The Effect of Dapagliflozin Treatment on Epicardial Adipose Tissue Volume and P-Wave Indices: An Ad-hoc Analysis of The Previous Randomized Clinical Trial

Takao Sato, Yoshifusa Aizawa, Sho Yuasa, Satoshi Fujita, Yoshio Ikeda and Masaaki Okabe

Cardiology, Tachikawa General Hospital, Nagaoka, Japan

Aim: Epicardial adipose tissue (EAT) may be associated with arrhythmogenesis. P-wave indices such as P-wave dispersion and P-wave variation indicated a slowed conduction velocity within the atria. This study investigated the effect of dapagliflozin on EAT volume and P-wave indices.

Methods: In the present ad hoc analysis, 35 patients with type 2 diabetes mellitus and coronary artery disease were classified into dapagliflozin group (n=18) and conventional treatment group (n=17). At baseline, EAT volume, HbA1c and plasma level of tumor necrotic factor-α (TNF-α) levels, echocardiography, and 12-lead electrocardiogram (ECG) were performed. EAT volume was measured using computed tomography. Using 12-lead ECG, P-wave indices were measured.

Results: At baseline, EAT volumes in the dapagliflozin and conventional treatment groups were 113 ± 20 and 110 ± 27 cm³, respectively. Not only HbA1c and plasma level of TNF-α but also echocardiography findings including left atrial dimension and P-wave indices were comparable between the two groups. After 6 months, plasma level of TNF-α as well as EAT volume significantly decreased in the dapagliflozin group only. P-wave dispersion and P-wave variation significantly decreased in the dapagliflozin group only (-9.2 ± 8.7 vs. 5.9 ± 19.9 ms, p=0.01; -3.5 ± 3.5 vs. 1.7 ± 5.9 ms, p=0.01). The change in P-wave dispersion correlated with changes in EAT volume and plasma level of TNF-α. In multivariate analysis, the change in EAT volume was an independent determinant of the change in P-wave dispersion.

Conclusion: Dapagliflozin reduced plasma level of TNF-α, EAT volume, and P-wave indices, such as P-wave dispersion. The changes in P-wave indices were especially associated with changes in EAT volume.

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Key words: SGLT-2 inhibitor, Epicardial adipose tissue, Atrial fibrillation, P-wave indices

Abbreviations: AF, atrial fibrillation; DM, diabetes mellitus; EAT, epicardial adipose tissue; CAD, coronary artery disease; ECG, electrocardiogram; SGLT-2, sodium–glucose cotransporter 2; CT, computed tomography.
Epicardial adipose tissue (EAT) is most commonly defined as adipose tissue surrounding the heart, located between the myocardium and the visceral pericardium. EAT is associated with fatal and nonfatal coronary events in the general population independent of traditional cardiovascular risk factors. Furthermore, EAT is known to be involved not only in the pathogenesis of coronary artery disease (CAD) but also in the development of arrhythmogenesis. EAT produces various bioactive molecules that significantly affect cardiac function.

P-wave duration represents the time required for a sinus impulse to propagate from the sinus node to the entire atrium. A prolonged P-wave duration correlates with a slowed conduction velocity within the atria. P-wave dispersion and P-wave variation are measured using P-wave duration in any of the 12 electrocardiogram (ECG) leads.

Sodium–glucose cotransporter-2 (SGLT-2) inhibitors reduce blood glucose by increasing urinary glucose excretion, which is associated with body weight loss. In addition, the administration of SGLT-2 inhibitors decreases EAT volume. The EMPA-REG OUTCOME trial, the CANVAS trial, and the DECLARE–TIMI 58 clinical trial reported reduced death from cardiovascular causes and decreased hospitalization for heart failure and progression to end-stage kidney disease in patients with type 2 DM treated with SGLT-2 inhibitors. However, there are no reports evaluating the association between P-wave indices such as P-wave dispersion and SGLT-2 inhibitor use. The present study was designed to investigate the effects of dapagliflozin on EAT volume, measured using multislice computed tomography (CT) and P-wave indices.

**Methods**

**Study Population (Fig. 1)**

This is an extension study of our previous one. Briefly, the study included 40 patients with type 2 DM and CAD. Patients were randomly allocated into the dapagliflozin group (5 mg dapagliflozin, n=20) or the conventional treatment group (n=20) by an independent administrator using permuted block method. Patients in the dapagliflozin group received only dapagliflozin, while those in the conventional treatment group were prescribed single or multiple glucose-lowering drugs, except SGLT-2 inhibitors.

The patients were followed for 6 months, and in addition to routine laboratory examination, EAT volume on CT, plasma level of TNF-α, HbA1c level, interactive 24-variable model homeostatic model assessment insulin resistance-2 (iHOMA2 %S), and HOMA-IR were measured at baseline and 6 months later. In the present study, echocardiography data was retrospectively collected at baseline. ECG was also ret-
nosed with stress electrocardiology or radioisotope, (2) significant stenosis on coronary angiography, and (3) previous acute coronary syndrome including unstable angina and myocardial infarction that was diagnosed with coronary angiography and treated with percutaneous coronary intervention. However, the patients who underwent percutaneous coronary intervention for acute coronary syndrome received optimal medical therapy and were enrolled 6 months after initial percutaneous coronary intervention.

**EAT Volume Measurement with Multislice CT**

To obtain EAT measurements, CT angiography images were assessed using electrocardiography-gated cardiac CT scans on a 320-slice multi-detector CT scanner (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan). The protocol has been described previously; briefly, volumetric measurements were performed on axial views with a 0.5-mm slice thickness. The superior border for measuring the EAT volume was set at the lower surface of the left pulmonary artery origin. The inferior border for the measurement was set at the left ventricular apex. The EAT area was calculated by tracing an ROI that included the heart and EAT. The ROI was manually placed outside the line of the visceral pericardium on the cross-sectional axial image. The area outside the traced pericardium was excluded (Fig. 2). EAT volumes were quantified by calculating the total volume of tissue having a CT density between -150 and -30 Hounsfield units. EAT volume measurement using CT was performed by an experienced cardiologist who was blinded to the quantitative analysis data and the base-

**Inclusion Criteria**

Patients with hemoglobin A1c (HbA1c) level ≥ 6.5% despite treatment with only diet and exercise therapy or treatment with oral antidiabetic agents were eligible for enrollment.

**Exclusion Criteria**

Conversely, patients aged >75 years who received insulin therapy; who had a history and current state of atrial AF, iodine-based contrast agent allergy, renal insufficiency (estimated glomerular filtration rate <45 mL/min/1.73 m²), or chronic inflammatory disease; or who underwent coronary artery bypass grafting surgery were excluded from the analysis.

**Definitions**

**iHOMA2 %S and HOMA-IR**

iHOMA2 %S was measured as an index of insulin resistance based on a previous report. In addition, HOMA-IR was calculated based on the following formula: HOMA-IR = [fasting serum insulin (µU/mL) x fasting blood sugar (mg/dL)]/405.

**CAD**

Documented CAD encompassed one or more of the following: (1) stable angina pectoris that was diagnosed with stress electrocardiology or radioisotope, (2) significant stenosis on coronary angiography, and (3) previous acute coronary syndrome including unstable angina and myocardial infarction that was diagnosed with coronary angiography and treated with percutaneous coronary intervention. However, the patients who underwent percutaneous coronary intervention for acute coronary syndrome received optimal medical therapy and were enrolled 6 months after initial percutaneous coronary intervention.

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line clinical characteristics.

**Echocardiography**

Transthoracic echocardiogram was obtained using an echocardiography system equipped with a 3.3-MHz cardiac sector transducer (Vivid E95, GE Healthcare, Japan). We collected left atrial dimension (LAD), left ventricular end-diastolic diameter (LVDd), left ventricular end-systolic diameter (LVDs), ejection fraction (EF), and E/e’ value to evaluate LV function, especially LA volume. For the analysis, we averaged measurements of three consecutive cardiac cycles.

**P-wave Indices (Fig. 3)**

Maximum and minimum P-wave durations were retrospectively calculated from the standard 12 ECG leads. P-wave dispersion was derived by subtracting the minimum P-wave duration from the maximum P-wave duration in any of the 12 ECG leads. P-wave onset was determined as the initial deflection from the isoelectric baseline defined by the T-P segment, and the P-wave offset was defined as the junction of the end of the P-wave and its return to baseline\(^{20}\). P-wave dispersion can be calculated by measurements on paper. Using handheld calipers, manual measurement was performed by increasing the ECG rate to 50 mm/s and the voltage to 20 mm/mV, accompanied by the use of magnification. Each P-wave duration of the 12 ECG leads was calculated three times, and the mean value was defined as a P-wave duration in any of the 12 ECG leads. In addition, P-wave variation was defined as the standard deviation of the P-wave duration. These evaluations of P-wave dispersion and P-wave variation were analyzed both at baseline and follow-up. These analyses were performed by an investigator blinded to the EAT volume measurement results.

**Statistical Analyses**

All statistical analyses were performed using SPSS version 22 (IBM Japan, Tokyo, Japan). Continuous data with a nonparametric statistical distribution are presented as means ± standard deviation, and categorical data are presented as count percentages. Comparisons between the dapagliflozin and conventional treatment groups were performed using Mann–Whitney’s U test for continuous data and Fisher’s exact test for categorical data. Comparisons between baseline and follow-up were performed using the Wilcoxon signed rank test. Correlations between the changes in metabolic parameters, including EAT volume, and the changes in P-wave indices, including P-wave dispersion, were evaluated using Spearman rank-order correlation coefficient analysis. Similarly, the correlations between P-wave dispersion and P-wave variation were also evaluated using Spearman rank-order correlation coefficient analysis. Multiple regression analysis (stepwise method) was performed to investigate indepen-

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**Fig. 3.** A representative P-wave dispersion measurement

(a) At baseline, measurement of leads II and V2 demonstrated maximum and minimum P-wave durations of 135 and 70 ms, respectively, and P-wave dispersion of 65 ms.

(b) At 6-month follow-up, measurement of leads V6 and aVL demonstrated maximum and minimum P-wave durations of 125 and 70 ms, respectively, and P-wave dispersion of 55 ms.
throughout the study, except when hyperglycemia, hypoglycemia, or adverse events occurred. The average HbA1c value of the 35 patients was 7.2 ± 0.5%. There were no significant differences in age, sex, body weight, lipid profile, glycemic marker, adipose-associated markers, such as EAT volume, and P-wave indices, such as P-wave dispersion, between the two groups at baseline (Table 1). Both groups had a comparable history of myocardial infarction prevalence. Table 2 shows the therapies prescribed for patients in both groups. In addition, LAD, LVDDd, LVDs, EF, and E/e' value were comparable between the two groups (Table 1).

### Results

**Patient Characteristics**

Of 40 patients, 5 did not receive a follow-up ECG. Thus, the present study consisted of 35 patients across the two treatment groups: dapagliflozin group (N=18) and conventional therapy group (N=17) (Fig. 1). The treatment regimen remained unchanged throughout the study, except when hyperglycemia, hypoglycemia, or adverse events occurred.

Table 1. Baseline clinical characteristics

|                        | Dapagliflozin (N=18) | Conventional therapy (N=17) | P-value |
|------------------------|-----------------------|----------------------------|---------|
| Age (years)            | 67 ± 5                | 68 ± 7                     | 0.75    |
| Male/female (n)        | 15 / 3                | 12 / 5                     | 0.44    |
| Body weight (kg)       | 71.7 ± 14.9           | 68.2 ± 11.4                | 0.43    |
| BMI                    | 26.2 ± 4.8            | 25.1 ± 3.3                 | 0.45    |
| Hypertension           | 13 (72)               | 11 (64)                    | 0.72    |
| Smoking, ever          | 5 (28)                | 5 (29)                     | 1.00    |
| Previous myocardial infarction | 8 (44) | 9 (53) | 0.58 |

| Lipid profile          |                       |                            |         |
|jabi LDL (mg/dL)        | 88 ± 28               | 82 ± 15                    | 0.44    |
| TG (mg/dL)             | 144 ± 95              | 153 ± 78                   | 0.75    |
| HDL (mg/dL)            | 46 ± 13               | 40 ± 9                     | 0.08    |

| Glycemic marker        |                       |                            |         |
| HbA1c (%)              | 7.1 ± 0.7             | 7.3 ± 1.0                  | 0.38    |
| FBS (mg/dL)            | 148 ± 42              | 133 ± 20                   | 0.28    |
| HOMA-IR                | 2.8 ± 1.6             | 2.6 ± 1.6                  | 0.80    |
| iHOMA 2 %S             | 118 ± 90              | 130 ± 71                   | 0.58    |

| Ultrasound cardiography|                       |                            |         |
| LAD (mm)               | 41.4 ± 6.1            | 40.5 ± 4.9                 | 0.61    |
| LVDDd (mm)             | 50.2 ± 5.6            | 48.3 ± 6.0                 | 0.32    |
| LVDs (mm)              | 35.3 ± 7.6            | 34.5 ± 6.1                 | 0.69    |
| EF (%)                 | 55.7 ± 10.6           | 54.8 ± 9.9                 | 0.77    |
| E/e'                   | 8.9 ± 2.8             | 8.6 ± 3.0                  | 0.78    |

| P-wave indices         |                       |                            |         |
| P-wave dispersion (msec)| 48.2 ± 12.4           | 44.6 ± 15.3                | 0.49    |
| P-wave variation (msec)| 15.6 ± 3.6            | 14.6 ± 3.6                 | 0.46    |

| Adipose-associated marker|                       |                            |         |
| EAT volume (cm³)        | 113 ± 20              | 110 ± 27                   | 0.52    |
| TNF-α (pg/mL)           | 2.2 ± 0.6             | 2.3 ± 0.5                  | 0.81    |

Data are presented as means ± SD or the number (percentage). LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment insulin resistance; iHOMA-2, interactive, 24-variable model homeostatic model assessment insulin resistance-2; LAD, left atrial dimension; LVDDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; EF, ejection fraction; EAT, epicardial adipose tissue; TNF-α, tumor necrotic factor-α.

dent determinants of the change in P-wave dispersion using the changes in EAT volume, plasma level of TNF-α, and HbA1c level as explanatory variables. A two-sided P-value of <0.05 was considered statistically significant for all analyses.

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However, the change in HbA1c level in the dapagliflozin group was comparable with that in the conventional treatment group (-0.33 ± 0.32% vs. -0.28 ± 0.29%, p = 0.58). Regarding insulin resistance, the changes in HOMA-IR and iHOMA2 values were similar in both groups, and both groups showed

Table 3. The change in each parameter after treatment

|                           | Dapagliflozin (n = 18) | Conventional therapy (n = 17) | P-value |
|---------------------------|------------------------|-------------------------------|---------|
| ∆Body weight (kg)         | -3.0 ± 3.9**           | 0.3 ± 3.0                     | 0.01    |
| Glycemic marker           |                        |                               |         |
| ∆HbA1c (%)                | -0.33 ± 0.32*          | -0.28 ± 0.29                  | 0.58    |
| ∆HOMA-IR                  | -0.97 ± 1.6*           | -0.42 ± 0.86*                 | 0.68    |
| ∆iHOMA2 %S                | 55.7 ± 62.9*           | 38.2 ± 53.1                   | 0.52    |
| P-wave indices            |                        |                               |         |
| ∆P-wave dispersion        | -9.2 ± 8.7             | 5.9 ± 19.9                    | 0.01    |
| ∆maximum P-wave duration  | -7.5 ± 12.0            | 5.9 ± 14.9                    | 0.01    |
| ∆minimum P-wave duration  | 1.7 ± 13.6             | 0.0 ± 14.8                    | 0.73    |
| ∆P-wave variation         | -3.5 ± 3.5             | 1.7 ± 5.9                     | 0.01    |
| Adipose-associated marker |                        |                               |         |
| ∆EAT volume (cm³)         | -15.2 ± 12.8**         | 3.0 ± 11.9                    | 0.01    |
| ∆TNF-α (pg/mL)           | -0.58 ± 0.74**         | 0.08 ± 0.30                   | 0.01    |

Data are expressed as means ± SD; **P<0.05 compared with baseline of each group, *P<0.1 compared with baseline of each group.
HOMA-IR, homeostatic model assessment insulin resistance; iHOMA-2, interactive, 24-variable model homeostatic model assessment insulin resistance-2; EAT, epicardial adipose tissue; TNF-α, tumor necrotic factor-α.

Changes in Body Weight and Laboratory Data (Table 3)

Compared with baseline, at the 6-month follow-up, the decrease in body weight in the dapagliflozin group was significantly greater than that in the conventional treatment group (-3.0 ± 3.9 vs. 0.3 ± 3.0 kg, p = 0.01). However, the change in HbA1c level in the dapagliflozin group was comparable with that in the conventional treatment group (-0.33 ± 0.32 vs. -0.28 ± 0.29%, p = 0.58). Regarding insulin resistance, the changes in HOMA-IR and iHOMA2 values were similar in both groups, and both groups showed
improved insulin resistance compared with baseline.

**Changes in Adipose Tissue-Associated Markers (Table 3)**

As shown in Table 3, at baseline, the EAT volumes in the dapagliflozin and conventional treatment groups were comparable at 113 ± 20 and 110 ± 27 cm³, respectively. At 6-month follow-up, EAT volume in the dapagliflozin group was significantly decreased compared with baseline. Furthermore, the change in EAT volume in the dapagliflozin group was significantly greater than that in the conventional treatment group (-15.2 ± 12.8 vs. 3.0 ± 11.9 cm³, p = 0.01). Plasma level of TNF-α at 6-month follow-up significantly decreased compared to baseline in the dapagliflozin group, but not in the conventional treatment group. In addition, the change in plasma level of TNF-α in the dapagliflozin group was significantly greater than that in the conventional treatment group (-0.58 ± 0.74 vs. 0.08 ± 0.30 pg/mL, p = 0.01).

**Changes in P-wave Dispersion and P-wave Variation (Table 3 and Fig. 4)**

At baseline, P-wave dispersion and P-wave variation were similar between the two groups. However, at 6-month follow-up, P-wave dispersion and P-wave variation were significantly shortened compared to baseline in the dapagliflozin group, but not in the conventional treatment group. Furthermore, the change in the maximum P-wave duration in the dapagliflozin group significantly decreased at 6-month follow-up compared to that in the conventional treatment group. The change in the minimum P-wave duration was comparable in both groups.

Furthermore, although the absolute value of P-wave dispersion did not correlate with the absolute values of EAT volume and plasma level of TNF-α (data not shown), changes in P-wave dispersion significantly correlated with changes in EAT volume and plasma level of TNF-α. A significant correlation was observed between the changes in P-wave dispersion and P-wave variation (R = 0.83, p < 0.01).

**Independent Determinants of the Change in P-Wave Dispersion**

In a previous study, there was a significant correlation between the changes in body weight and EAT volume (13). Therefore, the change in body weight was excluded from the multivariate logistic regression analysis. Multivariate analysis revealed that the change in EAT volume was an independent determinant of the change in P-wave dispersion (Table 4).
Fig. 4. Correlation between changes in P-wave dispersion or P-wave variation and changes in EAT volume or inflammatory marker (TNF-α)

(a, b): Figures (a) and (b) show the correlation between the change in P-wave dispersion and changes in epicardial adipose tissue volume and plasma level of TNF-α. See text for details.

(c, d): Figures (c) and (d) show the correlation between the change in P-wave variation and changes in epicardial adipose tissue volume and plasma level of TNF-α. See text for details.

Table 4. Multivariate logistic regression analysis

|                                | β    | P     |
|--------------------------------|------|-------|
| The change in P-wave dispersion|      |       |
| ΔEAT volume                    | 0.49 | <0.01 |
| Δplasma of TNF-α               | 0.12 | 0.46  |
| ΔHbA1c                         | -0.14| 0.34  |

β: standard regression coefficient
significantly correlated in the dapagliflozin group. The present finding might be congruous with those of the abovementioned reports. In addition, the decrease in EAT thickness also improved obesity-related cardiac morphological and functional changes during body weight loss. In the present study, a reduction in EAT volume and body weight loss were observed in the dapagliflozin group. In fact, the reversal of P-wave indices with obesity treatment has been reported. The present finding may be in line with these reports. Although speculative, P-wave indices might also be influenced by not only reduction in EAT volume alone but also by cardiac morphological and functional changes. Furthermore, according to a previous report, aggressive risk factor management, including body weight management, glycemic control, and other treatments, improves the long-term success of AF ablation; this might also be influenced by the reduction in EAT volume and inflammatory status.

Possibility of SGLT-2 Inhibitors that Reduce P-Wave Indices

Interestingly, DM has been reported to be associated with not only arrhythmogenesis such as the incidence of AF but also with the risk of heart failure. Thus, DM has a close association with arrhythmia and heart failure. However, there are few reports on the incidence of AF during administration of an SGLT-2 inhibitor. In several reports, SGLT-2 inhibitors had no significant effect on the incidence of AF. However, a previous report has described that only the dapagliflozin subgroups tended to have a decreased incidence of AF. In the present study, P-wave dispersion and P-wave variation in the dapagliflozin group were significantly decreased, via the reduction of EAT volume and inflammatory factors such as TNF-\( \alpha \) compared to those in the control group treated with other glucose-lowering drugs. However, whether the incidence of AF was reduced by SGLT-2 inhibitor administration remains unknown. As mentioned above, a P-wave dispersion of \( \geq 80 \) ms and a P-wave variation of \( \geq 35 \) ms were risk factors for incident AF. In the present study, the P-wave dispersion and P-wave variation in the present study were 48 ms and 15 ms in the dapagliflozin group and 44 ms and 14 ms in the control group, respectively. Therefore, with respect to P-wave indices, the present study might have included patients resistant to the development of AF. Therefore, a long-term follow-up study will be required in the future to determine whether the treatment investigated here leads to a decreased incidence of AF.

Limitations

This study had a few limitations. First, the number of study patients was small. Second, in the conventional treatment group, different antidiabetic medications were prescribed, which might be confounding factors in the present study. Third, whether the reduction in EAT volume was caused by dapagliflozin remains unclear because the reduction in EAT volume might be achieved with weight loss alone. Fourth, the present study evaluated the EAT volume that included the left ventricle. However, a previous report described that the EAT between the left atrium and the esophagus was the most significantly associated with AF, compared to the EAT in other areas. Therefore, regarding EAT volume, the EAT around the left atrium area should have been measured. In addition, EAT is not the only source of TNF-\( \alpha \). SGLT-2 inhibitors have also been reported to reduce the abdominal visceral adipose tissue. Therefore, other adiposity markers such as waist circumference and visceral adipose tissue should have be measured and correlated with the results in the present study. Furthermore, it has previously been reported that weight reduction caused a reduction in the pericardial adipose tissue and the left atrial volume in patients with atrial fibrillation. Therefore, left atrial volume (diameter) using echocardiography should have been also measured at the 6-month follow-up in the present study. Fifth, P-wave indices have been reported to be affected by other drugs, such as \( \beta \)-blockers. However, in the present study, with the exception of oral glucose-lowering drugs according to the protocol, no changes in any medication were undertaken. Sixth, the present study included patients with a history of CAD. Whether similar results will be observed in patients without a history of CAD is unclear. Finally, in the present study, dapagliflozin reduced P-wave dispersion and P-wave variation via changes in metabolic parameters including EAT volume. However, the aim of did not evaluate the effect of the present results on the incidence of AF. Therefore, a long-term follow-up study will be required in the future to determine whether the treatment investigated here leads to a decreased incidence of AF.

Conclusion

Dapagliflozin reduced plasma level of TNF-\( \alpha \), EAT volume, and P-wave indices, such as P-wave dispersion. The changes in P-wave indices were especially associated with changes in EAT volume.
Competing Interests
All authors declare no competing interests.

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