Possible Association Between Body Temperature and B-Type Natriuretic Peptide in Patients With Cardiovascular Diseases

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ABSTRACT

Background: In addition to various biological effects of natriuretic peptides (NP) on cardiovascular systems, we recently reported that NP raises intracellular temperature in cultured adipocytes. We herein examined the possible thermogenic action of NP in consideration of hemodynamic parameters and inflammatory reaction by proposing structural equation models.

Methods and Results: The study population consisted of 1985 consecutive patients who underwent cardiac catheterization. Covariance structure analyses were performed to clarify the direct contribution of plasma B-type NP (BNP) to body temperature (BT) by excluding other confounding factors. A hierarchical path model showed increase in BNP, increase in C-reactive protein and decrease in left ventricular ejection fraction were mutually associated. As expected, C-reactive protein was positively correlated with BT. Importantly, despite a negative correlation between BNP and left ventricular ejection fraction, a decrease in the left ventricular ejection fraction was associated with BT decrease, whereas elevation in BNP level was associated with BT increase independently of C-reactive protein level ($P = .007$).

Conclusions: Patients with LV dysfunction tend to manifest a decrease in BT, whereas BNP elevation is associated with an increase in BT independently of inflammatory response. These findings suggest the adaptive heat-retaining property of NP (and/or NP-associated factors) when BT falls owing to unfavorable hemodynamic conditions in a state of impaired cardiac function. (*J Cardiac Fail 2021;27:75–82*)

Key Words: Natriuretic peptides, temperature, thermogenic action, covariance structure analysis.

Both A-type natriuretic peptide and B-type natriuretic peptide (BNP) are produced in the heart, and the various biological effects of NPs on the cardiovascular system play a key role in the pathophysiology of heart failure. NPs classically act on the renal and cardiovascular systems, regulate blood pressure and fluid homeostasis through vasodilatory and diuretic actions, and improve cardiac remodeling.[1,2]

In addition to the classical action of hemodynamic regulation, there is increasing evidence to indicate that NPs also largely coordinate the interorgan metabolic crosstalk with adipose tissues, in which NP receptors are expressed and regulate energy balance.[3–13] In fact, recent studies have indicated that NPs stimulate triglyceride lipolysis, promote the uncoupling of mitochondrial respiration through the induction of adipose tissue browning, and activate thermogenesis.[5–8,14–17] Uncoupling protein 1 is specifically expressed in brown adipose tissue and enables mitochondrial uncoupled respiration, rather than adenosine triphosphate production, allowing for the dissipation of nutritional energy as heat.[18,19] We recently demonstrated that NP actually increases the intracellular temperature in cultured brown adipocytes in a low-temperature sensitive manner through the uncoupling protein 1 pathway.[20] Moreover, Bordicchia et al[15] reported that messenger RNA levels of A-type NP and BNP in the heart, as well as the plasma BNP levels, are increased in mice exposed to cold environments, which supports the idea that NPs could induce the activation of the adipose tissue thermogenic program in response to cold stimulus.[7]

Based on these previous findings, we hypothesized that NPs have an adaptive thermogenic action, or heat-retaining property, when the body temperature (BT) falls owing to unfavorable hemodynamic conditions in a state of cardiac systolic dysfunction. One of the difficulties faced in researching the correlations between NPs or the cardiac function and BT is the intractableness of the statistical approach, because these factors vary widely with individual clinical conditions and are associated with each other (ie, correlation between BNP and left ventricular ejection fraction [LVEF]) as well as numerous other factors

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(ie, correlations with the levels of inflammatory markers), namely, confounding variables. Although there are several ways of eliminating these confounding biases, for example, by adjustment of the independent variables, it is still difficult to control for them if multiple potential confounders are present or if the study population is of insufficient size.[13,21,22] A covariance structure analysis plays an important role in understanding how the relationships between observed variables may be generated in many areas using hypothesized latent variables, and it is useful for eliminating confounding biases and clarifying possible associations.[13,21–30]

Using a covariance structure analysis together with conventional single and multiple regression analyses, this study was designed to evaluate a possible thermogenic action of BNP in consideration of the hemodynamic parameters and inflammatory reaction in patients with cardiovascular diseases.

Methods

Study Patients

The study population consisted of 1985 consecutive patients who underwent cardiac catheterization at our institution for the evaluation of various cardiovascular diseases from April 2015 to July 2019. Patients were excluded if the data on plasma BNP and BT were not available. The ethics committee of Jikei University School of Medicine approved the study protocol (24-355[7121]), and we complied with the routine ethical regulations of our institution. All patients provided their written informed consent before undergoing the procedure, and all clinical investigations were conducted in accordance with the principles expressed in the Declaration of Helsinki. According to our routine ethical regulations, we also posted a notice about the study design and contact information in a public location in our institution.

Data Collection

The clinical characteristics were collected retrospectively from the hospital medical records. The axillary BT and blood samples were measured just before cardiac catheterization. The hemodynamic data were collected during cardiac catheterization.[13,21,22] We also measured the intravascular temperature of pulmonary artery during right heart catheterization study in order to assess the intracardiac temperature. Plasma and serum biochemical analyses, including the levels of BNP and C-reactive protein (CRP), were performed in a central laboratory of our hospital during the study period. To measure the plasma BNP levels, blood samples were collected in tubes containing ethylenediaminetetraacetic acid, and then were immediately centrifuged at 3000 rpm for 5 minutes at 17°C. Thereafter, the plasma BNP levels were immediately measured by chemiluminescent enzyme immunoassay using AIA-CL2400 (TOSOH Corporation, Tokyo, Japan). Some of the patients had comorbid cardiovascular diseases, such as ischemic heart disease, valvular disease, arrhythmia, cardiomyopathy and other conditions. Hypertension and diabetes mellitus were defined as described previously.[13,21,22,31] The estimated glomerular filtration rate were calculated as described previously.[13,21,22,31] The LVEF was measured at the time of left ventriculography.[13,21,22]

Statistical Analyses

Continuous variables are expressed as the median ± interquartile range. The correlations between BNP, CRP, LVEF, and BT in each group, as well as between intracardiac temperature and BT were investigated by a simple regression analysis and expressed as Spearman's correlation coefficient. BT levels were compared among 4 groups divided by the indicated BNP levels (Supplementary Fig. 1) with the Kruskal-Wallis test and Mann-Whitney *U* test. A multiple regression analysis was performed to compare multiple values. These statistical analyses were performed using the SPSS Statistics software program (version 24.0, SPSS Inc., Chicago, IL). *P* values of less than .05 were considered to indicate statistical significance.

A path analysis based on a covariance structure analysis was used to elucidate the direct contribution of BNP, CRP, and LVEF to BT levels. In other words, the path model was proposed to investigate the relationship among clinical factors in this study population and specifically to identify the possible impact of these clinical factors on BT. This analysis compares the power among the multiple independent variables that confound each other. The path analysis was performed using the IBM SPSS AMOS software program (version 25.0, Amos Development Corporation, Meadville, PA), as described previously in detail.[13,21–30] In brief, the model defines some hierarchical regression models between clinical factors and BT. For every regression, the total variance in the dependent variable is theorized to be affected either by independent variables that are included in the model or by extraneous variables (e). When obtaining the critical ratios of the differences between parameters, AMOS was used to display the matrix, which included a row and a column for each parameter of the model.[30] The obtained structural equation models (SEMs) were tested and confirmed at a significance level of a *P* value of less than .05.

In addition, we applied a Bayesian SEM using a program embedded in the IBM SPSS AMOS software program (version 25.0; Amos Development Corporation). The frequency polygon was described with the marginal posterior distributions of the estimands.[13,29] The selected 2-dimensional contour line was used in this study because it was easily visualized.

Results

Characteristics of the Study Patients

The clinical characteristics of the 1985 patients are shown in Table 1. The median BT was 36.4 (interquartile range [IQR] 36.1°C−36.6°C), the median BNP level was 52.6 pg/mL (IQR 20.2−163.3 pg/mL), the median CRP level was 0.09 mg/mL (IQR 0.04−0.33 mg/dL), and the median LVEF was 59.5% (IQR 49.1%−64.9%).

Table 1. Clinical Characteristics ($n = 1985$)

	Median (IQR) or Number (%)
Age, years	68 (58−75)
Male, gender	1605 (80.8)
Height, cm	166.0 (160.0−171.0)
Weight, kg	66.0 (57.1−74.6)
BMI, kg/m^2	24.0 (21.8−26.4)
BP, mm Hg	
Systolic	133 (116−150)
Diastolic	70 (61−79)
Mean	95 (85−106)
Body temperature, ˚C	36.4 (36.1−36.6)
Male, ˚C	36.3 (36.1−36.6)
Female, ˚C	36.4 (36.1−36.6)
Hb, g/dL	13.7 (12.1−14.8)
Cr, mg/dL	0.86 (0.73−1.04)
eGFR, mL/min/1.73 m^2	66.5 (53.0−79.1)
UA, mg/dL	5.9 (4.9−6.9)
Glucose, mg/dL	107 (95−130)
HbA1c, %	6.0 (5.6−6.7)
TG, mg/dL	99 (70−140)
HDL-C, mg/dL	48 (40−59)
LDL-C, mg/dL	98 (80−121)
BNP, pg/mL	52.6 (20.2−163.3)
CRP, mg/dL	0.09 (0.04−0.33)
LVEF, %	59.5 (49.1−64.9)
Underlying disease	
Ischemic heart disease	1475 (74.3)
Myocardial infarction	162 (8.7)
Valvular disease	173 (8.7)
Cardiomyopathy	241 (12.1)
Peripheral arterial disease	75 (3.8)
Aortic disease	119 (6.0)
Atrial fibrillation	191 (9.6)
Hypertension	1433 (72.2)
Diabetes mellitus	764 (38.5)
Dialysis	145 (7.3)
Cancer	187 (9.4)
Medication	
Diuretics	480 (24.2)
β-Blockers	845 (42.6)
Calcium channel blockers	947 (47.7)
ACE inhibitors	420 (21.2)
ARBs	707 (35.6)
Aspirin	1162 (58.5)
Statins	1117 (56.3)
Insulin	177 (8.9)
Oral antidiabetic agents	482 (24.3)
Antidepressants	51 (2.6)
Anti-Parkinson drugs	9 (0.5)
NSAIDs	47 (2.4)

IQR, interquartile range; BMI, body mass index; Hb, hemoglobin; Cr, creatinine; eGFR, estimated glomerular filtration rate; UA, uric acid; HbA1c, hemoglobin A1c; TG, triglycerides; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; BNP, B-type natriuretic peptide; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; ACE, angiotensin converting enzyme; ARB, angiotensin II type I-receptor blockers; NSAIDs, nonsteroidal anti-inflammatory drugs.

Correlation Between BT and Intracardiac Temperature

The intracardiac temperature in parallel with BT was measured using a thermodilution catheter in 330 patients. The median intracardiac temperature level was 36.7˚C (IQR 36.5˚C−36.9˚C), which is significantly higher than axillary BT ($P < .001$). We found a weak but significant positive correlation between BT and the intracardiac temperature (Supplementary Fig. 2), suggesting that the axillary BT measured in the present study reflects the core BT modestly, but not completely.

Multiple Regression Analysis to Determine the Factors Associated With BT Level

To assess the independent determinants of BT, a multiple regression analysis was performed (Table 2). The analysis identified BNP ($P = .030$) and CRP ($P < .001$) as significant factors, whereas the correlation between LVEF and BT did not reach statistical significance.

Correlation Coefficient Analysis to Search for Relationships Between BNP, CRP, LVEF, and BT

We next performed simple regression analyses in order to evaluate the correlations between BNP, CRP, LVEF, and BT, and to search for confounding biases among the independent variables (Table 3). We observed a positive correlation between CRP and BT ($P < .001$), and a negative correlation between LVEF and BNP ($P < .001$), as expected. Also, there was a significant positive correlation between BNP and BT ($P < .001$), and a negative correlation between LVEF and CRP. When the BT levels were compared among 4 groups divided according to the BNP levels based on the cut-off levels for the diagnosis of heart failure presented in Japanese Circulation Society guideline [32] (Supplementary Fig. 1), the patients with the highest BNP level (group IV) showed a significantly higher BT in comparison to the other 3 patient groups ($P \leq .001$). At any rate, the correlation coefficient analysis revealed that most pairs showed a significant association (Table 3). Thus, the results of the multiple regression analysis lost some of its meaning.

The Concept of the Proposed Path Model

To eliminate the confounding biases and clarify the possible correlations between LVEF or BNP and BT more directly, a path model based on a covariance structure analysis was proposed (Fig. 1). As a matter of logic, the theoretical path model was created by positioning the levels of BNP, CRP, and LVEF in parallel with consideration of the correlations between each pair of factors. The association between each pair of factors was linked by 2-way arrows. The paths between variables were drawn from independent variables to dependent variables with directional arrows for every regression model.

The Results of the Path Model

The precise results of the path model are shown in Table 4. The increase in BNP, the increase in CRP, and the decrease in LVEF were mutually associated ($P < .001$, respectively, Fig. 1), which was consistent with the results of the correlation coefficient analysis (Table 3). CRP was positively correlated with BT, as expected (a path from CRP to BT; $\beta = 0.169$, $P < .001$). Importantly, the exploratory factor analysis with consideration of the significant correlations among the independent factors (particularly,

Table 2. Results of the Multiple Regression Analysis to Identify the Clinical Factors Influencing Body Temperature

$R^2 = 0.034$	Nonstandard Coefficient		Standard Regression Coefficients	Test Statistic	*P* value	95% CI	VIF
	Regression Coefficient	Standard Error					
BNP	0.000045	0.000	0.051	2.166	0.030	0.000 to 0.000	1.114
CRP	0.035	0.005	0.165	7.193	< 0.001	0.025 to 0.044	1.080
LVEF	0.001	0.001	0.031	1.363	0.173	−0.001 to 0.003	1.043

R^2, adjusted coefficient of determination; CI, confidence interval; VIF, variance inflation factor; BNP, B-type natriuretic peptide; CRP, C-reactive protein; LVEF, left ventricular ejection fraction.

Table 3. The Results of Spearman's Correlation Coefficient Analysis Among the Clinical Factors

	BNP	CRP	LVEF	BT
BNP	–	0.347*	−0.415*	0.059*
CRP	0.347*	–	−0.208*	0.149*
LVEF	−0.415*	−0.208*	–	−0.016
BT	0.059*	0.149*	−0.016	–

BNP, B-type natriuretic peptide; BT, body temperature; CRP, C-reactive protein; LVEF, left ventricular ejection fraction.
*$P < 0.01$

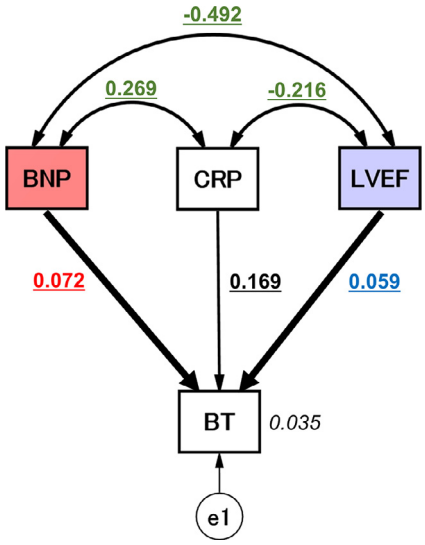

Fig. 1. Path diagrams against body temperature levels. The path model theoretically proposed to clarify the contribution of BNP, CRP, and LVEF to BT. The path has a coefficient showing the standardized coefficient of a regressing independent variable on a dependent variable of the relevant path. These variables indicate standardized regression coefficients (direct effect) (underlined portions indicate remarkable values), squared multiple correlations (narrow italics) and correlations among exogenous variables (green). BNP, B-type natriuretic peptide; BT, body temperature; CRP, C-reactive protein; e, extraneous variable; LVEF, left ventricular ejection fraction.

the negative correlation between BNP and LVEF) revealed that a low LVEF was significantly associated with a decrease in BT (a path from LVEF to BT; $\beta = 0.059$, $P = .046$), whereas a high BNP level was significantly associated with an increase in BT, independently of the CRP level (a path from BNP to BT; $\beta = 0.072$, $P = .007$).

When taken together, these covariance structure analyses indicate that LVEF and BNP individually showed a significant impact on BT. Next, we investigated which of these 2 parameters was more influential on BT by using a matrix containing rows and columns for each parameter of the AMOS model (the actual matrix data are omitted because they are large and contain unnecessary data). Interestingly, we found that BNP tends to have a stronger impact on BT compared with LVEF, indicating a significant compensatory role of BNP for hypothermia resulting from a decreased LVEF (ie, decreased blood flow).

To visualize the relationships among pairs of estimands, bivariate marginal posterior distributions are shown in Fig. 2. This figure visibly reveals that BT was positively correlated with the LVEF, CRP, or BNP, which is consistent with the path analyses (Fig. 1).

Discussion

Although the classical actions of NPs on the cardiovascular system, such as hemodynamic regulation, have been intensively investigated in both basic and clinical studies, recent studies have indicated that NPs also act on adipose tissues and regulate the energy balance.[14,16,17] It is of particular interest that NPs can actually promote heat generation through the activation of the brown fat thermogenic program.[6,7,11,20] In line with the findings of these basic studies, the present clinical study showed—using covariance structure analyses—that a decrease in the LVEF was significantly associated with a decrease in BT, whereas a high BNP level was significantly associated with an increase in BT, despite the negative correlation between LVEF and BNP. These findings at least partly indicate the potential heat-retaining property of NPs as an adaptive mechanism for the fall in BT owing to impaired hemodynamic conditions resulting from cardiac systolic dysfunction.

Although increasing attention is being paid to the possibility that NPs induce adipose tissue browning and activate the thermogenic program,[6,7,11,15,20] the direct effects of NPs on thermogenic action have not yet been clearly proven in humans, because many neurohumoral factors, as well as the hemodynamic status, are influenced by one another and contribute to the pathogenesis of various cardiovascular diseases. In fact, the BT range of the patients in the present study was small (almost within physiologic limits), and the changes in the BT in response to either the BNP level or

Table 4. Results of the Path Model Based on Covariance Structure Analyses

Clinical Factor			Estimate	Standard Error	Test Statistic	*P* Value
Body temperature ($R^2 = 0.035$)	←	BNP	0.000	0.000	2.703	0.007
	←	CRP	0.036	0.005	7.334	<0.001
	←	LVEF	0.002	0.001	2.000	0.046

The results of the path model theoretically proposed analysis to identify the clinical factors influencing between each other (see Fig. 1).
Root mean square error of approximation, 0.144; Akaike information criteria, 28.0.
R2, squared multiple correlations; BNP, B-type natriuretic peptide; CRP, C-reactive protein; LVEF, left ventricular ejection fraction.

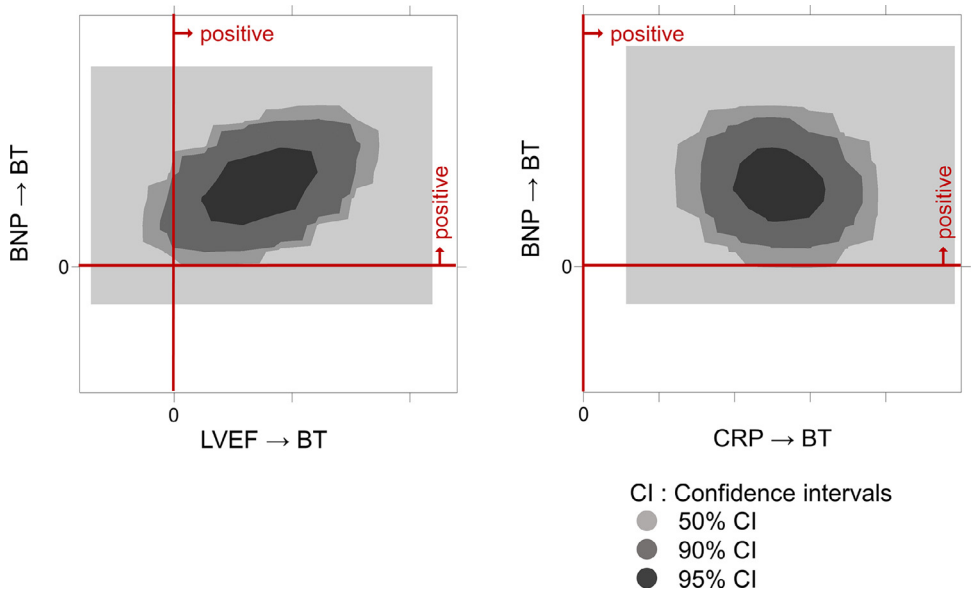

Fig. 2. Bayesian estimation. Bivariate marginal posterior distributions are shown to visualize the relationships among pairs of estimands. A credible region (indicated as CI) is conceptually similar to bivariate confidence region that is familiar to most data analysts acquainted with classical statistical inference methods.

LVEF seemed minor (eg, the association between the LVEF and BT was barely significant.). This finding is not surprising, because BT is naturally regulated by various neurohumoral factors and obviously influenced by individual clinical conditions, including the hemodynamic status. It was also reported that the BT variability and its dependence on the peripheral vascular function differ based on the presence of diabetes.[33,34] Therefore, the direct effects of BNP on BT may be hidden by or become ambiguous owing to other confounding factors. The covariance structure analysis used in the present study can be performed based on the confounding biases and is useful for inferring possible relationships.[13,21–30] Another merit of using a covariance structure analysis is that the analysis can package Bayesian networks to infer significant associations between 2 variables. However, the factors that are included in these analyses should be carefully selected, and the path model based on covariance structure analysis should be proposed based on consistent concepts and the clear direction of the study.[13,21,22] In a tangible way, we successfully proposed a path model based on a covariance structure analysis to clarify the direct influences of BNP, CRP, or LVEF on BT levels with consideration of the inherent correlation between BNP, CRP, and LVEF themselves. In fact, no significant correlation was observed between LVEF and BT in the conventional simple and multiple regression analyses. However, when using a covariance structure analysis, which eliminates potential confounding factors, the positive correlations between BT and these 3 factors were clearly delineated, with a significant negative correlation preserved between BNP and LVEF (namely, counterbalanced relation in regard to the BT regulation, although BNP was more tightly associated with BT as indicated by AMOS, Fig. 1). Accordingly, the bivariate marginal posterior distributions of Bayesian estimation clearly showed significant associations between the BT and each factor (Fig. 2). On the whole, the physiologic and clinical relevance of the present findings is supported by the proposed mechanism wherein NPs have an "adaptive" heat-retaining property in a low temperature-sensitive manner, as shown in our previous basic study.[20] This finding suggests that BNP might exert warming effects, particularly under relatively low temperature conditions, owing to an impaired cardiac systolic function and no longer increases the temperature under relatively high temperature conditions. This explains our present finding where the temperature tended to converge at physiologic limits. Given these findings, NPs might have minimal effects on the temperature regulation in patients

without impaired hemodynamic conditions resulting from heart failure. Further studies (including basic research) are required to elucidate the mechanism by which the thermogenic actions of NPs are sensitive to low temperature.

Previous studies showed that patients with heart failure associated with clinical hypoperfusion owing to an impaired cardiac output show a "cold" profile,[32,35,36] indicating a loss of heat in severe heart failure with reduced EF. Moreover, a recent study demonstrated that a low BT is associated with worse outcomes in patients with worsening heart failure.[37,38] In this context, the thermogenic actions of BNP could provide counter-regulatory therapeutic effects against severe heart failure with reduced EF, although there might be other multiple cardioprotective mechanisms by keeping the heart warm. Meanwhile, the temperature regulation achieved through peripheral and essential organ perfusion should be considered separately, as discussed in detail elsewhere in this article.

The interscapular brown adipose tissue depots were originally thought to have evolved as a compensatory defense system against hypothermia in mammals.[39] The epicardial fat, located within the heart, has been suggested to function similarly to brown adipose tissue and, thus, could provide heat directly to the myocardium.[40−43] Although we recently demonstrated the warming effects of NPs on brown adipocytes in a low temperature-sensitive manner via the activation of the p38−uncoupling protein 1 pathway,[20] accumulating evidence supports that a similar thermogenic program can be activated in the white adipose tissue by NP stimulation, through browning, which leads to the formation of beige adipocytes.[7,15] These findings suggest the following compensatory adaptive mechanisms: the failing heart may protect itself against a decrease in hypoperfusion-induced temperature by producing NPs and using their thermogenic actions in the fat tissue surrounding the myocardium.[20] The obesity paradox observed in the heart failure population[44] can be potentially explained—at least in part—by these proposed mechanisms. Namely, in patients with cardiac cachexia, the fat volume is too low to be burned by a large amount of BNP, a phenomenon that is referred to as running out of fuel.

It is known that men and women have different thermoregulation: Women have a larger ratio of body surface to body mass than men; thus, their thermal responses to exogenous heat load and heat dissipation might be differ from those in men. Moreover, women's BT varies based on a menstrual cycle, although most of the female patients in the present study were postmenopausal. Although there was no significant gender difference in BT as shown in Table 1, the sample was predominantly male in the current study. Thus, it might be reasonable to analyze larger subcohort of women separately to investigate the relations between BNP and BT in future studies.

It is highly possible that various factors, including the renal function and anemic condition, may have affected each parameter investigated in the present study. In fact, the results of the covariance structure analyses were inconsistent when including the renal function markers and/or hemoglobin, suggesting that both factors are also partly associated with each parameter of the current model. Furthermore, we also investigated the involvement of various other clinical factors possibly affecting the BT, such as cortisol, adrenaline, and the body mass index, and found that significant correlations between BNP, LVEF, CRP, and BT were consistently observed, even after these influential factors were included in the path model (data not shown). Although several other clinical factors may also affect BT, the path model proposed in the present study simply uncovered the positive correlation between BT and BNP interacting with LVEF.

According to the medication history record, 47 out of 1985 patients had taken nonsteroidal anti-inflammatory drugs, which might have influenced the results of the present study, although unfortunately precise data on the frequency and timing of taking these medicines were not available (ie, whether or not those patients took nonsteroidal anti-inflammatory drugs on the day of cardiac catheterization was unclear). However, the covariance structure analyses excluding patients taking nonsteroidal anti-inflammatory drugs confirmed that a positive correlation between BT and BNP was consistently observed ($P = .006$).

The present study is associated with some limitations. Because patients with various cardiovascular diseases were included in the present study, not all showed apparent LV systolic dysfunction and/or a substantial increase in plasma BNP levels, as patients in stage B according to the Guidelines of Heart Failure[32] were also included. This factor might have contributed, at least in part, to the relatively weak association between LVEF and BT. However, we applied a Bayesian SEM using a program embedded in the IBM SPSS AMOS software program (version 25.0; Amos Development Corporation). Although SEM applies the robust-weighted least-square approach, the Bayesian SEM implements the Gibbs sampler algorithm. Bayesianism permits uncertainty despite little information being available, and Bayesian approaches allow us to incorporate background knowledge into the analyses.[13] We believe that additional testing with Bayesian SEM would be rationalized and helpful for reassessing our data from a completely different angle of statistics. The selected 2-dimensional contour line was used in this study because it was easily visualized (Fig. 2).

Another limitation is that CRP values were less than 5 mg/dL in most of the subjects, and it should be considered to use ultrasensitive CRP kits for a better accuracy and precision of CRP value determination.

Furthermore, we measured the axillary BT, which may display some variation depending on various conditions, although it was measured at the same room temperature. To test the BT data reliability, we measured the intracardiac temperature using a thermodilution catheter, which is ought to be more sensitive and accurate, and found a weak but significant correlation between these 2 temperature data (Supplementary Fig. 2). One potential limitation is the fact that

the axillary BT and intracardiac temperature were not measured at exactly the same time. Meanwhile, BT is determined by the balance between thermogenesis and heat dissipation, both of which are finely regulated by hypothalamus. BNP may possibly affect skin blood flow that controls heat dissipation, as well as thermogenesis not only by adipose tissue but also by muscle and liver, directly and/or indirectly through hypothalamic signaling regulation. Furthermore, Amiya et al[33] reported very interesting findings that the relationship between BT variability (measured from axillary BT) and cardiovascular events in patients with ischemic heart disease differed by the presence of diabetes.[34] They found that the interrelationship between peripheral thermoregulation and the vascular function is disrupted in patients with diabetes, whereas the impact of inflammatory factors on thermoregulation is enhanced. Thus, it is reasonable to assume that temperature variability also differs between the body surface and intracardiac temperatures. Given the differences in possible temperature regulatory mechanisms and influencing factors, the results are expected to differ between the analyses using the axillary BT and those using intracardiac temperature. Further studies are warranted to fully delineate the direct contribution of BNP to core BT by measuring the intracardiac temperature with a larger sample size. It would also be interesting to see the impact of BNP on the temperature variability in patients with and without diabetes.

Finally, plasma BNP levels assessed in the present study may simply be a biomarker, and it cannot be denied that unknown factors that vary in parallel with plasma BNP (BNP-associated factors) may affect BT. Further mechanistic studies, including basic research, are required to determine whether or not the BT actually changes in response to the biological activity of BNP per se. Nevertheless, our previous basic study provides convincing data that indicate a significant impact of NPs on BT change.[20]

Conclusions

Patients with heart failure associated with clinical hypoperfusion owing to LV dysfunction tend to show a decreased BT, as supported by the present findings. In contrast, we showed in the present study that increases in plasma BNP (and/or BNP-associated factors) might be associated with an increase in BT independently of the inflammatory response. These findings suggest a previously underappreciated role of NP in the possible heat-retaining property when the BT decreases owing to unfavorable hemodynamic conditions in patients with cardiac dysfunction. The administration of agents that increase circulatory NP levels may have therapeutic benefits in patients with heart failure with reduced EF.[45–47]

Disclosures

None.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2020.08.012.

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