Assessment of body temperature (BT) is essential in the clinical setting to establish baseline measures and to assess patient response to, or the effectiveness of, treatments. Measurement of this vital sign is particularly important in subjects with cardiovascular disease, whose thermoregulation may have a clinical impact on adverse outcomes.1–4

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BT cycles regularly up and down throughout the day, a process controlled by the oscillation of circadian rhythm. BT is divided into peripheral and core BT, and each has its own rhythm.5 Core BT normally fluctuates during the day, with the lowest levels around 4 a.m. and the highest in the late afternoon. The circadian rhythm of core BT is mainly regulated by the anterior hypothalamic/preoptic areas at the top of the control hierarchy6 and is modified by various factors, both endogenous and exogenous.7 Peripheral BT is connected to this circadian core BT rhythm, but it is reported to vary slightly from the rhythm of core temperature.

Background: Differences in regulating factors and the clinical implications of body temperature variability (BTV) between subjects with and without diabetes have not been clarified to date.

Methods and Results: In 66 subjects with ischemic heart disease (33 with diabetes and 33 without diabetes), BTV, the difference between the highest and lowest temperature measurements, and body temperature standard deviation (BT SD) were measured from axillary body temperature (ABT) records of 3 consecutive days and followed for 16.4±8.4 months. In subjects without diabetes, BT and BT SD were closely associated with endothelial function as evaluated on flow-mediated dilation (BTV, R=0.33, P=0.026; BT SD, R=0.41, P=0.029), whereas there was a poor association in subjects with diabetes. In the absence of an interrelationship between vascular function and thermoregulation, the contribution of inflammation to BT was increased in subjects with diabetes (BTV, 0.59±0.21°C for C-reactive protein [CRP] <0.08 mg/dl vs. 0.79±0.28°C for CRP >0.08 mg/dl, P=0.014). Event-free survival analysis showed that in subjects with diabetes, higher BT SD was associated with shorter event-free survival (log-rank P=0.012), but this relationship was not found in subjects without diabetes.

Conclusions: In subjects with diabetes, the interrelationship between thermoregulation and vascular function was disrupted and the effect of inflammation on thermoregulation was enhanced, so that BTV had a sufficient predictive value for cardiovascular events in diabetic subjects. (Circ J 2013; 77: 1844–1853)

Key Words: Body temperature variability; Diabetes; Endothelial function; Ischemic heart disease
In the regulatory mechanism of BT, vasculature is an effective heat radiating system and controls the flow of blood to the skin, which is the most effective mechanism for heat transfer from the body core to the skin. Of special importance is the existence of a continuous venous plexus that is supplied by an inflow of blood from the skin capillaries. Heat conduction to the skin by the blood is controlled by the degree of vasoconstriction of the arterioles and the arteriovenous anastomoses that supply blood to the venous plexus of the skin. Additionally, neurological regulation is another crucial factor that regulates BT. For example, the vascular regulation of BT is coordinated through neural mechanisms such as sympathetic vasoconstrictor and parasympathetic vasodilator systems. The sweating process, another heat-regulating system, is mainly controlled by the activity of the autonomic nervous system. These regulatory mechanisms are connected to temperature-sensing neurons in the skin. Therefore vasculature and neurological pathways are major factors that contribute to thermoregulation and closely interact with each other.

Subjects with ischemic heart disease (IHD) have a generally impaired endothelium and vascular function because of the presence of several coronary risk factors such as hypertension, smoking, and diabetes. In these subjects thermoregulation can presumably be impaired by vascular dysfunction but, among coronary risk factors, diabetes is different with respect to thermoregulation because the presence of diabetes induces not only vascular injury but also autonomic neuropathy. These two dysfunctions appear to have marked impacts on thermoregulation. In addition, there has recently been reported to be a close link between the pathogenesis of diabetes and thermoregulation. The difference of interaction between vascular function and thermoregulation between diabetes and non-diabetes, however, had not been elucidated concisely.

The objective of this study was to compare subjects with diabetes and without diabetes complicated with IHD with respect to the interrelationship between vascular function and thermoregulation and the clinical implications of BT parameters.

Methods

A retrospective study was conducted at Tokyo University Hospital. We recruited 33 subjects with diabetes who were hospitalized for coronary angiography and had angiographically documented coronary artery disease (CAD). Thirty-three subjects without diabetes who had a similar age distribution with a comparative risk profile were also recruited from the same group of hospitalized patients who had angiographically documented CAD. Subject recruitment and clinical evaluation were performed between January 2010 and August 2011. Clinical data were analyzed in August 2012. CAD was defined as the presence of at least one of the following: >50% luminal diameter narrowing of ≥1 epicardial coronary arteries on angiography; history of coronary revascularization; and history of myocardial infarction. Exclusion criteria were unstable clinical condition and significant valvular dysfunction. The patients were considered to have diabetes if they were having medical treatment with hypoglycemic agents or insulin injection, or if they had hemoglobin (Hb) A1c >6.5% (Japan Diabetes Society) at the time of recruitment. Endothelial function was assessed on flow-mediated dilation (FMD) and the data for ABT were extracted from the medical records of the 3 consecutive days after FMD measurement. We excluded patients with significant pathologic causes that could raise BT (such as infection). Autonomic nerve system activity was evaluated on heart rate variability monitoring as described previously. Electrocardiograms (ECGs) were also recorded during FMD measurements using a 3-lead ECG system, and converted to R-R intervals using the built-in A/D converter (UNEXEF18G). All components of a standard informed consent including purpose of study, risks, and benefits were fully explained to each patient and written informed consent was obtained. The study protocol conformed to the principles of the Declaration of Helsinki and was reviewed and approved by the University of Tokyo Institutional Review Board.

Measurement of BT

ABT was measured using the Terumo Digital Clinical Thermometer C202. ABT was recorded at 3 times during the day (in the morning, at noon and in the evening). We evaluated the diurnal fluctuation of ABT using the variability and standard deviation (Figure 1). The variability of ABT (BT variability; BTV) was defined as the difference between the highest and lowest temperature measurements. The standard deviation of ABT was also calculated (BT SD).

To determine the degree to which mean ABT, BTV, and BT SD were reproducible, the intra-class correlation coefficients (ICCs) for mean ABT, BTV, and BT SD were measured. Using the first consecutive 3-day and second consecutive 3-day BT measurements separately in 17 subjects with long-stay hospitalization, the ICCs for BT parameters were calculated. The ICC of BT SD was 0.66 (95% confidence interval [CI]: 0.29–0.86) and the ICC of BTV was 0.71 (95% CI: 0.37–0.88). The ICC of mean ABT was 0.78 (95% CI: 0.47–0.92).

Endothelial Function

FMD measurement was performed according to the International Brachial Artery Reactivity Task Force guidelines. The subjects were instructed to abstain from food, smoking, and caffeine consumption for at least 4 h prior to the start of the study, and to lie down for 20 min. FMD measurement in the brachial artery was evaluated on amplitude and brightness-mode ultrasonography with the use of a linear-array 10-MHz transducer (UNEXF18G, UNEX, Nagoya). After baseline diameter measurements for 30 s, the cuff was inflated to 50 mmHg.
above the patient’s systolic blood pressure (SBP) for 5 min, and then deflated. Brachial artery diameter (BAD) was continuously recorded for 2 min after the cuff was deflated. Then, all diameters were measured again in the end-diastolic phase, which was defined as the beginning of R wave on ECG. FMD was calculated as the percentage change in diameter from baseline before cuff release to the peak value after cuff release.

Definition of Clinical Events
All registered cardiovascular events were verified by review of hospital records. A cardiovascular event was defined as any of the following adjudicated events: death due to cardiovascular disease; myocardial infarction; congestive heart failure; percutaneous transluminal coronary angioplasty or cardiac bypass graft surgery. Myocardial infarction was defined as an increase of at least 2-fold from the pre-event level in creatine kinase-MB with typical ECG changes. Percutaneous transluminal coronary angioplasty was counted only when performed in a de novo coronary stenosis during follow-up. Congestive heart failure was counted when subjects were hospitalized for worsening of heart failure. For subjects who had more than 1 event, only the first was included in the analysis.

Blood Collection/Analysis
Fasting blood samples were collected for analysis. Hb, estimated glomerular filtration rate (eGFR), C-reactive protein (CRP), brain natriuretic peptide (BNP), HbA1c, total cholesterol, high-density lipoprotein (HDL) and triglyceride were measured with standard laboratory methods (Tokyo University Hospital).

Statistical Analysis
Data are presented as mean±SD, and the difference between 2 groups was analyzed on independent t-test. Categorical variables were analyzed on Chi-square test. To improve skewness and kurtosis, variables that were not distributed normally were log-transformed when possible and then back-transformed to their natural units for presentation. The potential relationships between parameters were explored using Pearson correlation test. The differences between 2 correlation coefficients were analyzed using the Fisher r-to-z transformation. The following parameters were evaluated first in a univariate model for pre-

| Table 1. Subject Clinical Characteristics vs. Presence of Diabetes |
|-----------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                       | All                          | Without diabetes            | Diabetes                    | P-value†                    |
|                       | n                            | 66                          | 33                          | 33                          |
| Age (years)           | 68.6±7.3                     | 69.1±7.8                    | 68.1±6.9                    | 0.67                        |
| Sex (M/F)             | 43/23                        | 23/10                       | 20/13                       | 0.30                        |
| History of smoking    | 39/66                        | 18/33                       | 21/33                       | 0.31                        |
| SBP (mmHg)            | 127.4±15.4                   | 128.5±13.8                  | 126.3±16.9                  | 0.28                        |
| DBP (mmHg)            | 66.8±12.0                    | 69.2±11.3                   | 62.0±10.3                   | 0.012*                      |
| BMI (kg/m²)           | 24.6±3.3                     | 24.3±3.7                    | 24.7±2.9                    | 0.60                        |
| BSA (m²)              | 1.65±0.15                    | 1.66±0.16                   | 1.64±0.14                   | 0.71                        |
| Heart rate (min)      | 65.3±11.1                    | 63.1±9.6                    | 67.4±12.2                   | 0.062                       |
| Hb (g/dl)             | 13.0±1.9                     | 13.1±1.7                    | 12.9±2.0                    | 0.31                        |
| eGFR (ml·min⁻¹·1.73m⁻²) | 66.8±21.8                  | 68.1±18.9                   | 65.6±24.6                   | 0.30                        |
| CRP (mg/dl)           | 0.25±0.46                    | 0.15±0.21                   | 0.35±0.61                   | 0.041*                      |
| HbA1c (%)             | 6.10±0.95                    | 5.38±0.35                   | 6.80±0.85                   | <0.0001*                    |
| TC (mg/dl)            | 177.6±36.8                   | 174.7±27.0                  | 180.4±44.8                  | 0.28                        |
| HDL (mg/dl)           | 58.3±18.9                    | 58.3±19.9                   | 58.2±17.5                   | 0.49                        |
| Triglyceride (mg/dl)  | 157.4±103.3                  | 132.4±68.7                  | 167.9±18.4                  | 0.090                       |
| BNP (pg/ml)           | 88.2±175.7                   | 57.7±91.8                   | 117.9±227.5                 | 0.085                       |
| BAD (mm)              | 4.2±0.74                     | 4.3±0.85                    | 4.1±0.60                    | 0.10                        |
| FMD (%)               | 3.7±1.5                      | 4.1±1.5                     | 3.3±1.3                     | 0.067                        |
| SDNN (ms)             | 26.6±12.5                    | 29.8±15.1                   | 23.6±8.7                    | 0.034*                      |
| β-blockers            | 27/66                        | 12/33                       | 15/33                       | 0.31                        |
| Statins               | 58/66                        | 27/33                       | 31/33                       | 0.12                        |
| ACEs/ARBs             | 52/66                        | 24/33                       | 29/33                       | 0.18                        |
| Anti-platelet drugs   | 62/66                        | 30/33                       | 32/33                       | 0.31                        |
| No. diseased vessels  |                             |                             |                             |                             |
| 1/2/3 vessel disease  | 20/14/32                     | 12/5/16                     | 8/9/16                      | 0.37                        |
| BT parameters         |                             |                             |                             |                             |
| Mean ABT (°C)         | 36.3±0.30                    | 36.3±0.28                   | 36.3±0.32                   | 0.54                        |
| BTV (°C)              | 0.76±0.32                    | 0.79±0.34                   | 0.74±0.30                   | 0.56                        |
| BT SD (°C)            | 0.30±0.12                    | 0.31±0.12                   | 0.29±0.12                   | 0.59                        |

Data given as mean±SD. *P<0.05. †Independent t-test. ACE, angiotensin-converting enzyme inhibitor; ABT, axillary body temperature; ARB, angiotensin receptor blocker; BAD, brachial artery diameter; BMI, body mass index; BNP, brain natriuretic peptide; BSA, body surface area; BT, body temperature; BT SD, body temperature standard deviation; BTV, body temperature variability; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FMD, flow-mediated dilation; Hb, hemoglobin; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; SBP, systolic blood pressure; SDNN, standard deviation of normal R-R intervals; TC, total cholesterol.
Table 2. Association Between Mean ABT, BTV, BT SD and Clinical Variables

|                          | All                  | Without diabetes       | Diabetes               |
|--------------------------|----------------------|------------------------|------------------------|
|                          | r (P-value)          | r (P-value)            | r (P-value)            |
| n                        | 66                   | 33                     | 33                     |
| Age (years)              | –0.064 (0.61)        | –0.17 (0.36)           | 0.13 (0.48)            |
| SBP (mmHg)               | 0.041 (0.74)         | –0.091 (0.62)          | 0.13 (0.48)            |
| DBP (mmHg)               | –0.014 (0.91)        | 0.051 (0.81)           | –0.019 (0.93)          |
| Heart rate (/min)        | 0.094 (0.47)         | 0.21 (0.25)            | 0.027 (0.88)           |
| BSA (m²)                 | 0.31 (0.011)*        | 0.38 (0.031)*          | 0.24 (0.19)            |
| BMI (kg/m²)              | 0.36 (0.0030)*       | 0.42 (0.015)*          | 0.33 (0.068)           |
| Hb (g/dl)                | –0.20 (0.10)         | –0.12 (0.52)           | –0.27 (0.88)           |
| eGFR (ml·min⁻¹·1.73m⁻²)  | –0.13 (0.30)         | 0.22 (0.22)            | –0.081 (0.65)          |
| CRP (mg/dl)              | 0.13 (0.33)          | –0.19 (0.30)           | 0.21 (0.25)            |
| HbA1c                    | –0.031 (0.81)        | –0.031 (0.81)          | –0.031 (0.81)          |
| TC (mg/dl)               | –0.11 (0.42)         | –0.17 (0.35)           | –0.064 (0.73)          |
| HDL (mg/dl)              | 0.26 (0.042)*        | 0.20 (0.28)            | 0.32 (0.078)           |
| Triglyceride (mg/dl)     | –0.18 (0.15)         | –0.37 (0.046)*         | –0.10 (0.59)           |
| BNP (pg/ml)              | 0.015 (0.91)         | 0.17 (0.36)            | 0.069 (0.70)           |
| FMD (%)                  | –0.076 (0.54)        | –0.20 (0.25)           | 0.0082 (0.96)          |
| BAD (mm)                 | 0.25 (0.039)*        | 0.38 (0.025)*          | 0.096 (0.59)           |
| SDNN (ms)                | –0.14 (0.32)         | –0.26 (0.20)           | –0.025 (0.89)          |
| BTV                       | r (P-value)/β-value† | r (P-value)/β-value† | r (P-value)/β-value† |
| n                        | 66                   | 33                     | 33                     |
| Age (years)              | –0.012 (0.92)        | –0.095 (0.60)          | 0.074 (0.68)           |
| SBP (mmHg)               | –0.033 (0.79)        | 0.064 (0.72)           | 0.074 (0.68)           |
| DBP (mmHg)               | –0.097 (0.45)        | –0.073 (0.70)          | –0.22 (0.31)           |
| Heart rate (/min)        | –0.021 (0.87)        | –0.013 (0.48)          | 0.16 (0.43)            |
| BSA (m²)                 | –0.29 (0.021)*       | –0.27 (0.13)           | –0.40 (0.025)*         |
| BMI (kg/m²)              | –0.16 (0.21)         | –0.12 (0.51)           | –0.22 (0.23)           |
| Hb (g/dl)                | –0.024 (0.85)        | 0.039 (0.83)           | 0.025 (0.89)           |
| eGFR (ml·min⁻¹·1.73m⁻²)  | 0.14 (0.27)          | 0.37 (0.035)*          | 0.095 (0.60)           |
| CRP (mg/dl)              | 0.11 (0.38)          | –0.19 (0.30)           | 0.31 (0.068)/0.25 (0.14)|
| HbA1c                    | –0.066 (0.60)        | –0.14 (0.46)           | –0.086 (0.63)          |
| TC (mg/dl)               | 0.085 (0.52)         | 0.22 (0.24)            | 0.017 (0.92)           |
| HDL (mg/dl)              | –0.026 (0.84)        | 0.098 (0.61)           | –0.18 (0.32)           |
| Triglyceride (mg/dl)     | 0.032 (0.81)         | 0.37 (0.046)*          | –0.13 (0.50)           |
| BNP (pg/ml)              | 0.058 (0.65)         | –0.17 (0.37)           | 0.16 (0.37)            |
| FMD (%)                  | 0.27 (0.030)*        | 0.39 (0.023)*          | 0.0081 (0.96)          |
| BAD (mm)                 | –0.27 (0.025)*       | –0.34 (0.056)          | –0.30 (0.090)          |
| SDNN (ms)                | 0.13 (0.35)          | 0.17 (0.39)            | 0.035 (0.86)           |
| Min ABT (°C)             | –0.76 (<0.0001)      | –0.87 (<0.0001)*       | –0.68 (<0.0001)*       |
| Max ABT (°C)             | –0.084 (0.50)        | –0.21 (0.23)           | 0.0001 (0.99)          |
| Mean ABT (°C)            | –0.54 (<0.0001)*     | –0.68 (<0.0001)*       | –0.42 (0.014)<–0.42 (0.015)* |
| BT SD (°C)               | 0.95 (<0.0001)*      | 0.95 (<0.0001)*        | 0.98 (<0.0001)*        |
| BT SD r (P-value)/β-value† | r (P-value)/β-value† | r (P-value)/β-value† |
| Age (years)              | –0.0002 (0.99)       | –0.084 (0.62)          | 0.084 (0.64)           |
| SBP (mmHg)               | 0.045 (0.72)         | 0.11 (0.51)            | –0.15 (0.39)           |
| DBP (mmHg)               | –0.086 (0.50)        | 0.022 (0.91)           | –0.22 (0.21)           |
| Heart rate (/min)        | –0.064 (0.62)        | –0.12 (0.53)           | –0.053 (0.77)          |
| BSA (m²)                 | –0.34 (0.056)*       | –0.29 (0.10)           | –0.47 (0.007)*         |
| BMI (kg/m²)              | –0.15 (0.22)         | –0.044 (0.81)          | –0.22 (0.23)           |
| Hb (g/dl)                | –0.0093 (0.94)       | 0.075 (0.68)           | 0.0009 (0.99)          |
| eGFR (ml·min⁻¹·1.73m⁻²)  | 0.19 (0.13)          | 0.40 (0.020)*          | 0.13 (0.45)            |
| CRP (mg/dl)              | 0.078 (0.54)         | –0.21 (0.28)           | 0.26 (0.16)            |
| HbA1c                    | –0.098 (0.44)        | 0.18 (0.32)            | –0.15 (0.42)           |
| TC (mg/dl)               | 0.062 (0.64)         | 0.29 (0.12)            | –0.059 (0.76)          |
| HDL (mg/dl)              | –0.037 (0.77)        | 0.12 (0.52)            | –0.22 (0.23)           |

(Table 2 continued the next page.)
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Results

Behavior of ABT

Table 1 lists the baseline clinical characteristics of the 33 subjects without diabetes and 33 subjects with diabetes complicated with IHD. There was no significant difference between the 2 groups with respect to age, sex, SBP, heart rate, BMI, and BSA. Mean DBP was significantly higher in the subjects without diabetes (without diabetes, 69.2±11.3 mmHg; diabetes, 73.7±12.8 mmHg; P<0.05).

Table 1. Baseline clinical characteristics of the 33 subjects without diabetes and 33 subjects with diabetes complicated with IHD.

|                  | Without diabetes | Diabetes | P    |
|------------------|------------------|----------|------|
| Age (yrs)        | 65 (61–71)       | 67 (63–73) | 0.40 |
| Sex (M/F)        | 18/15            | 19/14    | 0.87 |
| SBP (mmHg)       | 120 (110–130)    | 125 (115–135) | 0.04 |
| Heart rate (bpm)| 70 (60–80)       | 72 (65–85)   | 0.12 |
| BMI (kg/m²)      | 25 (22–27)       | 27 (24–29)   | 0.02 |
| BSA (m²)         | 1.8 (1.6–2.0)    | 1.9 (1.7–2.1) | 0.07 |
| Hb (g/dl)        | 13.5 (12.0–15.0) | 13.0 (12.0–14.0) | 0.03 |
| eGFR (ml/min/1.73m²)| 90 (80–100)   | 85 (75–95)   | 0.09 |
| CRP (mg/l)       | 0.3 (0.1–0.5)   | 0.4 (0.2–0.6) | 0.05 |
| BNP (pg/ml)      | 40 (30–50)      | 60 (50–70)  | 0.01 |
| FMD (%)          | 5 (3–7)         | 6 (4–8)    | 0.03 |
| BAD (mm)         | 4 (3–5)         | 4 (3–5)    | 0.78 |
| SDNN (ms)        | 70 (50–90)      | 70 (50–90)  | 0.23 |

Variables with P<0.15 were then entered into multiple linear regression for predicting BTV and BT SD. Among temperature parameters only mean ABT was entered into the multiple linear regression model. P<0.05 was considered to be statistically significant. The results of comparison are represented as box plots (middle hash of the box indicating the median; 25th–75th percentiles represented by end caps of the box; whiskers extend to the last observed value). Data analysis was performed using PASW statistics 18 (SPSS, Chicago, IL, USA) and JMP pro 9 (SAS Institute, Cary, NC, USA).
Body Temperature Variability in Diabetes

investigated the relationship between minimum and maximum ABT and the clinical variables. Minimum ABT was clearly correlated with BTV and BT SD, whereas maximum ABT was not related to these parameters (Table 2; Figure 2). This suggests that the ability to decrease BT determines BTV. In addition, BTV and BT SD were well-correlated in subjects regardless of diabetes status.

Regarding the parameters of vascular function, BAD was closely correlated with mean ABT (R=0.38, P=0.025) in subjects without diabetes. BTV and BT SD were also closely associated with FMD in subjects without diabetes (R=0.39, P=0.023; BT SD: R=0.41, P=0.019; Figure 3A). These correlations between vascular function and BT parameters were not observed in subjects with diabetes (Figure 3B). The correlations of BTV or BT SD and FMD were different with regard to diabetes status (Figure 3C). In subjects without diabetes, BTVFMD >4% was significantly higher than that of

Figure 3. Relationship between vascular parameters and body temperature variability (BTV) or body temperature standard deviation (BT SD). Correlation between brachial artery diameter (BAD) and mean axillary body temperature (ABT) and correlation between flow-mediated dilatation (FMD) and BT in (A) subjects without diabetes and (B) subjects with diabetes. Pearson's R-values are shown. (C, D) Comparison of (C) BTV and (D) BT SD between subjects with FMD >4% and those with FMD <4% vs. diabetes status.

tes, 62.0±10.3 mmHg, P=0.012) and mean CRP was higher in the subjects with diabetes (without diabetes, 0.15±0.21 mg/dl; diabetes, 0.35±0.61 mg/dl, P=0.041; Table 1). Standard deviation of normal R-R intervals (SDNN), an index of parasympathetic nerve activity, was significantly smaller in subjects with diabetes (without diabetes, 29.8±15.1 ms; diabetes, 23.6±8.7 ms, P=0.034), which was presumably due to the neuropathy of diabetes. The majority of subjects in this study used statin and anti-platelet drugs. The prevalence of history of smoking, β-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEs/ARBs) was similar between the 2 groups. We compared temperature parameters between the subjects with diabetes and without diabetes. There was no significant difference in ABT, BTV, and BT SD between the 2 groups.

Regulating Factors of ABT Parameters

The interaction between mean ABT and each clinical parameter was investigated in subjects with diabetes and without diabetes (Table 2). In subjects without diabetes, mean ABT was closely associated with BMI (R=0.42, P=0.015), BSA (R=0.38, P=0.031) and HDL (R=0.26, P=0.042). These correlations were weaker in subjects with diabetes. To characterize the behavior of ABT more concisely, we
Figure 4. Relationship between inflammation and body temperature variability. Comparison of (A) body temperature variability (BTV) and (B) BT standard deviation (BT SD) between subjects with C-reactive protein (CRP) <0.08 mg/dl and those with CRP >0.08 mg/dl vs. diabetes status.

Figure 5. Comparison between subjects with high body temperature standard deviation (BT SD) (>0.27°C) and low BT SD (<0.27°C). (A) Event-free survival curve for the total subject group. (B) Comparison of flow-mediated dilation (FMD), C-reactive protein (CRP), standard deviation of normal R-R intervals (SDNN), body mass index (BMI), estimated glomerular filtration rate (eGFR) and brain natriuretic peptide (BNP), between subjects with high BT SD (>0.27°C) and low BT SD (<0.27°C) vs. diabetes status. (C) Event-free survival curves in subjects with BT SD >0.27°C vs. BT SD <0.27°C in those with and without diabetes.
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The present female subjects were in the postmenstrual period. In addition, in subjects with diabetes, those with BT SD >0.27°C had a significantly higher event rate during follow-up compared to those with BT SD ≤0.27°C (P=0.012), whereas a similar difference was not observed in subjects without diabetes. These results suggest that the magnitude of BT is a useful clinical marker to predict the risk of cardiovascular events in subjects with diabetes (Figure 5C).

Discussion

ABT is the most frequently measured indicator in the clinical setting, but the interaction between ABT and vascular function has not yet been clearly reported. This study has shown that diurnal variation of ABT is closely associated with peripheral endothelial function, but that the correlation between the 2 is disrupted in the presence of diabetes.

ABT seems to be significantly affected by environmental conditions according to the degree of heat loss, which depends on environment temperature, air movement, humidity, sunshine, microclimate under clothing, bedding, and so on. In the present study with hospitalized patients, environment temperature, air movement, humidity, sunshine, clothing, type of beverage and meal, and the effect of smoking was fixed. The level of physical activity was also restricted within a certain range. The present female subjects were in the postmenstrual period. ABT is particularly susceptible to these masking factors and therefore these factors were controlled in this study.

BT is determined by the balance of heat production and heat loss. In this study BT and BT SD were negatively correlated with ABT itself. This corresponds to the interaction between ABT minimum and BT SD (Figure 2). BT and BT SD mainly reflect the ability to lower BT by the vascular heat-shine, microclimate under clothing, bedding, and so on. These results suggest that the vascular system is a factor that corridors, which regulates heat loss. It is reasonable to propose that the ability to dilate the vessel corresponds to BTV. There have been several reports demonstrating that vascular injury leads to impairment of thermoregulation. Indeed, thermoregulatory cutaneous vasodilatation may be compromised in hypertensive humans and experimental animals with vascular injury.22 The presence of vascular injuries impaired the ability to lower ABT via dysfunction of the vascular dilatory effect. These results suggest that the vascular system is a factor that

Clinical Implication of BT Parameters

The mean follow-up after FMD measurement was 16.4±8.4 months. During follow-up, a total of 11 subjects (5 subjects with diabetes and 6 subjects without diabetes) experienced a cardiovascular event (cardiovascular death, n=1; coronary angioplasty, n=5; congestive heart failure, n=3; and myocardial infarction, n=2) (Figure 5A). In order to evaluate the clinical usefulness of BT parameters, the subjects were divided into 2 groups according to the presence or absence of cardiovascular events during follow-up, and the BT parameters were compared between the 2 groups. Mean ABT, BTV and BT SD were not significantly different between the 2 groups in subjects without diabetes, but in subjects with diabetes BTV and BT SD were significantly different between the 2 groups (BTV: 0.68±0.29°Cevent(–) vs. 0.94±0.32°Cevent(+), P=0.035; BT SD: 0.26±0.11°Cevent(–) vs. 0.35±0.11°Cevent(+), P=0.053). Next, the subjects were divided according to whether the BT SD was greater or smaller than the median (0.27°C) according to diabetes status. In subjects without diabetes (Figure 5B), the group with high BT SD (>0.27°C) had increased FMD (4.6±1.37% for BT SD >0.27°C vs. 3.11±1.36% for BT SD ≤0.27°C, P=0.0023) and eGFR (74.5±18.9 ml·min⁻¹·1.73 m⁻² for BT SD >0.27°C vs. 56.8±13.0 ml·min⁻¹·1.73 m⁻² for BT SD ≤0.27°C, P=0.0037). In contrast, these differences were not observed in subjects with diabetes, whereas CRP and DBP were increased in the group with high BT SD (CRP: 0.69±0.26 mg/dl vs. 0.17±0.29 mg/dl, SD ≤0.27°C, P=0.010), DBP: 67.0±8.6 mmHg SD ≤0.27°C vs. 58.5±11.2 mmHg SD ≤0.27°C, P=0.011). In addition to CRP, SDNN was significantly different between subjects with and without diabetes, SDNN, however, was not significantly different between subjects with high and low BT SD, regardless of diabetes status, suggesting that the contribution of autonomic nervous system on BT is considered to be small. In addition, in subjects with diabetes, those with BT SD >0.27°C had a significantly higher event rate during follow-up compared to those with BT SD ≤0.27°C (P=0.012), whereas a similar difference was not observed in subjects without diabetes. These results suggest that the magnitude of BT is a useful clinical marker to predict the risk of cardiovascular events in subjects with diabetes (Figure 5C).

The effects of β-blockers and ACEs/ARBs on BT parameters were not significant (mean ABT: 36.36±0.28°C[β-blocker(–)] vs. 36.24±0.30°C[β-blocker(+)], P=0.13; 36.20±0.25°C[ACE/ARB(–)] vs. 36.10±0.20°C[ACE/ARB(+)], P=0.11; BTV: 0.75±0.32°C[β-blocker(–)] vs. 0.77±0.31°C[β-blocker(+)], P=0.38; 0.84±0.39°C[ACE/ARB(–)] vs. 0.73±0.30°C[ACE/ARB(+)], P=0.13; BT SD: 0.29±0.12°C[β-blocker(–)] vs. 0.30±0.12°C[β-blocker(+)], P=0.44; 0.33±0.13°C[ACE/ARB(–)] vs. 0.28±0.12°C[ACE/ARB(+)], P=0.11). With regard to anti-diabetic medications, 6 subjects were using biguanide, 10 subjects were on insulin therapy. In order to evaluate the clinical usefulness of BT parameters, the subjects were divided into 2 groups according to the presence or absence of cardiovascular

Clinical Implication of BT Parameters

The mean follow-up after FMD measurement was 16.4±8.4 months. During follow-up, a total of 11 subjects (5 subjects with diabetes and 6 subjects without diabetes) experienced a cardiovascular event (cardiovascular death, n=1; coronary angioplasty, n=5; congestive heart failure, n=3; and myocardial infarction, n=2). In order to evaluate the clinical usefulness of BT parameters, the subjects were divided into 2 groups according to the presence or absence of cardiovascular

Discussion

ABT is the most frequently measured indicator in the clinical setting, but the interaction between ABT and vascular function has not yet been clearly reported. This study has shown that diurnal variation of ABT is closely associated with peripheral endothelial function, but that the correlation between the 2 is disrupted in the presence of diabetes.

ABT seems to be significantly affected by environmental conditions according to the degree of heat loss, which depends on environment temperature, air movement, humidity, sunshine, microclimate under clothing, bedding, and so on. In the present study with hospitalized patients, environment temperature, air movement, humidity, sunshine, clothing, type of beverage and meal, and the effect of smoking was fixed. The level of physical activity was also restricted within a certain range. The present female subjects were in the postmenstrual period. ABT is particularly susceptible to these masking factors and therefore these factors were controlled in this study.

BT is determined by the balance of heat production and heat loss. In this study BT and BT SD were negatively correlated with ABT itself. This corresponds to the interaction between ABT minimum and BT SD (Figure 2). BT and BT SD mainly reflect the ability to lower BT by the vascular heat-shine, microclimate under clothing, bedding, and so on. These results suggest that the vascular system is a factor that...
Contributes to the regulation of skin temperature. Regarding temperature variability, Ahmed et al recently reported that BT circadian rhythm variability correlates with cardiac function in decompensated cardiomyopathic hamsters23,34 and may have some associations with endothelial function.

The close association between vascular function and thermoregulation did not hold true for the subjects with diabetes, and the absence of diabetes further impacted on the regulation of ABT. Most of the effect of diabetes on the regulation of BT appeared to be associated with the presence of autonomic nervous neuropathy. In previous studies, it was shown that the regulation of vascular tones was impaired by the injured autonomic nerves and that defective sweating also resulted from the autonomic disorders in subjects with diabetes.25,26 Therefore, these mechanisms can interfere with the relationship between vascular function and BT in diabetes. In addition, the magnitude of CRP also affected BTV. The enhanced contribution of inflammation to thermoregulation may be derived from the absence of the buffering action of vascular regulation. Previous research has established that CRP is higher in people with diabetes.9,10 The higher level of CRP in the present subjects with diabetes as compared with the subjects without diabetes corresponded to that in these previous reports.

Analysis of the predictive value of BT parameters for cardiovascular disease has led to unexpected results. BTV and BT SD were finely correlated with FMD in subjects without diabetes, but these parameters did not have sufficient predictive value for cardiovascular events. Meanwhile, BTV and BT SD in subjects with diabetes had no relevant clinical correlates other than BMI and CRP, but these variables had a strong predictive value for cardiovascular events in subjects with diabetes.12,13 The subjects with diabetes and high BT SD had increased BNP and CRP, suggesting that inflammation or cytokines induced by heart failure may affect the magnitude of BT SD in diabetes. The absence of a contribution from vascular factors in subjects with diabetes may enhance the effect on thermoregulation from other factors, such as inflammatory factors or other hormonal factors. Therefore, the effect of inflammation appeared to exceed that derived from vascular dysfunction on predictive power of BT SD for cardiovascular events. Further studies are needed to investigate the mechanisms underlying the association between BT SD and clinical outcomes.

In this study, we performed a retrospective analysis of subjects with IHD, investigating the differences between those with and without diabetes with respect to the regulatory factors of BT parameters and the clinical implications for prediction of cardiovascular events.

We identified a close association between endothelial function and BTV in subjects with IHD in the absence of diabetes. In contrast, this interrelationship was markedly disrupted in subjects with diabetes, whereas the contributions of inflammatory factors were increased in thermoregulation in subjects with diabetes. In addition, the magnitude of BT fluctuation was found to have a predictive value for cardiovascular events in subjects with diabetes, whereas a similar predictive value was not observed in subjects without diabetes. The finding of a marked different meaning in BTV between subjects with and without diabetes will help the clarification of vascular injury observed in diabetic subjects.

Study Limitations
This study has several limitations because the results were derived from a retrospective analysis of a small sample size. The absence of a predictive value of BT parameters in subjects without diabetes may be due to insufficient power of this study because of the small sample size. Marked differences, however, between subjects with and without diabetes with respect to regulatory factors of BT parameters and predictive value for cardiovascular events were found, and these results were statistically significant. The derived hypothesis needs to be proven by prospective investigations.

We analyzed the fluctuation of ABT using BTV and BT SD. The Cosinor method to calculate the amplitude of circadian oscillation is considered to be more accurate to determine the fluctuation of BT. Furthermore, more measurements of ABT would increase the accuracy of ABT analysis. The method used in this study, however, was sufficient to detect the association between vascular function and ABT. Indeed ABT was reported to fluctuate by as much as 1.0–1.5°C,8 which is almost the same as the BTV found in this study.

Conclusions
BTV was closely associated with vascular function in non-diabetic subjects. This association was disrupted, however, in subjects with diabetes, and the effect of inflammation was pronounced in thermoregulation in subjects with diabetes. In addition, the magnitude of BT fluctuation was found to have a predictive value for cardiovascular events in subjects with diabetes.

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