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Ambient Temperature and Cardiorenal Connection in Elderly Patients with Stable Heart Failure

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Heart failure increases among the elderly; however, the influence of ambient temperature on cardiorenal function has not been well investigated. Patients (n = 110, mean age 82.9 years, 43 males) with stable heart failure and creatinine < 3.0 mg/dl were studied. Medical records, such as ejection fraction, B-type natriuretic peptide (BNP), and estimated glomerular filtration rate (eGFR) at each visit every 1-3 months were collected by the end-point for death, additional prescription to treat heart failure, or heart failure hospitalization. The ambient temperatures at each visit were obtained from the Japan Meteorological Agency. During the follow-up period (median 399 days and 7 visits), follow-up BNP showed a trend toward a positive correlation with the diurnal temperature range. After dividing into two groups by median baseline eGFR, follow-up BNP was positively correlated with minimum temperature ($p = 0.039$) and the diurnal temperature range ($p = 0.007$) in the Low-eGFR group but not in the High-eGFR group. Follow-up eGFR was negatively correlated with the ambient day temperature in both groups ($p \leq 0.002$). Follow-up BNP was positively correlated with follow-up eGFR ($p < 0.0001$) only in the Low-eGFR group and not in the High-eGFR group, suggesting that BNP and eGFR increase in winter and BNP and eGFR decrease in summer in the Low-eGFR group. In conclusions, heart failure may be worsened by larger diurnal temperature range or in winter in patients with renal impairment. This population should be carefully managed in the clinic according to the ambient temperature.

Keywords: ambient temperature; heart failure; natriuretic peptide; renal function
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Introduction

Establishing a cardiorenal connection is a key pathophysiological, diagnostic, and therapeutic target for the treatment of heart failure (HF). Reduced myocardial pump function in HF causes a subsequent reduction in arterial pressure and/or an increase in venous pressure. This response then impairs renal perfusion and induces sodium and water retention, resulting in congestion and diuretic resistance (Mullens et al. 2009). The key role played by the kidney in HF proceeds the vicious cycle of impaired cardiovascular homeostasis which increases the risk for poor HF outcomes (Damman et al. 2014), however, other factors which possibly worsen the cardiorenal connection in HF has not been fully established.

The key endocrine hormones, the natriuretic peptides (NPs) synthesized from the heart are activated to regulate sodium and water homeostasis in HF (Braunwald 2015). Today, two molecular forms derived from the B-type natriuretic peptide (BNP) precursor, BNP and NT-proBNP, continue to grow in use as prognostic biomarkers for future adverse cardiovascular outcomes (McKie et al. 2010), and as a guide to therapy in HF (Lainchbury et al. 2009). The importance of the neurohumoral systems became even more recognized in HF with the discovery that modulation of NP system with the newly approved drug, angiotensin-neprilysin inhibitor, sacubitril/valsartan (McMurray et al. 2014), improved the outcomes of HF. Therefore, monitoring the circulating neurohormones or cardiorenal function is important in understanding the pathophysiology, diagnosis, and therapeutic strategies of HF (Braunwald 2015).

In the real clinical setting, seasonal variations, especially in cold climates, may be linked to cardiovascular events. The incidence of ischemic heart disease and cardiac

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death is known to increase in cold climates, perhaps due to upregulation of the sympathetic nerve system (Argacha et al. 2018). A greater temperature change within a day has also been associated with increased emergency hospital admissions for HF, especially in female and elderly patients (Qiu et al. 2013). Similar effects of temperature shifts on cardiorenal function have not yet been investigated. Therefore, the aim of the current study was to determine the effects of ambient temperature on the severity of HF and renal function in elderly patients with chronic stable HF.

We used BNP as a marker of HF and estimated glomerular filtration rate (eGFR) as a marker of renal function. To determine the effect of renal function on HF, we divided the HF population into two groups by the median value of baseline eGFR. We sought to determine the relationship between ambient temperatures and BNP/eGFR in patients with HF. We hypothesize that ambient temperatures are associated with BNP levels and with eGFR, especially in cold climates.

Materials and Methods

Study design

The current human study was designed as a retrospective and observational study conducted in adult patients with stable HF and serum creatinine (Cre) < 3.0 mg/dl. The patients visited the outpatient clinic at our hospital, International University of Health and Welfare – Shioya Hospital in Yaita City, Tochigi, Japan, every 1 to 3 months. The protocols used in the current study were approved by the Institutional Review Board at the International University of Health and Welfare (No.13-B-302).

The inclusion criteria were patients who 1) were aged 18 years or older; 2) had a plasma BNP level >100 pg/ml and were diagnosed and treated as HF; and 3) had visited the clinic repeatedly for more than 6 months.

The exclusion criteria were: 1) Cre 3.0 mg/dl or above, and 2) hospitalization for any reason within the period 3 months before or after the beginning of data collection.

Patient data collection

Medical records, such as patient characteristics at the beginning of data collection and BNP and eGFR values at each clinical visit every 1 to 3 months, were collected from January 2017 to December 2018. Data collection was terminated by the following endpoints: 1) death, 2) HF hospitalization, or 3) additional prescription of diuretics or vasodilators to treat HF which potentially affect on BNP or eGFR.

Collection of ambient temperature data

Meteorologic information, including the daily maximum, minimum, and mean temperatures, for the Shioya area of Tochigi Prefecture in Japan were obtained from the Japan Meteorological Agency for the day of each patient visit. In the study area, the average daytime temperature in 2017 was 12.2℃, with the highest average temperature at 18.1℃ and lowest average temperature at 6.9℃; the maximum and minimum temperatures in 2017 were 33.7℃, and −8.5℃, respectively. In 2018, the average daytime temperature was 13.1℃, with the highest average temperature at 19.2℃ and the lowest at 7.8℃; the maximum and minimum temperatures were 35.6℃, and −12.6 ℃, respectively. The diurnal temperature range (DTR), which was defined as the difference between maximal and minimal temperatures within a day, was calculated by subtracting the minimum temperature from the maximum temperature of the same day.

Statistical analysis

The data were reported as mean ± SD if the data were normally distributed, or as the median (interquartile range) if the data were not normally distributed. An unpaired t-test was performed for comparison between groups. The baseline and follow-up BNP data were not normally distributed, so they were log transformed. All data were analyzed with a mixed model for repeated measurements. The model included the subject as a random effect, each temperature data point, or the follow-up eGFR as a fixed effect, and the follow-up log-transformed BNP (lnBNP) or eGFR as a dependent variable. The follow-up lnBNP analyses were also included stratification by the baseline eGFR. All statistical analyses were performed with SPSS version 22.0 for Windows (IBM Japan, Tokyo, Japan). A p-value of less than 0.05 was considered statistically significant.

Results

Patient characteristics

In total, 110 patients with stable HF were enrolled (age 82.9 ± 7.6 years, 43 males), and all patients were also divided into two groups based on median baseline eGFR: High-eGFR group (eGFR ≥ 45.8 ml/min/1.73m^2) and Low-eGFR group (eGFR < 45.8 ml/min/1.73m^2). The patient baseline characteristics are shown in Table 1. Most patients were NYHA class I–II and showed a preserved ejection fraction with atrial fibrillation and/or valvular disease. No deaths occurred during the follow-up period (median 399 days and 7 visits), but 10 re-hospitalizations were required for HF. The Low-eGFR group had a greater prevalence of hypertension and anemia, diuretic treatments, and a history of HF hospitalization.

Relationship between follow-up lnBNP levels and ambient temperatures

Table 2 shows the relationship between the follow-up lnBNP and the ambient temperatures at each visit for all patients, the High- and Low-eGFR groups. The follow-up lnBNP showed a weak positive correlation with the DTR on each visit day (Table 2, p = 0.081).

Regarding eGFR groups, the High-eGFR group showed no relationship between the follow-up lnBNP and the ambient temperatures. In contrast, the Low-eGFR group showed a negative correlation with the minimum

Table 1. Patient baseline characteristics.

Variable	All (n = 110)	High-eGFR group eGFR ≥ 45.8 (n = 55)	Low-eGFR group eGFR < 45.8 (n = 55)	p-values
Age (years old)	84 (79, 88)	83 (78, 87)	85 (81, 90)	0.073
Male (%)	43 (39.1)	25 (45.5)	18 (32.7)	0.1714
Body mass index	22.9 ± 4.1	23.3 ± 3.8	22.5 ± 4.4	0.2856
NHYA I/II/III	52/57/1	30/25/0	22/32/1	0.2133
Past History				
Hypertension (%)	81 (73.6)	**33 (60)**	**48 (87.3)**	**0.0012**
Hyperlipidemia (%)	49 (44.5)	25 (45.5)	24 (43.6)	0.8479
Diabetes mellitus (%)	29 (26.4)	12 (21.8)	17 (30.9)	0.2783
(ex) Smoking (%)	24 (21.8)	8 (14.5)	16 (29.0)	0.307
Stroke (%)	14 (12.7)	7 (12.7)	7 (12.7)	1.000
Cancer (%)	15 (13.6)	8 (14.5)	7 (12.7)	0.7811
Pulmonary disease (%)	17 (15.5)	11 (20)	6 (10.9)	0.1872
Ischemic heart disease (%)	29 (26.4)	12 (21.8)	17 (30.9)	0.2783
Valvular disease (%)	88 (80)	45 (81.8)	43 (78.2)	0.6336
Atrial fibrillation/flutter (%)	84 (76.4)	44 (80)	40 (72.7)	0.3693
Myopathy (%)	7 (6.4)	5 (9.1)	2 (3.6)	0.2413
ex Hospitalization (%)	36 (32.7)	**13 (23.6)**	**23 (41.8)**	**0.0422**
Baseline Data				
Systolic BP (mmHg)	127.2 ± 16.7	126.3 ± 14.5	128.2 ± 18.8	0.5685
Diastolic BP (mmHg)	71.9 ± 14.2	72.2 ± 13.8	71.6 ± 14.8	0.8324
BNP (pg/ml)	168.2 (125.3, 274.7)	154.8 (120.1, 242.7)	184.9 (126, 294.7)	0.4009
Blood urea nitrogen (mg/dl)	19.5 (15.9, 25.0)	**16.9 (14.7, 19.7)**	**22.5 (19.3, 27.9)**	**< 0.0001**
Creatinine (mg/dl)	0.96 (0.858, 1.185)	**0.86 (0.76, 0.93)**	**1.18 (0.97, 1.42)**	**< 0.0001**
eGFR (ml/min/1.73 m^2)	47.9 ± 12.7	**57.9 ± 8.8**	**37.9 ± 6.8**	**< 0.0001**
eGFR < 30 ml/min/1.73 m^2	9 (8.2)	0 (0)	9 (16.4)	
Total protein (g/dl)	7.18 ± 0.54	7.17 ± 0.55	7.20 ± 0.53	0.7498
Hemoglobin (g/dl)	12.9 ± 1.92	**13.4 ± 1.80**	**12.4 ± 1.92**	**0.0072**
Echocardiography				
Left ventricular hypertrophy (%)	21 (19.1)	12 (21.8)	9 (16.4)	0.4667
Local asynergy (%)	18 (16.4)	9 (16.4)	9 (16.4)	1.000
Ejection fraction (%)	66.5 (57.63, 74.9)	65.1 (57.4, 72)	68.5 (57.7, 76.7)	0.1358
Medication				
Inotrope (%)	12 (10.9)	7 (12.7)	5 (9.1)	0.5408
Beta blocker (%)	53 (48.2)	24 (43.6)	29 (52.7)	0.34
Ca channel blocker (%)	61 (55.5)	26 (47.3)	35 (63.6)	0.0843
ARB/ACEi (%)	44 (40.7)	19 (35.2)	25 (46.3)	0.24
Diuretics (%)	71 (64.5)	**30 (54.5)**	**41 (74.5)**	**0.0283**
Anti-arrythmics (%)	9 (8.2)	3 (5.5)	6 (10.9)	0.2967
Statin (%)	37 (33.6)	20 (36.4)	17 (30.9)	0.5449
Follow up				
Duration (days)	399 (262.8, 573.3)	**455 (313, 618)**	**343 (219, 497)**	**0.0215**
Follow up visits (times)	7 (5, 9)	6 (4, 9)	7 (5, 9)	0.6311

Values are mean ± SD, n (%), or median (interquartile range). Data of p-value < 0.05 are indicated in bold font.
eGFR, estimated glomerular filtration rate; NHYA, New York Heart Association Classification; BP, blood pressure; BNP, B-type natriuretic peptide; ARB, angiotensin II receptor blocker; ACEi, angiotensin-converting enzyme inhibitor.

temperature (p = 0.039) and a positive correlation with the DTR at each visit (p = 0.007).

These data suggest that BNP levels increase in colder temperatures and that the DTR is broader in the Low-eGFR group.

Relationship between follow-up eGFR levels and ambient

temperatures

Table 3 shows the relationship between the follow-up eGFR and the ambient temperatures at each visit for all patients, the High- and the Low-eGFR groups. The follow-up eGFR in all patients showed a strong negative correlation with the minimum, mean, and maximum temperatures (all $p < 0.0001$), and a positive correlation with the DTR ($p = 0.025$) for each visit day.

When dividing the patients into two groups, both showed strong negative correlation with the minimum, mean, and maximum temperatures for each visit day (all $p < 0.0001$ in the High-eGFR group; $p \leq 0.002$ in the Low-eGFR group); however, the significant effect of DTR was not observed in both groups.

The data suggest that renal function is worsened at higher temperatures (i.e., in summer) and improved at lower temperatures (i.e., in winter).

Relationship between follow-up lnBNP and follow-up eGFR levels

To better understand cardiorenal connection, especially in the Low-eGFR group, we analyzed the relationship between follow-up lnBNP and follow-up eGFR. Table 4 shows the results for all patients, the High- and the Low-eGFR groups. Follow-up lnBNP showed a significant positive correlation with follow-up eGFR for each visit day in the Low-eGFR group ($p < 0.0001$) but there is no correlation in all patients or High-eGFR group.

These data suggest that BNP levels increased when renal function was improved, and BNP levels decreased when renal function was impaired in the Low-eGFR group.

Discussion

This is the first study to investigate the relationship between ambient temperature and the cardiorenal connection in elderly patients with HF. Most patients with HF in the present study had atrial fibrillation and valvular disease but preserved left ventricular systolic function. We assume that these patient characteristics reflected our selection of only "stable HF patients". Consequently, elderly patients with reduced EF and HF patients with severe renal failure have been excluded due to the instability of their disease.

The link between hot or cold weather and HF is controversial. In the cold climate of Scotland, significantly more HF admissions and deaths were reported between 1990 and 1996, especially in patients aged > 75 years (Stewart et al. 2002). By contrast, in Denver, Colorado, higher temperatures were associated with an increase in hospitalizations for acute myocardial infarction and HF in a cohort studied between 1993 and 1997 (Koken et al. 2003). A meta-analysis conducted between 2001 to 2008 indicated an association between elevated ambient temperature and

Table 2. Relationship between follow-up log-transformed B-type natriuretic peptide (lnBNP) and ambient temperatures.

	All			High-eGFR group			Low-eGFR group		
	B	β	p-value	B	β	p-value	B	β	p-value
Mean temperature, (°C)	−0.001	−0.007	0.684	0.002	0.024	0.363	−0.003	−0.039	0.084
Maximum temperature, (°C)	0.000	−0.001	0.962	0.002	0.024	0.377	−0.002	−0.026	0.256
Minimum temperature, (°C)	−0.001	−0.013	0.452	0.001	0.019	0.469	**−0.003**	**−0.047**	**0.039**
Diurnal temperature range (DTR), (°C)	0.005	0.031	0.081	0.001	0.003	0.897	**0.010**	**0.065**	**0.007**

Data of p value < 0.05 are indicated in bold font.

Table 3. Relationship between follow-up estimated glomerular filtration rate (eGFR) and ambient temperatures.

	All			High-eGFR group			Low-eGFR group		
	B	β	p-value	B	β	p-value	B	β	p-value
Mean temperature, (°C)	**−0.125**	**−0.086**	**< 0.0001**	**−0.155**	**−0.107**	**< 0.0001**	**−0.089**	**−0.061**	**0.002**
Maximum temperature (°C)	**−0.126**	**−0.084**	**< 0.0001**	**−0.155**	**−0.103**	**< 0.0001**	**−0.092**	**−0.061**	**0.002**
Minimum temperature, (°C)	**−0.115**	**−0.087**	**< 0.0001**	**−0.137**	**−0.103**	**< 0.0001**	**−0.088**	**−0.066**	**0.001**
Diurnal temperature range (DTR), (°C)	**0.099**	**0.031**	**0.025**	0.093	0.029	0.1035	0.098	0.031	0.149

Data of p-value < 0.05 are indicated in bold font.

Table 4. Relationship between follow-up log-transformed B-type natriuretic peptide (lnBNP) and follow-up estimated glomerular filtration rate (eGFR).

	All			High-eGFR group			Low-eGFR group		
	B	β	p-value	B	β	p-value	B	β	p-value
eGFR (ml/min/1.73 m^2)	0.003	0.064	0.1255	−0.002	−0.041	0.546	**0.011**	**0.223**	**< 0.0001**

Data of p value < 0.05 are indicated in bold font.

an increased risk of death from cardiovascular diseases, such as ischemic heart disease and HF (Basu 2009). The most recent meta-analysis concluded that a 1℃ temperature rise increased both cardiovascular mortality and morbidity (Bunker et al. 2016).

Some studies of cardiovascular disease (CVD) risks and DTR have also been reported only from China. In Shanghai, China, the DTR had an association with daily deaths from coronary heart disease in a cohort studied between 2001 and 2004 (Cao et al. 2009). ER admissions also increased with a broader DTR in Beijing, China, among elderly patients examined between 2009 and 2011 (Zheng et al. 2016). Emergency hospital admissions for HF peaked in winter from 2000 to 2007 in Hong Kong and were associated with a wider DTR, especially in female and elderly patients (Qiu et al. 2013). These studies suggest that a wider DTR may result in a greater incidence of CVD, including HF. In the current study, a broader DTR was associated with increased BNP in the Low-eGFR group, suggesting increased myocardial dysfunction, volume or pressure in the presence of greater renal insufficiency in our patient population.

Interestingly, the relationship detected between renal function and ambient temperature in the current study was very strong (Table 3), and the results were similar to those previously report by Sagy et al. (2016), who showed that renal function worsens with high ambient temperature in hypertensive patients. Similarly, Wang and Lin (2014) reported that higher temperatures are associated with an increased risk of emergency room visits for chronic renal failure. In elderly people in the USA, a renal injury biomarker, neutrophil gelatinase-associated lipocalin (NGAL), was increased by 1.89% for every 1℃ increase in temperature > 10℃, suggesting an association between higher ambient temperature and kidney injury (Honda et al. 2019). Therefore, the observation of an association between ambient temperature and renal function in the current study was similar to the findings of previous studies.

In the current study, BNP showed a trend toward a higher value with a broader DTR. The Low-eGFR group showed an increase in BNP as the ambient temperature decreased or the DTR widened. These results suggest that HF may be exacerbated in patients with renal impairment when the DTR broadens and/or during the winter months.

Table 4 shows a positive correlation between follow-up BNP and follow-up eGFR only in the Low-eGFR group, suggesting that HF worsened when renal function improved in the renal dysfunction group. We create Table 5 which illustrates the main results of the current study. Because follow-up eGFR had a strong negative relationship with ambient temperatures, renal function was found to worsen in summer and improve in winter. Thus, in only the Low-eGFR group, HF improves in summer and worsens in winter, according to the relationship with follow-up eGFR.

These findings raise the question of the possible pathophysiological relationship between HF with renal impairment and ambient temperature. Argacha et al. (2018) elegantly reviewed the relationship between CVD and environmental factors and showed that the sympathetic nerve system responds to cold exposure by release of catecholamines. This release, in turn, induces peripheral microcirculatory vasoconstriction, as well as increased blood viscosity and hemoconcentration. A similar increase in the concentration of blood cells and clotting factors has also been associated with heat exposure. Other neurohumoral factors, such as the plasma level of endothelin-1 and atrial natriuretic peptide, also show increases toward the end of a 2 hour cold-room exposure (Hassi et al. 1991). Only a few studies have been performed on the environmental pathophysiology of BNP, so further studies are needed.

Contrary to our results regarding the positive relationship between BNP and eGFR, most studies have reported an inverse relationship between BNP and eGFR. For instance, Takase and Dohi (2014) reported that BNP had an inverse relationship with eGFR in patients from the outpatient clinic of cardiology and hemodialysis departments, although the positive relationship between NT-proBNP and eGFR was more prominent than the relationship between BNP and eGFR. Tsutamoto et al. (2006) also reported that BNP levels from the aorta had an inverse relationship with eGFR but there was no significant relationship between the concentration difference of BNP levels between coronary sinus and aorta and eGFR, suggesting that the inverse relationship may be due to the clearance of BNP by the kidney, not BNP synthesis by the heart. Notably, these studies analyzed BNP and eGFR as a one-point observation, not individual time changes. We speculate the reasons the current study did not find an inverse relationship between BNP and eGFR were: 1) patients with renal failure, whose BNP clearance was damaged, were excluded, and 2) the condi-

Table 5. Summary: Changes of B-type natriuretic peptide (BNP) and estimated glomerular filtration rate (eGFR) according to changes in climate.

		Summer	Winter	Large DTR	Small DTR
High-eGFR group	eGFR	↓	↑	-	-
	BNP	-	-	-	-
Low-eGFR group	eGFR	↓	↑	-	-
	BNP	↓	↑	↑	↓

The ↓ arrow indicates decreases in the eGFR or BNP; the ↑ arrow indicates increases in the eGFR or BNP; - indicates no significant change in eGFR or BNP. DTR, diurnal temperature range.

tion of volume overload increases eGFR and BNP through increased ventricular filling pressure.

Global warming is a major worldwide issue for various reasons and is likely to lead to extreme heat or cold weather in upcoming years (Johnson et al. 2018). For this reason, following renal function in HF management in association with climate change may be important when considering treatments for cardiorenal protection. The angiotensin-neprilysin inhibitor sacubitril/valsartan (Entorest®) was recently approved for HF treatment, and some studies have reported renal protective effects/improvement of renal function with this medication (Damman et al. 2018; Spannella et al. 2019). Sodium glucose cotransporter 2 (SGLT2) inhibitor, which has been used therapeutically for type 2 diabetes, has also been approved for HF treatment. Two large phase III clinical trials for HF using Dapagliflozin (Forxiga®) (McMurray et al. 2019) and Empagliflozin (Jardiance®) (Packer et al. 2020) reported that both drugs improve outcomes regardless of the presence of diabetes. Rangaswami et al. (2020) reviewed about the therapeutic opportunities of SGLT2 inhibitors that the cardiorenal protection may be through glucose-independent mechanisms. Therefore, therapeutics like angiotensin-neprilysin inhibitor and SGLT2 inhibitors may have protective effects against the cardiorenal impairments that may occur in response to climate change.

This study had several limitations. One was its retrospective nature. Another was that the study cohort came from a single center in Japan and consisted mostly of elderly patients. The relationship between ambient temperature and cardiorenal connection may differ in younger patients with HF, in patients with HF with reduced EF, or in patients residing in other locations. The study population number was also small. We assume that the prognosis may differ between the Low-eGFR group and the High-eGFR group, so further study is required in a larger population and a prospective design.

In conclusions, renal function in HF may worsen at high temperatures, whereas HF itself may be worsened by cold temperatures or a broader DTR in patients with HF plus renal impairment. Elderly patients with HF and renal impairment should be followed for their renal function in summer, and also be monitored BNP in winter or in seasons with broader DTR. This population should be carefully managed in the clinic according to the ambient temperature.

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Conflict of Interest

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