Potential Risk of Hypoglycemia in Patients with Heart Failure

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Summary
The properties of glucose changes in patients with chronic heart failure remain elusive. In the present study, we investigated the sequential changes of interstitial glucose concentrations in patients with chronic heart failure and heart disease who were not undergoing antidiabetic therapy.

A glucose monitoring device (FreeStyle Libre Pro) was attached to the backside of an upper arm and the interstitial glucose concentration was monitored every 15 minutes for 1 week. Eleven patients with chronic heart failure (Heart failure (+)) and 7 patients with chronic heart diseases but not with heart failure (Heart failure (−)) were enrolled. The average level and peak value of interstitial glucose concentrations, and the duration of hyperglycemia (≥ 140 mg/dL) were not significantly different between Heart failure (+) and Heart failure (−). The duration of hypoglycemia (< 80 mg/dL) was significantly longer and the trough value was significantly lower in Heart failure (+) compared with Heart failure (−). Most of the patients in Heart failure (+) were exposed to a long duration of hypoglycemia from midnight to morning. Importantly, none of the patients who showed hypoglycemia complained of any subjective symptoms during hypoglycemia. Malabsorption may be one of the mechanisms of hypoglycemia.

In summary, patients with chronic heart failure are at risk of developing hypoglycemia even if they do not undergo any antidiabetic therapy.

Key words: Hyperglycemia, Continuous glucose monitoring

Heart failure is one of the most serious health issues in industrialized countries and is a major cause of death. Abnormal glucose metabolism is an independent risk factor for the development of heart failure. The recent progress in blood glucose monitoring devices has enabled us to measure continuous blood glucose levels for more than a week. These data revealed that blood glucose levels in diabetic patients changed more dynamically than expected.

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Methods

Subjects and study design: Eighteen patients who regularly undergo medical examinations in the outpatient service of the Cardiology Department of Oita University Hospital were enrolled. The protocol was in agreement with the guidelines of the ethics committee of our institution, and written informed consent was obtained from each patient before enrollment. None of the patients were taking glucose fluctuations impaired the salvage of acute myocardial infarction and that perioperative glucose fluctuations increased the risk of postoperative atrial fibrillation.

Taken together, we hypothesized that plasma glucose concentrations may change dynamically in patients with chronic heart failure, which potentially affect pathogenesis and the progression of heart failure. In the present study, we investigated the sequential changes in interstitial glucose levels in patients with chronic heart failure who had not been taking any antidiabetic agents or undergoing insulin therapy.

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Comparison of baseline characteristics, comorbidity, laboratory data, and echocardiography data: The baseline characteristics of the patients are shown in Table I. Among the 7 Heart failure (−) patients, 6 had ischemic heart disease and 1 hypertensive heart disease. Among the 11 Heart failure (+) patients, 4 had dilated cardiomyopathy, 3 hypertrophic cardiomyopathy, 2 valvular heart disease, 1 cardiac sarcoidosis, and 1 ischemic heart disease. There was no significant difference in age between the groups. Body mass index (BMI) and geriatric nutritional risk index (GNRI), an indicator of nutrition status, were significantly lower in the Heart failure (+) than the Heart failure (−) group. There was no significant difference in alcohol habits between the groups and there were no current smokers in either group. The comorbidity rates for diabetes mellitus, hypertension, and hyperuricemia were not significantly different between the groups, while the comorbidity rate for dyslipidemia was significantly higher in Heart failure (−) compared to Heart failure (+). The levels of blood urea nitrogen (BUN), creatinine, and HbA1c were not significantly different between the groups. The NT-proBNP level was significantly higher, CTR was significantly larger, and ejection fraction (EF) was significantly decreased in Heart failure (+) compared with Heart failure (−). Early diastolic left ventricular filling velocity/peak atrial filling velocity ratio (E/A) and early diastolic left ventricular filling velocity/early diastolic mitral annular velocity ratio (E/e’). Values are the mean ± SD.

### Results

**Table I. Baseline Characteristics, Laboratory Data, and Echocardiography Data**

|                      | Heart failure (−) | Heart failure (+) | P value |
|----------------------|-------------------|-------------------|---------|
| **Age (years)**      | 69.6 ± 6.4        | 71.8 ± 11.2       | 0.342   |
| **Male/female**      | 5/2               | 7/4               |         |
| **BMI (kg/m²)**      | 27.1 ± 4.4        | 21.9 ± 3.3        | 0.016   |
| **GNRI**             | 117.6 ± 6.4       | 93.1 ± 13.3       | < 0.01  |
| **Alcohol drinkers** | 28.6%             | 36.4%             | 0.73    |
| **Current smokers**  | 0%                | 0%                |         |
| **Comorbidity**      |                   |                   |         |
| Diabetes mellitus    | 42.9%             | 18.2%             | 0.25    |
| Hypertension         | 57.1%             | 54.5%             | 0.91    |
| Dyslipidemia         | 85.7%             | 36.4%             | 0.04    |
| Hyperuricemia        | 28.6%             | 45.5%             | 0.47    |
| **BUN (mg/dL)**      | 18.3 ± 4.3        | 21.0 ± 7.4        | 0.556   |
| **Cr (mg/dL)**       | 0.88 ± 0.24       | 1.14 ± 0.37       | 0.124   |
| **NT-proBNP (pg/mL)**| 46.1 ± 27.6       | 1440.8 ± 1189.4   | < 0.01  |
| **HbA1c (%)**        | 5.9 ± 0.3         | 5.8 ± 0.5         | 0.807   |
| **CTR (%)**          | 47.4 ± 2.1        | 61.5 ± 6.8        | < 0.01  |
| **EF (%)**           | 64.1 ± 5.8        | 48.7 ± 15.1       | 0.021   |
| **E/A**              | 0.88 ± 0.35       | 1.93 ± 1.38       | 0.056   |
| **E/e’**             | 12.2 ± 2.7        | 23.6 ± 16.3       | 0.113   |

BMI indicates body mass index; GNRI, geriatric nutritional risk index; BUN, blood urea nitrogen; Cr, creatinine; NT-proBNP, N-terminal pro-brain natriuretic peptide; CTR, cardio-thoracic ratio; EF, ejection fraction; E/A, early diastolic left ventricular filling velocity/early diastolic mitral annular velocity ratio. Values are the mean ± SD.

Glucose monitoring and examinations: All participants were connected to a glucose monitoring device (Freestyle Libre Pro: Abbott Japan Co., Ltd, Tokyo) on the back side of the right or left upper arm for at least 7 days, and the interstitial glucose level was monitored every 15 minutes. All of the participants underwent chest X-rays, echocardiography, and blood examinations including NT-proBNP. Echocardiography was performed using a Vivid E9 (GE Healthcare Japan Co., Ltd, Tokyo) by an ultrasonographer who had no relation to this study.

Statistical analysis: Statistical analysis was performed with StatView 5.0.1 statistical software (SAS Institute Inc., Cary, NC, USA). Quantitative data are presented as the mean ± SD. Differences between the two groups were evaluated by the Mann-Whitney U test. The rates of smoking, alcohol drinking, comorbidity, and drug usage between the 2 groups were evaluated by the chi-square test. A P value < 0.05 was considered statistically significant.
the results of sequential monitoring of interstitial glucose levels. The average level and peak value of interstitial glucose concentrations, and the duration of hyperglycemia (≥ 140 mg/dL) were not significantly different between Heart failure (+) and Heart failure (−). The duration of hypoglycemia (< 80 mg/dL) was significantly longer and the trough value was significantly lower in Heart failure (+) compared to Heart failure (−). There was no significant difference in mean amplitude of glycemic excursions (MAGE), which is an indicator of glucose fluctuations, between the groups.

**Time course of hyperglycemia and hypoglycemia:** Figure 1 demonstrates the representative time course of hyperglycemia and hypoglycemia during randomly selected 24 hours in individual patients. The black areas indicate hypoglycemia < 80 mg/dL, and the oblique lines indicate hyperglycemia ≥ 140 mg/dL. Most of the Heart failure (+) patients demonstrated hypoglycemia with a long duration, from midnight to early morning. Meanwhile, the Heart failure (−) patients exhibited a lower incidence and shorter duration of hypoglycemia than Heart failure (+).

**Representative contrast-enhanced abdominal computed tomography (CT):** Figure 2 shows images of contrast-enhanced abdominal CT of the patient labeled “Q” in Figure 1 who was assigned to Heart failure (+) and showed a long duration of hyperglycemia. The white arrows indicate slight thickening of the intestinal wall.

**Influence of medication:** Drug use which may influence hypoglycemia is shown in Table III. No patients involved in the present study took any antiarrhythmic agents or α blockers. There were no significant differences in the usage rate of both β blockers and ACEi/ARB between Heart failure (+) and Heart failure (−) patients.

**Discussion**

To the best of our knowledge, this is the first report that shows the risk of hypoglycemia in patients with chronic heart failure without antidiabetic therapy. In general, antidiabetic therapy is regarded as a major cause of hypoglycemic events. A previous study has shown that patients who underwent insulin and/or oral antidiabetic therapy sometimes exhibit hypoglycemia with or without subjective symptoms. Severe hypoglycemia was more common in the participants randomized to intensive glycemic

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**Table II. Results of Sequential Glucose Monitoring**

|                        | Heart failure (−) (n = 7) | Heart failure (+) (n = 11) | P value |
|------------------------|---------------------------|---------------------------|---------|
| Average glucose level (mg/dL) | 114.2 ± 20.5              | 104.2 ± 16.3              | 0.258   |
| Peak glucose level (mg/dL)    | 208.4 ± 28.1              | 204.5 ± 38.3              | 0.786   |
| Hyperglycemic duration (minutes) | 1763.6 ± 1826.2          | 1348.6 ± 1146.4           | 0.964   |
| Hypoglycemic duration (minutes) | 758.6 ± 1241.1            | 2260.0 ± 1510.4           | 0.027   |
| Trough glucose level (mg/dL)   | 71.4 ± 19.0               | 53.9 ± 10.1               | 0.037   |
| MAGE                    | 64.0 ± 13.8               | 80.0 ± 19.4               | 0.135   |

MAGE indicates mean amplitude of glycemic excursions. Values are mean ± SD. Hyperglycemia was defined as an interstitial glucose level ≥ 140 mg/dL while hypoglycemia was an interstitial glucose level < 80 mg/dL.
control than in those randomized to standard control in the ACCORD study. It is noteworthy that non-diabetic patients sometimes experienced severe hypoglycemia without any glucose lowering interventions. In the present study, the patients who developed hypoglycemia had no subjective symptoms and they did not notice the hypoglycemia. These results indicate that heart failure may be one of the causes of hypoglycemia without antidiabetic therapy. Unconscious hypoglycemia is a life-threatening event and may eventually worsen the prognosis of patients with heart failure. Several previous studies have demonstrated that severe hypoglycemic episodes increased the mortality risk in patients with type 1 and type 2 diabetes mellitus. Another study showed that patients suffering from severe hypoglycemia have a 1.77-fold higher all-cause mortality in type 2 diabetes compared to patients without severe hypoglycemia. Cardiac ischemia or fatal arrhythmia during recognized or unrecognized episodes of hypoglycemia may be the mechanism responsible for the results. Cardiac ischemia or QT dispersion were reportedly observed during hypoglycemic episodes. The mechanisms by which heart failure provokes hypoglycemia have yet to be clarified. Appetite reduction and subsequent body weight loss and malnutrition may be a possible mechanism of the hypoglycemia in heart failure. GNRI, an indicator of nutrition status, and BMI were significantly lower in Heart failure (+) than Heart failure (−) in the present study. These results may suggest inadequate calorie intake in the Heart failure (+) group. However, no patients reported that they skipped their breakfast in the questionnaire surveys which were collected at the end of glucose monitoring. As a limitation, it was difficult to determine the caloric intake, because the breakfast menu varied and no information about the amount of breakfast eaten was available from the simple description in the questionnaire. We also did not find any obvious signs or symptoms indicating neurohumoral disorder in the patients. Malabsorption of nutrients due to gastrointestinal edema and insufficient peripheral circulation are other possible mechanisms. In fact, we found that the intestinal wall was slightly thickened in contrast-enhanced abdominal CT images of the Heart failure (+) patients, which might have had an influence on nutrient absorption. Cachectic state is an independent risk factor for mortality in patients with chronic heart failure. A diagnosis of cachexia is difficult due to the lack of well-established diagnostic criteria. The lower BMI level and GNRI in the Heart failure (+) group may indicate nutritional disturbance in this group.

The possible influence of medication should also be taken into account. Antiarrhythmic agents, angiotensin-converting enzyme inhibitors (ACEi), β blockers, α blockers, and angiotensin II receptor blockers (ARB) may potentially induce hypoglycemia. However, we did not find a significant difference in medications between the groups.

**Table III. Medications That May Influence Hypoglycemia**

|                          | Heart failure (−) | Heart failure (+) | *P* value |
|--------------------------|------------------|------------------|-----------|
| Cibenzoline/disopyramide | 0 (0%)           | 0 (0%)           |           |
| α blockers               | 2 (28.6%)        | 1 (9.1%)         | 0.27      |
| β blockers               | 3 (42.9%)        | 8 (72.7%)        | 0.20      |
| ACE inhibitor/ARB        | 5 (71.4%)        | 7 (63.6%)        | 0.73      |
| ACE inhibitor            | 1                | 5                | 0.17      |
| ARB                      | 4                | 2                | 0.09      |

ACE inhibitor indicates angiotensin-converting enzyme inhibitors; and ARB, angiotensin II receptor blockers.
Conclusions

Patients in the present study with chronic heart failure had a risk of hypoglycemia even if they did not take any antidiabetic therapy. Most of the patients had no subjective symptoms during hypoglycemic events.

Disclosure

Conflicts of interest: None to declare.

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