What Determines the Response to Landiolol?
— Reply —

We appreciate the comments from Drs. Nitta et al with their interest in our study.¹ We agree that patients with severely reduced left ventricular ejection fraction (LVEF) might be associated with non-response to landiolol treatment. In our study, LVEF tended to be lower in the non-responder group than in the responder group (P-value: 0.060), although LVEF was not a predictor of non-response to landiolol by multivariate analysis. There were several reasons for the discrepancy of the result.

Firstly, our study included both heart failure with reduced EF (HFrEF; EF <40%) and HF with mid-range EF (HFmrEF; EF 40–50%). The mean LVEF was 34.3±13.0% and 26.8±15.9%, respectively, for the AF and AFL/AT groups (P=0.083); however, the proportion of patients with HFrEF did not differ between the 2 groups (67.7% vs. 66.7%, P=1.000). Four patients in the AFL/AT group were non-responders to landiolol treatment despite LV function being relatively preserved (i.e., HFmrEF), which could offset the influence of low LVEF that might be associated with non-response to landiolol. Secondly, the AFL/AT group consisted of 12 patients (≈16%), which was a higher AFL/AT proportion in comparison with previous studies.²³ Most of the patients (75%) in the AFL/AT group developed tachycardia-induced cardiomyopathy leading to severely reduced LV function. These patients were hospitalized for newly diagnosed HF, and it was speculated that their cardiac function were normal before persistent atrial tachyarrhythmia, considering the fact that their LV function recovered after controlling the tachyarrhythmia. In this study, HF patients with extremely low LVEF and severe hemodynamic compromise requiring intensive care management were excluded. Thirdly, as Dr. Nitta mentioned, the small study population would not have enough statistical

Figure. Example of heart rate trend during landiolol treatment in an 85-year-old man with heart failure with reduced ejection fraction (EF 26%) caused by a previous myocardial infarction. Although he was in sinus rhythm at the time of admission, paroxysmal atrial fibrillation (PAF), which spontaneously terminated within a few minutes, was recorded after admission (A). The frequency of atrial firing gradually increased and AF became persistent (B). Landiolol treatment (maximum dose 2μg/kg/min) decreased the heart rate and finally resulted in AF termination and maintenance of regular sinus rhythm (C).
The mechanism of AT is classified as macro-reentry, micro-reentry, enhanced automaticity or triggered activity. Sometimes it is difficult to differentiate the mechanism of AT in the clinical setting even by electrophysiological study. In some patients with AF, an automatic mechanism is considered to play an important role in the initiation and perpetuation of AF. Therefore, landiolol might be effective in patients with AF and AT in whom the mechanism is associated with enhanced automaticity. Indeed, we have experienced a case of repetitive atrial firing that was suppressed by landiolol resulting in maintenance of regular sinus rhythm (Figure). Landiolol might be effective for AF termination, especially in cases of enhanced trigger-based AF rather than substrate-based AF. However, as show in Figure 2B of the original article, the heart rate (HR) trend graph during AFL/AT was constant with very low RR interval variability. If the mechanism of the AT was associated with abnormal automaticity, the HR trend might show warming up and cooling down or high RR interval variability. In addition, 3 of 7 patients with AT underwent catheter ablation at later date and clinical AT was reproducibly induced and terminated by programmed stimulation, the activation map during AT did not show a centrifugal pattern and the post-pacing interval measured by entrainment pacing from more than 2 remote sites during AT were almost identical to the atrial tachycardia cycle length. Therefore, we confirmed that the mechanism of AT in these cases was macro-reentry. The mechanism of the other cases of AT was uncertain. Patients with typical AFL and macro-reentrant AT belonged to the non-responder group, and it was hard to control their HR if landiolol did not reduce the atrioventricular conduction ratio.

Disclosures

The authors declare no conflicts of interest.

Acknowledgments

None.

References


Eiichiro Oka, MD, PhD
Yu-ki Iwasaki, MD, PhD
Wataru Shimizu, MD, PhD
Department of Cardiovascular Medicine, Nippon Medical School, Tokyo, Japan