Novel rate control strategy with landiolol in patients with cardiac dysfunction and atrial fibrillation

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Abstract

While patients with acute heart failure often have tachycardia with atrial fibrillation, there have been no established medical tools that control tachycardia safely and definitely. Digoxin has been recommended as a first choice in the former guidelines, but it takes time to affect and has a risk of adverse events particularly for those with chronic kidney disease. Landiolol is a recently innovated ultra-short-acting beta-blocker with 251-fold β1/β2 selectivity, which was originally indicated only to control peri-operative supra-ventricular tachyarrhythmia by 2013 in Japan. We aimed to review how to use landiolol in patients with cardiac dysfunction and tachycardia due to atrial fibrillation. We reviewed recently conducted randomized control trials using landiolol, recently updated guidelines, as well as current practical use of landiolol. Japan landiolol vs. Digoxin (J-Land) study demonstrated that landiolol was more effective to control tachycardia than digoxin in atrial fibrillation patients with left ventricular dysfunction in 2013. Given the result, the revised Japanese heart failure guideline recommends landiolol for rate control during atrial fibrillation in acute heart failure patients as Class IIa with evidence level B. Currently in Japan, landiolol is used for rate control, even in patients with advanced heart failure receiving continuous infusion of inotropes. The clinical use of landiolol in patients with cardiac dysfunction and tachycardia due to atrial fibrillation is increasing. Further studies are warranted to investigate the implication of faster and safer rate control using landiolol.

Keywords  Haemodynamics; Beta-blocker; Atrial fibrillation

Background

Patients with acute heart failure often have tachyarrhythmias as a history or as a present form on admission. Particularly, approximately 30% of such cohorts have atrial fibrillation on admission as a cause of tachyarrhythmia. A sustained rapid ventricular response further deteriorates cardiac function, and rapid managements are required for such a situation.

Electronic cardioversion is the first choice for cardiogenic shock, whereas in most other situations with relatively preserved haemodynamics, definite rate control tools would be a key to successful management of acute heart failure.

Former Japanese guidelines for pharmacotherapy of atrial fibrillation (Japanese Circulation Society 2008) and for treatment of acute heart failure (Japanese Circulation Society 2011) recommended digoxin as the first choice for rate control with reduced cardiac function, given its positive inotropic effects. However, digoxin is not so fast to get sufficient reduction in heart rate, because digoxin has a slowly developing negative chronotropic effect by way of vagal stimulation. Furthermore, digoxin might be proarrhythmic provoking delayed after depolarization especially in failing myocytes. Amiodarone might also be considered, but it would be insufficient for rapid rate control even during the intravenous infusion. We should also be cautious about its serious adverse drug effects including lung fibrosis and thyrotoxicosis. Beta-blockers are good alternatives, but most of them had been available only as an oral form until 2010s. More definite and safer medications have been warranted.

Beta-blocker as an alternative of digoxin

Currently, there are three commercially available major intravenous forms of β-blockers in Japan: landiolol, esmolol, and
propranolol. In Europe, atenolol and metoprolol are also available as intravenous forms of β-blockers, both of which are indicated for hypertension.\(^1\)\(^9\)

Propranolol has a 2 h half-life.\(^1\)\(^9\) It would take a long time to be resolved once adverse events including hypotension occur. Propranolol may not be safe in patients with reduced cardiac function. As Sasao and colleagues demonstrated in rabbits,\(^1\)\(^9\) both landiolol and esmolol reduced heart rate dose-dependently. However, mean blood pressure declined significantly within 1 min following the administration of esmolol, particularly when at high dose (5 mg/kg), whereas mean blood pressure remained maintained following the administration of landiolol at any doses (1, 3, and 10 mg/kg). Given very short half-time and high selectivity of β1 receptor (4 min and 251-fold β1/β2 selectivity),\(^2\)\(^0\) landiolol might be theoretically the most ideal medication to control tachycardia in patients with reduced cardiac function. Nevertheless, the indication of landiolol had been restricted for the use of supra-ventricular tachyarrhythmias,\(^2\)\(^4\) and its use for congestive heart failure had been contraindicated until 2013 when the result of Japan landiolol vs. Digoxin (J-Land) study was presented.\(^2\)\(^2\)

**J-Land study**

We conducted the J-Land study to demonstrate the efficacy and safety of landiolol to control heart rate in patients with reduced cardiac function.\(^2\)\(^2\) In this trial, patients with atrial fibrillation or atrial flutter who had left ventricular ejection fraction 25–50%, New York Heart Association functional Class III or IV, and heart rate ≥120 b.p.m. were randomized into the landiolol arm or digoxin arm. Digoxin was set as a control agent given it was a first choice for the rate control in patients with left ventricular systolic dysfunction at that time.\(^9\)\(^,\)\(^1\)\(^0\) Primary end point was the percentage of patients who achieved both a heart rate <110 b.p.m. and a ≥20% reduction in heart rate at 2 h following the administration of either agent. There had been no consensus for the target heart rate in atrial fibrillation patients except for the RACE II trial,\(^2\)\(^3\) and we adopted the same goal as a primary end point.

Following the randomization, the landiolol arm received landiolol at an initial dose of 1 μg/kg/min, which was titrated up to 10 μg/kg/min until the target heart rate was attained within the tolerance of patients (Figure 1). The digoxin arm received an intravenous bolus administration of 0.25 mg digoxin followed by an additional one if necessary. Any anti-arrhythmic agents, sympathomimetic agents, sympathetic agents, defibrillator use, catheter ablation, or pacemaker implantation were prohibited during the first 2 h when the primary end point was assessed.

The primary end point was successfully met, and the landiolol was significantly superior for the achievement of faster heart rate control compared with the digoxin (48% vs. 14%, \(P < 0.001\)). The superiority of landiolol was demonstrated also in any subgroup analyses stratified by baseline characteristics including age, sex, heart rate, blood pressure, left ventricular ejection fraction, and renal function.\(^2\)\(^4\) Among the patients with an estimated glomerular filtration ratio <30 mL/min/1.73 m\(^2\), the landiolol arm had less adverse events compared with the digoxin arm, probably given that digoxin is excreted via kidney. Nevertheless, we should pay special attention to up-titrate the dose of landiolol to prevent hypotension, bradycardia, and worsening heart failure.

*Figure 1* The protocol of J-Land study (reused with permission).\(^2\)\(^2\) *Dose of digoxin could be reduced down to 0.125 mg in patients being treated with oral digoxin. **Additional digoxin was administered if necessary.*
Landiolol is not widely used for those with cardiac dysfunction in Europe thus far, although such an indication is receiving great concern. In the current European Society of Cardiology guideline published in 2016, the smallest dose of β-blocker is recommended as a first-line to achieve rate control in case of atrial fibrillation with cardiac dysfunction, followed by amiodarone and digoxin.

## Practical use of landiolol in real-world practice

The post-marketing surveillance for landiolol in Japan investigated the real-world use of landiolol in atrial fibrillation or atrial flutter patients with heart failure. Of 1121 patients from 209 institutes, the rate of successful heart rate control with landiolol was achieved in 77.5% with only 3% of hypotension. Other investigators reported favourable outcomes with landiolol was achieved in patients with atrial fibrillation who receive continuous infusion of rate control in case of atrial fibrillation with cardiac dysfunction, followed by amiodarone and digoxin.

We want to present a case for better understanding of the practical use of landiolol in advanced heart failure patients with atrial fibrillation. The 21-year-old male patient with non-ischaemic cardiomyopathy receiving a continuous infusion of dobutamine was referred to our institute to consider durable ventricular assist device implantation, given his progressive deterioration of cardiac function with left ventricular end-diastolic diameter of 82 mm and left ventricular ejection fraction of 34%. In Japan, we can implant durable ventricular assist devices only as bridge to transplantation, and all patients should receive careful examinations to be listed for heart transplantation before the surgery.

On admission, his haemodynamics was relatively preserved with heart rate of 110 b.p.m. with sinus rhythm and systolic blood pressure of 96 mmHg (Figure 2). Following the onset of atrial fibrillation, systolic blood pressure decreased down to below 80 mmHg due to >180 b.p.m. of tachycardia, which was refractory to 0.25 mg i.v. of digoxin. We initiated intravenous administration of landiolol at 2 μg/kg/min and titrated up to 8 μg/kg/min under the inotropes support, followed by immediate rate control with heart rate below 120 b.p.m. and eventual sinus conversion, leading to the successful heart transplant listing and durable ventricular assist device implantation bridged by up-titration of inotropes and intra-aortic balloon pumping support. Note that incremental dose of landiolol by itself did not result in lowering blood pressure.

A recent retrospective study in 11 patients with sinus tachycardia after on-pump cardiovascular surgery showed that concomitant use of low-dose landiolol (2.6 ± 1.3 μg/kg/min) with inotrope infusion reduced heart rate, improving stroke volume. Another study in 20 patients with acute decompensated heart failure showed that low-dose landiolol therapy (1.5 μg/kg/min) in combination with milrinone reduced heart rate by 11%, maintaining haemodynamics. Positive inotropic effect via β2 receptor may not be inhibited by...

### Table 1 Previous studies investigating the efficacy of landiolol in patients with heart failure and tachyarrhythmia

| References | Year | Patients characteristics | Design | Control | N | LVEF |
|------------|------|--------------------------|--------|---------|---|------|
| Kobayashi S41 | 2012 | ADHF + milrinone | Retrospective | - | 20 | 24 ± 7% |
| Nagai R (J-Land)22 | 2013 | Af + LV dysfunction | Prospective | Digoxin | 200 | 25–50% |
| Adachi T37 | 2014 | SVT + HF | Retrospective | - | 52 | 32 ± 12% |
| Kobayashi S35 | 2014 | Af + ADHF | Retrospective | - | 23 | 34.5 ± 8.6% (HFrEF, N = 12) |
| Wada Y31 | 2016 | Af or VT + LV dysfunction | Retrospective | - | 51 | 34 ± 16% |
| Kikuchi S32 | 2017 | SVT + ADHF | Retrospective | Diltiazem | 59 | 42% (landiolol) |
| Matsui Y33 | 2019 | AT + ADHF | Retrospective | - | 51 | 41 ± 13% |
| Yamashita T (AF-CHF landiolol survey)35 | 2019 | Af + HF | Prospective | - | 1,121 | 40.7 ± 15.9% |
| Oka E34 | 2019 | Af/AT + LV dysfunction | Retrospective | - | 77 | 33.1 ± 13.7% |

ADHF, acute decompensated heart failure; Af, atrial fibrillation; AT, atrial tachycardia; HF, heart failure; HFrEF, heart failure with preserved ejection fraction; HfPEF, heart failure with reduced ejection fraction; LV, left ventricular; SVT, supraventricular tachycardia; VT, ventricular tachycardia.
low-dose landiolol due to its high selectivity to $\beta_1$ receptor. Landiolol may rather facilitate a longer diastolic filling time, which enables heart to work in a better economic way with improved cardiac output. We have preliminary data showing more improved New York Heart Association functional class in responders with landiolol compared with those with digoxin in the sub-analysis of J-Land study (data not shown).

There are several ongoing prospective trials investigating the impact of landiolol on reducing heart rate, preventing atrial fibrillation, or conversion to sinus rhythm, in adults or paediatric patients with left ventricular dysfunction, those with septic shock, or those following cardiac surgery. Further implications of landiolol therapy on successful rate control and improved clinical outcomes in patients with heart failure or any other conditions are future concerns.

Conclusions

The J-Land study demonstrated that landiolol, an ultra-short-acting $\beta_1$ super-specific blocker, achieved faster rate control targeting below 110 b.p.m. within 2 h compared with digoxin, a former guideline-recommended first choice, among acute heart failure patients with reduced cardiac function and atrial tachyarrhythmia. Faster rate control by landiolol was not associated with increased adverse events, whereas digoxin was accompanied by more adverse events among those with severe renal dysfunction.

Even though patients with advanced heart failure require inotropes infusion, landiolol can effectively reduce heart rate without interfering concomitantly used inotropes. Further studies are warranted to investigate the implication of faster and safer rate control using landiolol.

Conflict of interest

None declared.

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