventricular or ventricular extrasystoles.

Cardiac magnetic resonance imaging performed on day 18 of hospitalization revealed only minor late gadolinium enhancement in the inferior region of the mid-left ventricle. Cardiac catheterization was performed on day 30 of hospitalization. Her coronary arteriograms revealed no significant atherosclerotic narrowing, and she had a cardiac index of  $2.50 \text{ L min}^{-1} \text{ m}^{-2}$  and a mean pulmonary capillary wedge pressure of 5 mm Hg. Endomyocardial biopsy of the right ventricular septum revealed mild atrophy of the myocardium and interstitial fibrosis, including deposits of fat tissue, but no inflammatory cells. Diagnostic genetic testing was not performed for the LQTS. Thus, our patient was diagnosed with cardiomyopathy of unknown etiology complicated by AF. The patient was discharged on day 36 of hospitalization, and her clinical course is shown in Figure 5.

The patient remained in good general condition until paroxysmal AF developed approximately 6 months after discharge. Meanwhile, sinus rhythm continued to be observed on the ECGs, although we observed complete left bundle branch block at 1 month after discharge (Figure 4b). The amiodarone hydrochloride dose was decreased from 200 mg/day to 100 mg/day at 1 month after discharge and then from 100 mg/day to 50 mg/day at 2 months after discharge. The left ventricular ejection fraction on the echocardiograph remained unchanged. However, paroxysmal AF occurred despite continued oral treatment with amiodarone hydrochloride at a dose of 50 mg/day (trough serum N-desethylamiodarone, 137 ng/ml; trough serum amiodarone, 142 ng/ml), and the patient developed ADHF again. Electrical cardioversion of AF was performed, and sinus rhythm was restored. Therefore, we made a diagnosis of AF-mediated cardiomyopathy because of the temporal correlation between the onset of AF, heart failure, and rapid aggravation of heart failure symptoms with AF recurrence, despite the optimal medical therapy for heart failure. Thus, the patient underwent catheter ablation to prevent AF.

### 3 | DISCUSSION

Amiodarone is an antiarrhythmic drug commonly used to treat supraventricular and ventricular arrhythmias. However, in Japan, medical insurance does not cover intravenous administration of amiodarone for AF (although oral administration is covered) or amiodarone doses of  $>400 \text{ mg/day}$  for AF. In the United States, amiodarone is not approved by the Food and Drug Administration to treat AF, although it is commonly used for this purpose (Colunga Biancatelli et al., 2019; Zimetbaum, 2012). For adult patients with ventricular fibrillation or hemodynamically unstable ventricular tachycardia, amiodarone is usually administered intravenously during the first 48 hr of therapy at an initial dose of 1,475 mg. After the first 48 hr, the

intravenous administration of amiodarone is continued at a maintenance dose of 600 mg/day for days or weeks, as needed, and then converted to oral administration.

LQTS is a cardiac ion channelopathy (Antzelevitch & Burashnikov, 2011); thus, it is important to understand cardiac ion channels when interpreting ECG tracings. A reduced net repolarizing current could be a possible mechanism for QT interval prolongation, which can be related to reduced outward  $\text{K}^+$  currents (i.e., the rapidly activating delayed rectifier  $\text{K}^+$  current [ $I_{\text{Kr}}$ ] and the slowly activating delayed rectifier  $\text{K}^+$  current [ $I_{\text{Ks}}$ ]), a reduced inward rectifier  $\text{K}^+$  current, or an increased inward late  $\text{Na}^+$  current ( $I_{\text{NaL}}$ ). The changes in the  $\text{Na}^+/\text{Ca}^{2+}$  exchange current ( $I_{\text{NaCa}}$ ) also influence the QT interval. Most cases of drug-induced LQTS are primarily related to blocking of the  $I_{\text{Kr}}$ , although some drugs can also increase the  $I_{\text{NaL}}$  (Hegyí et al., 2020). Changes in  $I_{\text{Kr}}$ ,  $I_{\text{Ks}}$ , and  $I_{\text{NaCa}}$  occur simultaneously with cardiomyopathy.

Antzelevitch (2005) reported that prolongation of the QT interval is not the sole determinant of a drug's potential to cause TdP, and transmural heterogeneity of repolarization is the necessary substrate for developing TdP. Repolarization dispersion in LQTS is enhanced by amplification of electrical heterogeneities intrinsic to the ventricular myocardium due to differences in the time course of repolarization of endocardial cells, midmyocardial cells, and epicardial cells. Moreover, prolonged action potential in LQTS causes phase 2 early afterdepolarization (EAD) by promoting the L-type  $\text{Ca}^{2+}$  current ( $I_{\text{CaL}}$ ) and phase 3 EAD by  $\text{Ca}^{2+}$  overload leading to activation of the inward  $I_{\text{NaCa}}$ . Phase 2 and 3 EADs are major triggers of TdP (El-Sherif et al., 2019).

Although amiodarone is a class III antiarrhythmic agent, it has the electrophysiological characteristics of all four classes (Kodama et al., 1999; Zimetbaum, 2012). Short-term amiodarone treatment primarily blocks  $I_{\text{Kr}}$  and  $\text{Na}^+$  and  $\text{Ca}^{2+}$  channels, whereas long-term treatment primarily blocks  $I_{\text{Ks}}$  (Kamiya et al., 2001). Shenthar et al. (2017) reported that the incidence of drug-induced TdP is approximately 1.5% after intravenous administration of amiodarone. In our patient, we observed "giant (negative) T-U waves" (Kirchhof et al., 2009) 6 days after starting intravenous administration of amiodarone (Figure 2). We suspect that this reflects a combined block of  $I_{\text{Kr}}$  and  $I_{\text{Ks}}$ , together with large transmural dispersion of repolarization and EAD in the ventricular myocardium (Emori & Antzelevitch, 2001). However, the main mechanism of QT interval prolongation and TdP could be the blockade of  $I_{\text{Kr}}$ , because a short-long-short sequence preceded the TdP, and this pause dependence of TdP onset in genetic LQTS is genotype-specific (predominant in LQTS type 2 but absent in LQTS type 1) (Tan et al., 2006). In addition, supraventricular bigeminy might have resulted from the EAD in the atrial myocardium and might have been the first beats of TdP.

The recommended treatment of drug-induced TdP involves (a) discontinuation of the culprit drug, (b) intravenous administration of magnesium and potassium, and (c) intravenous administration of isoproterenol or temporary cardiac pacing. We considered amiodarone essential to prevent AF in our patient with left ventricular systolic dysfunction and thus decreased the dose rather discontinuing the culprit

drug. Moreover, we suspected that intravenous isoproterenol administration would aggravate the transmural dispersion of repolarization (Kang et al., 2017), despite its ability to shorten the QT interval by increasing the heart rate. Thus, we administered  $\beta$ -adrenergic blocker, landiolol, intravenously. In practice,  $\beta$ -blockers prevent TdP in patients with genetic LQTS type 1 or type 2, although  $\beta$ -blockers could induce bradycardia that might aggravate QT interval prolongation.

Landiolol was approved in Japan for controlling rapid heart rate in AF/atrial flutter patients with left ventricular dysfunction and for treating life-threatening ventricular tachyarrhythmias (Ikeda et al., 2019). However, there is limited evidence regarding the effect of landiolol on TdP in LQTS (Kitajima et al., 2017). Landiolol can prevent an increase in the transmural dispersion of repolarization and inhibit  $\text{Ca}^{2+}$  leakage through the type-2 ryanodine receptor, which suppresses EAD as a trigger of TdP, without changing the QT interval. In our patient, the  $T_{\text{peak}}-T_{\text{end}}$  interval reflecting spatial dispersion of ventricular repolarization (Antzelevitch & Burashnikov, 2011) remained prolonged even after landiolol administration, while supra-ventricular extrasystoles resulting from the EAD disappeared. In our patient with pause-dependent TdP, it might have been preferable to administer landiolol under temporary pacing to prevent pauses that trigger TdP (Tan et al., 2006).

Most patients with drug-induced TdP have one or more risk factors, such as advanced age, female sex, hypopotassemia, latent congenital LQTS, underlying structural heart diseases, impaired hepatic drug metabolism, bradycardia, or abrupt slowing of heart rate (a "short-long-short" pattern of R-R cycles), and polypharmacy (Drew et al., 2010). Drugs are contributors to the overall risk, rather than the sole cause of TdP. Our patient had many of these risk factors. Her recent conversion of AF might also have been a risk factor for drug-induced LQTS. It is important to recognize interactions between culprit drugs inducing TdP and other iatrogenic risk factors, such as electrolyte disturbances and polypharmacy. This recognition may be useful for avoiding potentially disastrous consequences, especially in patients with advanced age, female sex, and underlying structural heart disease.

## 4 | CONCLUSIONS

The main mechanism of amiodarone-induced TdP developing in a patient with ADHF caused by AF-mediated cardiomyopathy could be the blockade of  $I_{\text{Kr}}$ . TdP could be suppressed by intravenous administration of landiolol plus magnesium and potassium without discontinuing the culprit drug or overdrive cardiac pacing, mainly by inhibiting EAD as a trigger of TdP.

## ACKNOWLEDGMENTS

We would like to thank Editage (www.editage.com) for English language editing.

## CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this article.

## AUTHOR CONTRIBUTIONS

All authors participated in the conception, design, and writing and revision of the article, and the analysis and interpretation of the data. All authors approved the final version of the manuscript to be published and agreed to act as guarantors of the work.

## ETHICAL APPROVAL

The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board of our hospital.

## CONSENT

Informed consent was obtained from this patient for publication of this case history and associated images.

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**How to cite this article:** Takahashi K, Yamashita M, Sakaue T, et al. Suppression of amiodarone-induced torsade de pointes by landiolol in a patient with atrial fibrillation-mediated cardiomyopathy. *Ann Noninvasive Electrocardiol*. 2021;26:e12842. <https://doi.org/10.1111/anec.12842>