Landiolol suppression of electrical storm of torsades de pointes in patients with congenital long-QT syndrome type 2 and myocardial ischemia

Ryota Kitajima, MD\textsuperscript{a,b}, Takeshi Aiba, MD\textsuperscript{a,6}, Tsukasa Kamakura, MD\textsuperscript{a}, Kohei Ishibashi, MD\textsuperscript{a}, Mitsuru Wada, MD\textsuperscript{a}, Yuko Inoue, MD\textsuperscript{a}, Koji Miyamoto, MD\textsuperscript{a},Hideo Okamura, MD\textsuperscript{a}, Takashi Noda, MD\textsuperscript{a}, Satoshi Nagase, MD\textsuperscript{a}, Yu Kataoka, MD\textsuperscript{a}, Yasuhide Asaumi, MD\textsuperscript{a}, Teruo Noguchi, MD\textsuperscript{a}, Satoshi Yasuda, MD\textsuperscript{a}, Kengo Kusano, MD\textsuperscript{a}

\textsuperscript{a}Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan
\textsuperscript{b}Department of Cardiology, Yokohama Municipal Citizen’s Hospital, Yokohama, Japan

\textbf{A R T I C L E  I N F O}

Article history:
Received 28 December 2016
Received in revised form 24 May 2017
Accepted 30 May 2017
Available online 27 June 2017

Keywords:
Torsade de pointes
Long-QT syndrome
\(\beta\)-blocker
Landiolol

\textbf{A B S T R A C T}

A 76-year-old man who had been diagnosed with long-QT syndrome type 2 had frequent syncopal attacks. The electrocardiogram was monitored, and frequent torsades de pointes (TdP) was detected despite administration of conventional medications: oral propranolol, verapamil, intravenous magnesium sulfate, verapamil, and lidocaine. In contrast, 2 µg/kg/min landiolol could completely suppress TdP. Subsequently, an implantable cardioverter defibrillator was placed, and he was diagnosed with silent myocardial ischemia using myocardial perfusion scintigraphy and coronary angiography. This is the first case report wherein landiolol effectively suppressed TdP due to long-QT syndrome with silent myocardial ischemia.

© 2017 Japanese Heart Rhythm Society. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Landiolol, an ultra-short-acting, \(\beta\)1-superaselective intravenous \(\beta\)-adrenergic blocker, is effective for controlling rapid heart rate in patients with atrial fibrillation or flutter (AF/AFL) with LV dysfunction [1] and immediate recurrence of AF after radiofrequency catheter ablation [2]. Landiolol is applicable not only for atrial tachyarrhythmias, but also for some life-threatening ventricular tachyarrhythmias [3,4].

Congenital long-QT syndrome (LQTS) is characterized by QT prolongation on electrocardiogram (ECG) and polymorphic ventricular tachycardia named torsades de pointes (TdP), resulting in syncope or sudden cardiac death [5]. In long-QT type 2 (LQT2), \(\beta\)-blockers can prevent TdP in almost 60%-70% of the patients; however, some experience an electrical storm of TdP even after receiving a full of medications. Here, we report a case of LQT2 with an electrical storm of TdP due to a silent myocardial ischemia, wherein landiolol suppressed the arrhythmias.

2. Case report

A 76-year-old man had syncopal attacks with remarkable QT interval prolongation (QT > 600 ms) since he was 62 years old. Along with the LQT on ECG, a KCNH2 mutation (e.g., 7 c.1930 G > T p.V644F) was identified using genetic tests, a mutation also present in his son, grandson, and granddaughter, all were diagnosed with LQT on ECG (Supplemental Figure); thus, he was diagnosed with LQT2. Subsequently, he was administered propranolol (30 mg/day) and verapamil (120 mg/day); however, he was admitted to our hospital because of repetitive syncopal attacks and convulsions. ECG at admission showed a QT prolongation (Fig. 1A), but laboratory results were within normal limits (serum [K\textsuperscript{+}] level = 4 mEq/l). ECG monitoring after admission showed frequent TdP (Fig. 1B), and intravenous administration of magnesium sulfate (2 g), verapamil (5 mg), lidocaine (50 mg), and serum [K\textsuperscript{+}] correction was unable to suppress TdP. Although infusion of 1 µg/kg/min landiolol did not have an effect, a concentration of 2 µg/kg/min was able to completely suppress frequent TdP without significant change of the QT-interval (Fig. 1B, C). Landiolol did not change the blood pressure, but the heart rate slightly reduced (minimum, 53 beats per minute [bpm]); therefore, we performed temporary pacing at 80 bpm. No arrhythmias occurred after landiolol administration and pacing; thus, landiolol was gradually

* Correspondence to: Department of Cardiovascular Medicine, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan. Fax: +81 6 6872 7486.
E-mail address: aiba@ncvc.go.jp (T. Aiba).

http://dx.doi.org/10.1016/j.joa.2017.05.007
1880-4276/© 2017 Japanese Heart Rhythm Society. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
tapered off and replaced with 2.5 mg/day bisoprolol. Landiolol was stopped on the 4th day, and an implantable cardioverter defibrillator (ICD) was placed (AAI-DDDR: 80–120 bpm).

Cardiac echocardiography revealed a significantly reduced left ventricular (LV) contraction (LVEF: 20%–25%), myocardial perfusion scintigraphy showed a perfusion redistribution in the infero-septum and antero-septum area of the LV (Fig. 2A, arrow), and coronary angiography revealed 90% stenosis at #6 in the left anterior descending (LAD) artery and 75% stenosis at #1 and #4 PD in the right coronary artery (RCA) (Fig. 2B), which were consistent with the ischemic area. Percutaneous coronary intervention was performed in both LAD and RCA regions. After one-year follow-up, LVEF was normalized (> 50%). Atrial pacing with 2.5 mg/day bisoprolol shortened the QT (QTc) interval to 422 (484) ms, and no arrhythmic event occurred.

3. Discussion

Landiolol is considered to be useful not only for atrial tachyarrhythmias [1,2], but also for ventricular tachyarrhythmias [3,4]; however, evidence for the effect of landiolol for TdP in LQTS is limited. Most of the LQTS-related cardiac events, such as syncope and TdP, occur at a younger age, but some experience events at the middle or elderly age due to some additional triggers, such as bradycardia, hypokalemia, and drugs. In this case, silent myocardial ischemia and reduced LV contraction may increase arrhythmogenicity by increased Ca$^{2+}$ leakage from the ryanodine receptor. Furthermore, the failing heart and myocardial ischemia may increase and/or decrease action potential duration (APD) by changing several ion channel functions, whereas conduction velocity in the ischemic border area is reduced; thus, increased
dispersion of APD and conduction delay worsen the substrate of reentrant arrhythmias.

Beta-blockers regulate phosphorylation of Ca$^{2+}$ handling proteins by not increasing the intracellular [Ca$^{2+}$], resulting in suppression of early afterdepolarization, a trigger of lethal ventricular arrhythmias, without changing the QT interval. Low-dose landiolol may directly inhibit Ca$^{2+}$ transient alternans and Ca$^{2+}$ leakage by suppression of RyR2 hyper-phosphorylation [6]. Thus, landiolol might play an important role, not only as a β1-blocker, but also by having a direct effect on RyR2 and diastolic Ca$^{2+}$ leakage, resulting in suppressed TdP in this case. However, β-blockers also suppress sinus node function, which may induce bradycardia that might often aggravate TdP in LQT2. Therefore, temporary pacing or pacing from ICD could suppress bradycardia and shorten the QTc interval (from 533 to 484 ms) and prevent sudden cardiac death. Based on the 2012 ACCF/AHA/HRS guidelines for device-based therapy of cardiac rhythm abnormalities [7], ICD therapy is not indicated for patients with a completely reversible disorder in the absence of structural heart disease. Furthermore, the 2014 EHRA/HRS/APHRS Expert Consensus on Ventricular Arrhythmias [8] recommended a wearable defibrillator for re-evaluation of LVEF after 90 days of revascularization. In patients with LVEF > 35%, ICD implantation is not necessary, but patients may have a benefit only under medical treatment. Thus, in this case, we should have used a wearable defibrillator for 3 months and re-evaluated the indications of ICD.

However, this patient was diagnosed not only with a coronary arterial disease, but also with LQT2. This KCNH2-V644F mutation is located in segment 6 (S6) of the KCNH2 (HERG) channel, indicating a higher risk of cardiac events because of the S5-pore-S6 lesion compared with other non-pore lesions [9,10]. Although revascularization...
could perfectly normalize coronary perfusion and LVEF, a risk for LQTS still existed. He has also a significant family history, with his son, grandson, and granddaughter having the same KCNH2 mutation and repetitive syncope due to TdP even after beta-blocker medications. Thus, ICD has already been indicated for his son and grandson. Based on the 2012 JCS guideline for diagnosis and management of patients with long-QT and Brugada syndromes [11] and the 2013 EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of patients with Inherited Primary Arrhythmic Syndromes [12], ICD indication for patients with LQT with repetitive syncope even after adequate beta blocker therapy is class IIa. In contrast, this patient had been syncope-free for > 14 years under medical treatment until the events described in this report; thus, indication for ICD in this patient was only class IIb.

Conflict of interest

Takeshi Aiba has received consulting fees from Ono Pharmaceutical. The other authors declare no conflict of interest related to this study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.joa.2017.05.007.

References

[1] Nagai R, Kinugawa K, Inoue H, et al. Urgent management of rapid heart rate in patients with atrial fibrillation/flutter and left ventricular dysfunction: comparison of the ultra-short-acting beta1-selective blocker landiolol with digoxin (J-Land Study). Circ J 2013;77:908–16.
[2] Ishigaki D, Arimoto T, Hayama T, et al. Prevention of immediate recurrence of atrial fibrillation with low-dose landiolol after radiofrequency catheter ablation. J Arrhythm 2015;31:279–85.
[3] Wada Y, Aiba T, Tsujita Y, et al. Practical applicability of landiolol, an ultra-short-acting beta1-selective blocker, for rapid atrial and ventricular tachyarrhythmias with left ventricular dysfunction. J Arrhythm 2016;32:82–8.
[4] Miwa Y, Ikeda T, Mera H, et al. Effects of landiolol, an ultra-short-acting beta1-selective blocker, on electrical storm refractory to class III antiarrhythmic drugs. Circ J 2010;74:856–63.
[5] Shimizu W. Update of diagnosis and management of inherited cardiac arrhythmias. Circ J 2013;77:2867–72.
[6] Kobayashi S, Susa T, Ishiguchi H, et al. A low-dose beta1-blocker in combination with milrinone improves intracellular Ca2+ handling in failing cardiomyocytes by inhibition of milrinone-induced diastolic Ca2+ leakage from the sarcoplasmic reticulum. PLoS One 2015;10:e0114314.
[7] Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2013;61:e6–75.
[8] Pedersen CT, Kay GN, Kalman J, et al. EHRA/HRS/APHRS expert consensus on ventricular arrhythmias. Europace 2014;16:1257–83.
[9] Nagaoa K, Shimizu W, Itoh H, et al. Mutation site dependent variability of cardiac events in Japanese LQT2 form of congenital long-QT syndrome. Circ J 2008;72:694–9.
[10] Shimizu W, Moss AJ, Wilde AA, et al. Genotype-phenotype aspects of type 2 long QT syndrome. J Am Coll Cardiol 2009;54:2052–62.
[11] Aonuma K, et al. Guidelines for diagnosis and management of patients with long QT syndrome and Brugada syndrome (JCS 2012). Circ J 2011.
[12] Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. J Arrhythm 2014;30:1–28.