Effects of GLP-1 Receptor Agonists on Heart Rate and the Autonomic Nervous System Using Holter Electrocardiography and Power Spectrum Analysis of Heart Rate Variability

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Long- and short-acting glucagon-like peptide 1 receptor agonists (GLP-1RAs) liraglutide and lixisenatide, which are available for diabetes therapy, may act on the autonomic nervous system to increase heart rate (1,2). We performed a prospective, single-center, randomized, open-label study with a 1:1 allocation ratio using a 24-h Holter electrocardiogram to compare the effects of these GLP-1RAs on the autonomic nervous system. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008. Informed consent was obtained from all patients participating in this study. The study is registered at University Hospital Medical Information Network Clinical Trials Registry (UMIN000017770).

Sixty patients with type 2 diabetes who were admitted for diabetes treatment and had not received dipeptidyl peptidase-4 inhibitors or GLP-1RAs were randomly divided into a liraglutide (age 64.9 ± 12.7 years, HbA_{1c} 10.3 ± 2.5% [89.1 mmol/mol], BMI 24.6 ± 4.8 kg/m^2, diabetes duration 7.8 ± 7.8 years) or lixisenatide group (age 62.1 ± 15.6 years, HbA_{1c} 10.7 ± 2.3% [93.4 mmol/mol], BMI 25.2 ± 2.1 kg/m^2, diabetes duration 7.2 ± 6.6 years) after completing a 24-h Holter electrocardiography recording. There were no differences in the baseline characteristics between the groups. Three patients in each group had a previous history of coronary vascular events.

Liraglutide administration was by titration starting at 0.3 mg and increasing by 0.3 mg every week until reaching 0.9 mg. Lixisenatide administration started at 10 μg and increased by 5 μg every week until reaching 20 μg. After the maximum dose of the drugs had continued for 1 week or more, the Holter electrocardiography was repeated. Each component at a frequency of 0.04–0.15 Hz was regarded as low frequency (LF), and at 0.2–0.4 Hz, high frequency (HF). The LF/HF ratio was calculated by power spectral analysis with a sampling time of 1,024 s and then performed at 30-min intervals using an R-R interval spectral analysis.

Mean daily heart rates using Holter electrocardiography increased significantly from baseline in the liraglutide group at all times (66.5 ± 10.2 to 79.7 ± 10.5 bpm, $P = 0.00021$). By contrast, heart rates of the lixisenatide group increased significantly after only 5 h following administration of lixisenatide (09:00–13:00 h, $P = 0.001$ to 0.015), but mean heart rates per day remained unchanged (69.1 ± 8.6 to 71.7 ± 10.6 bpm, $P = 0.172$) (Fig. 1). In the liraglutide group, significant differences were observed in 16 of the 24 points examined in the LF/HF ratio (mean 1.58 ± 0.78 to 1.95 ± 0.89, $P = 0.017$), whereas in the lixisenatide group, no significant changes were found in the LF/HF ratio from the baseline value at any point (mean 1.95 ± 1.16 to 1.75 ± 0.74, $P = 0.330$).

Previous studies have indicated that liraglutide increases the heart rate by sympathetic nervous system enhancement (3), which would suggest that similar increases of heart rate due to sympathetic nervous system enhancement should also increase the LF/HF ratio in the lixisenatide group during the same hours. However, no such changes were detected, suggesting that another mechanism is involved in heart rate increase. Recent studies report that GLP-1 receptors are distributed at the sinoatrial node of the heart (4,5). This is consistent with the finding that lixisenatide increases heart rates only during its action duration without increasing the LF/HF ratio. Liraglutide may have markedly increased heart rates through the persistent, relative sympathetic enhancements, but sinoatrial node stimulation was also present during the pharmacological

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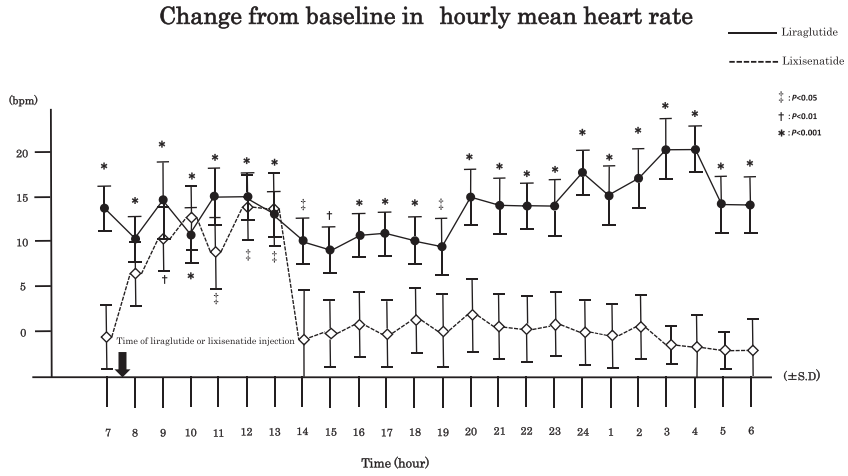

Figure 1—Diurnal profile of heart rate changes in patients with type 2 diabetes at baseline and after treatment with liraglutide or lixisenatide. Data are mean ± SD. ‡$P < 0.05$, †$P < 0.01$, *$P < 0.001$ vs. baseline

action duration, similar to lixisenatide. As a result, heart rate may have increased more markedly at night when parasympathetic activity is predominant. Increases in heart rate associated with GLP-1RAs have been attributed to relative sympathetic enhancements related to the inhibition of the autonomic nervous system, especially the parasympathetic nervous system. The current results suggest that not only relative sympathetic enhancements but also direct sinoatrial node stimulation contribute to GLP-1RA–related increases in heart rate.

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