Correlation Between Increased Urinary Sodium Excretion and Decreased Left Ventricular Diastolic Function in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Background: Increased salt intake may induce hypertension, lead to cardiac hypertrophy, and exacerbate heart failure. When elderly patients develop heart failure, diastolic dysfunction is often observed, although the ejection fraction has decreased. Diabetes mellitus (DM) is an established risk factor for heart failure. However, little is known about the relationship between cardiac function and urinary sodium excretion (U-Na) in patients with DM.

Methods: We measured 24-hour U-Na; cardiac function was evaluated directly during coronary catheterization in type 2 DM (n = 46) or non-DM (n = 55) patients with preserved cardiac systolic function (ejection fraction ≥60%). Cardiac diastolic and systolic function was evaluated as −dp/dt and +dp/dt, respectively.

Results: The average of U-Na was 166.6 ± 61.2 mEq/24 hour (mean ± SD). In all patients, stepwise multivariate regression analysis revealed that −dp/dt had a negative correlation with serum B-type natriuretic peptide (BNP; $\beta = -0.23$, $P = .021$) and U-Na ($\beta = -0.24$, $P = .013$). On the other hand, +dp/dt negatively correlated with BNP ($\beta = -0.30$, $P < .001$), but did not relate to U-Na. In the DM-patients, stepwise multivariate regression analysis showed that −dp/dt still had a negative correlation with U-Na ($\beta = -0.33$, $P = .025$).

Conclusion: The results indicated that increased urinary sodium excretion is associated with an impairment of cardiac diastolic function, especially in patients with DM, suggesting that a reduction of salt intake may improve cardiac diastolic function.

Introduction

A large amount of clinical and experimental evidence has shown that excess salt intake is linked not only with hypertension but also cardiovascular disease.[1,2] In the clinic, many physicians have realized that high salt intake can easily worsen clinical symptoms in patients with congestive heart failure (CHF). Congestive heart failure is a common cardiovascular disease and is one of the most important causes of death, but the ejection fraction (EF) of these patients was not always decreased.[3–5] Congestive heart failure patients with preserved EF have been shown to be older, to more often be women, and to have a lower prevalence of prior myocardial infarction.[3,5] Cardiac diastolic dysfunction, which has been characterized by impaired isovolumic relaxation,[6] is one of the first manifestations of heart failure even though the patient is free from clinical symptoms. It is often seen in decompensated CHF patients with preserved EF[5] and is an independent risk factor for mortality.[7,8] The pathophysiological mechanisms of diastolic dysfunction are not fully understood, but myocardial fibrosis, which is often seen in hearts that have experienced diastolic heart failure,[9] might decrease the elasticity of the heart and lead to maladaptation to volume expansion. Salt is one of the most important regulators of fluid volume and causes cardiac fibrosis in experimental animals; however, only a few studies have shown the correlation between salt intake and cardiac diastolic function.[10–12]

Diabetes mellitus (DM) is an independent and established risk factor for cardiovascular disease,[13] and it has been reported that cardiac diastolic function is decreased in patients with DM.[14,15] However, there has been no study

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showing the relationship between dietary salt and cardiac function in patients with DM. In the present study, we examined the association between cardiac function, as obtained from a transluminal direct cardiac catheter, and urinary sodium excretion (U-Na), which reflects dietary salt, in patients with or without DM.

Methods

Study Population

We designed a cross-sectional study in patients who were undergoing elective coronary angiography (CAG) due to suspected coronary artery disease or because of a regular check-up for an implanted stent. A total of 172 patients participated in this study from August 2005 to March 2006. Informed consent was obtained from each patient. Blood samples were taken before admission for CAG. The subjects with DM were defined as having a fasting blood glucose of 126 mg/dL or higher, a casual blood glucose of 200 mg/dL or higher, or currently taking an antidiabetic drug. All patients were admitted in the morning, and 24-hour urine collection was performed from the time of admission until noon the following day. Most of the patients ate from a salt-restricted menu (NaCl = 7 g/d), but several participants ate a non-salt-restricted diet (NaCl = 10 g/d).

Cardiac Measurement

The coronary angiography was performed using a cardiac imaging system (Integris Allura Xper FD10, (Philips Medical Systems, Netherlands Best) in the afternoon on the second day of admission, and the operators of the CAS (coronary angiography systems) were blinded to the patients baseline characteristics to avoid selection bias. After routine CAG, cardiac functional parameters from a left ventricular (LV) pressure transducer were automatically calculated except for the EF. Ejection fraction was calculated as the ratio of an end-systolic LV area to an end-diastolic LV area of the LV contrastography. The +dp/dt and EF were used as indexes of LV systolic function, and −dp/dt was used as an index of LV diastolic function. The preserved LV systolic function was defined as an EF of 0.6 or more.

Urinary Sodium Excretion

Estimated 24-hour urinary creatinine (U-Cre) was calculated from the following equation: for male U-Cre = body weight (kg) × 10.8 + height (cm) × 4.5 − age × 9.0 + 359; for female U-Cre = body weight (kg) × 7.3 + height(cm) × 4.9 − age × 4.7 − 38.[16] The 24-hour urinary collection was considered to be adequate if the ratio of the calculated 24-hour U-Cre to the estimated 24-hour U-Cre was between 0.5 and 1.5. We excluded 71 participants for the following reasons: 11 participants whose cardiac function at the CAG could not be evaluated, because of arrhythmia or technical difficulty and 30 participants whose 24-hour urine collection could not be completed, and 30 participants whose EF values were lower than 0.6. As a result, 101 participants were used for the following analysis.

Statistical Analysis

Data were analyzed using SPSS 15.0.1 statistical software (SAS Institute Inc., USA. NC). Simple associations of the variables were initially assessed by calculation of Pearson correlation coefficients. To determine the variables influencing the +dp/dt or −dp/dt, multiple stepwise regression analyses were carried out. In the multiple regression analysis, the independent variables that we included were gender, age, DM (presence or absence), smoking (current smoker or not), body mass index, systolic blood pressure, heart rate, glucose, hemoglobin concentrations, plasma low-density lipoprotein (LDL), plasma B-type natriuretic peptide (BNP), and U-Na. Comparisons between the DM patient group and the non-DM patient group were performed by χ^2 tests or the student t test. Values are presented as the mean ± SD. P values $< .05$ were considered statistically significant.

Results

Total Subjects

Table 1 shows the baseline characteristics of the subjects in this study. U-Na was higher in men than in women, and the other clinical and laboratory variables that were significantly correlated with U-Na were age ($r = -0.264$, $P < .01$), plasma glucose ($r = 0.258$, $P < .05$), and hemoglobin A_1c ($r = 0.253$, $P < .05$). A simple association of the +dp/dt with U-Na was not observed, but the −dp/dt was negatively correlated with U-Na (Figure 1). The other simple associations with cardiac function were as follows: +dp/dt was significantly inversely correlated with plasma BNP ($r = -0.202$, $P < .05$), and −dp/dt was significantly inversely correlated with hemoglobin concentrations ($r = -0.331$, $P < .01$). In the stepwise multiple regression analysis, the independent variables that we included were gender, age, DM, smoking, body mass index, systolic blood pressure, heart rate, glucose, hemoglobin concentrations, plasma LDL, plasma BNP, and U-Na. In this analysis, the U-Na and hemoglobin concentrations were determinants of −dp/dt, and BNP was the only determinant of the +dp/dt (Table 2).

Subgroup Analysis between DM Patients and non-DM Patients

In DM patients, LV function was reported to be decreased compared with nondiabetic patients[14,15]; we also investigated the effects of DM on the relationships between U-Na and LV diastolic function. Table 1 shows the baseline characteristics and indicates that body mass index, heart rate, plasma glucose, hemoglobin A_1c, and U-Na were higher in DM patients than in non-DM patients, and age and plasma LDL were higher in non-DM patients than in DM patients. The reason why plasma LDL was lower in DM patients than in non-DM patient was that the number of the patients who

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Table 1. Baseline Clinical Data and Cardiac Function in the Study Population

Variables	All subjects Mean ± SE	DM (+) Mean ± SE	DM (−) Mean ± SE	
n	101	46	55	
Age, y	68.4 ± 9.4	66.2 ± 10.6	70.3 ± 7.9	*
Sex, M/F	60/41	27/19	33/22	
Smoker, %	26.7	26.1	27.3	
Body mass index, kg/m²	24.5 ± 3.1	25.6 ± 3.6	23.6 ± 2.4	**
Systolic blood pressure, mmHg	138.3 ± 19.0	141.5 ± 19.8	135.5 ± 18.0	
Diastolic blood pressure, mmHg	76.3 ± 11.7	77.3 ± 12.6	75.5 ± 11.0	
Heart rate, bpm	70.0 ± 11.8	72.9 ± 11.8	67.6 ± 11.3	*
Creatinine, mg/dl	0.84 ± 0.28	0.82 ± 0.31	0.85 ± 0.25	
Glucose, mg/dl	149.6 ± 70.1	192.4 ± 81.3	113.2 ± 24.9	**
HbA1c, %	6.5 ± 1.3	7.2 ± 1.3	5.5 ± 0.4	**
Hemoglobin concentration, g/dl	13.6 ± 1.7	13.6 ± 1.4	13.6 ± 1.9	
Triglyceride, mg/dl	141.3 ± 77.0	152.9 ± 84.5	131.6 ± 69.5	
HDL-C, mg/dl	52.9 ± 14.9	51.2 ± 14.0	54.4 ± 15.8	
LDL-C, mg/dl	119.3 ± 28.0	112.1 ± 27.2	125.4 ± 27.4	*
BNP, pg/ml	46.0 ± 58.3	34.8 ± 30.2	55.1 ± 72.8	
Urinary NaCl, mEq/24hr	166.6 ± 61.2	183.6 ± 68.0	151.3 ± 49.3	*
Drug, %				
ARB	33.7	37.0	30.1	
ACE	14.9	19.6	10.9	
Ca antagonists	50.5	56.5	45.5	
β-blockers	10.9	13.0	9.1	
Diuretics	10.9	15.2	7.3	
Lipid-lowering drugs	35.1	48.9	23.6	**
Ejection fraction, %	73.2 ± 7.0	74.3 ± 6.7	72.2 ± 7.2	
+dp/dt, mmHg/s	1898.6 ± 451.7	1874.4 ± 421.0	1918.9 ± 478.9	
−dp/dt, mmHg/s	1683.3 ± 498.0	1682.1 ± 485.7	1684.2 ± 512.5	
LVEDP, mmHg	13.0 ± 4.4	12.9 ± 4.2	13.1 ± 4.7	

Abbreviations: y indicates years; M, male; F, female; BNP, B type natriuretic peptide; ACE angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; EF, ejection fraction; LVEDP, left ventricular end diastolic pressure.
* $p < 0.05$,
** $p < 0.01$.

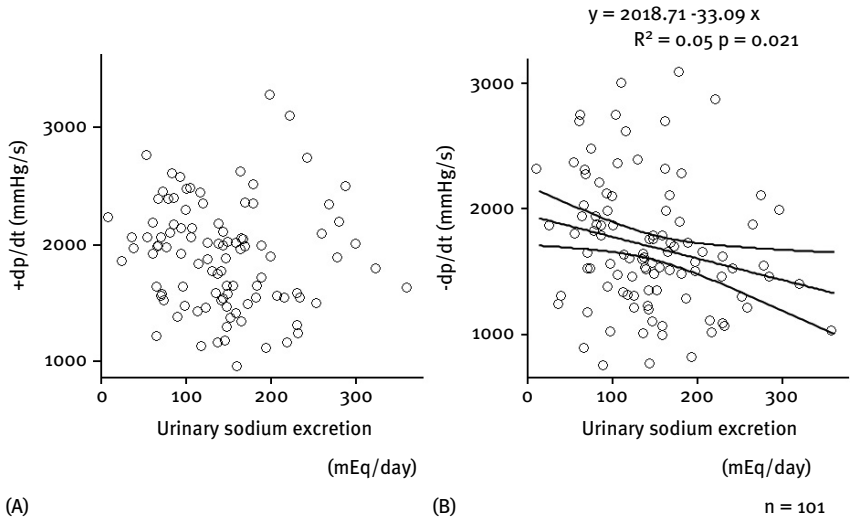

Figure 1. (A) Correlation between left ventricular systolic function (+dp/dt) and urinary sodium excretion (U-Na). (B) Correlation between left ventricular diastolic function (−dp/dt) and U-Na.

Table 2. Variables Associated With Cardiac Systolic and Diastolic Function

	+dp/dt		−dp/dt					
	total subjects ($n = 101$)		total subjects ($n = 101$)		DM (+) ($n = 46$)		DM (−) ($n = 55$)	
Parameter	β	P	β	P	β	P	β	P
U–Na, mEq/day			−0.24	0.013	−0.33	0.025		
Hemoglobin concentration, g/dl			−0.41	<0.001	−0.32	0.029	−0.39	0.004
BNP, pg/ml	−0.30	<0.001	−0.23	0.021				
Age, years							−0.33	0.013

were taking lipid-lowering agents was significantly higher in DM patients than in non-DM patients. Among the DM patients, we found a significant negative correlation between U-Na and −dp/dt ($r = -0.354$, $P < .01$), but did not find a correlation in non-DM patients ($P = .44$; Figure 2). In the multiple regression analysis, U-Na and hemoglobin concentrations were determinants of −dp/dt in DM patients (Table 2). On the other hand, age and hemoglobin concentrations were determinants of −dp/dt in non-DM patients.

Discussion

In the present study, we showed that (1) U-Na was inversely correlated with LV diastolic function, as measured by direct cardiac catheterization in patients who underwent CAG; (2) the patients with DM showed an inverse association between LV diastolic function and U-Na and non-DM patients did not.

The intimate relationship between dietary salt and blood pressure has been reported by the worldwide INTERSALT survey,[1] and increased dietary salt is known to have adverse effects on the cardiovascular system independently of blood pressure (BP).[17] It has been reported that in the heart, dietary salt is positively related to LV mass[18]; however, there have been few studies that have investigated the relationship between dietary salt and cardiac or vascular function.[10,12,19] Dahl salt-sensitive hypertensive rats have been used as an experimental model for heart failure. In these rats, heart failure does not develop without salt load, and cardiac systolic function is preserved until heart failure develops; diastolic function, however, declines at the first stage of salt load.[20] Just recently, Tzemos et al have reported that acute salt loading in young normotensive individuals increases systolic BP and decreases diastolic function as evaluated by echocardiography.[12] They also reported that the vascular reactivity to acetylcholine is blunted by salt load, but that the vascular response to sodium nitroprusside is not affected by salt load, suggesting that endothelium-dependent vascular function is impaired by salt load. The precise mechanisms of this process, however, remain under investigation.

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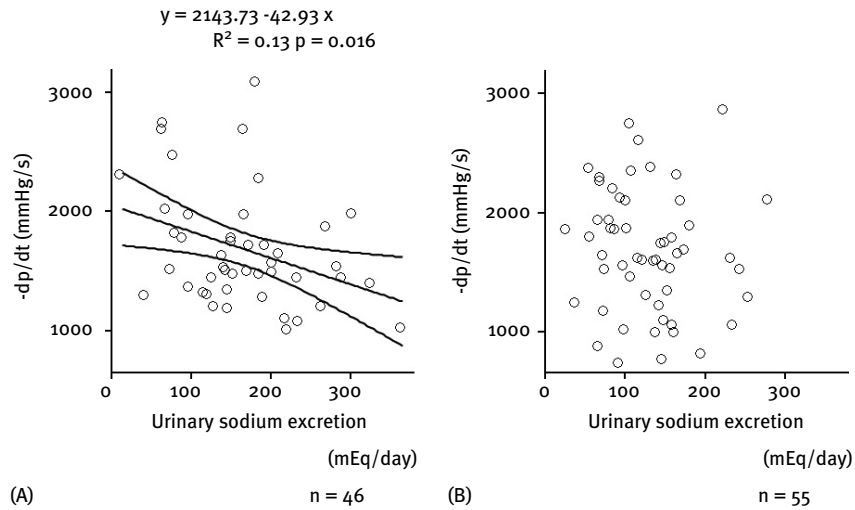

Figure 2. Correlation between left ventricular diastolic function (−dp/dt) and U-Na in patients with diabetes mellitus (A) and without diabetes mellitus (B).

Several studies have shown that cardiac function is decreased in DM patients compared with non-DM patients,[14,15] and another study has focused on the relationship between enhanced salt-sensitivity in patients with DM compared with non-DM patients.[21] However, there have been no studies to examine the relationship between increased U-Na and diastolic function in DM patients. The examination of hearts, obtained at autopsy, of patients with hypertension, DM, or both has revealed that the amount of cardiac fibrosis of hypertensive-diabetic hearts is significantly higher than that of diabetic or hypertensive hearts.[22] Duration of DM or presence of proteinuria might affect the result of cardiac function, but we did not consider it. However, levels of hemoglobin A_1c or the current therapy for DM (diet, oral antidiabetic agents, or insulin therapy) did not affect cardiac function.

In the present study, high levels of hemoglobin were negatively correlated with LV diastolic function, and this finding was consistent with those obtained in previous studies.[23,24] The potential mechanisms of the negative association of hemoglobin and diastolic function have been explained primarily in 2 ways: effects on the blood viscosity or on the increase in peripheral vascular resistance. Because tissue hypoxia is reduced in response to high levels of hemoglobin, hypoxia-mediated vasodilatation is diminished; as a result, peripheral vascular resistance might be increased.

U-Na measurement was easily affected by meals, and it was somewhat difficult to evaluate the sodium intake accurately. U-Na in this study was examined under admission and most of the participants ate a sodium-restricted diet. However, U-Na was distributed over a relatively wide range and the average U-Na in the present study was comparable to that in another study in which data were collected from outpatients.[25] Some studies have indicated that several days are needed for U-Na to converge from the change of sodium content in the diet.[26] Indeed, the U-Na in our subjects who ate a salt-restricted diet ($n = 82$, 166.1 ± 58.2 mEq/24 hr) did not differ from that those who ate a non-salt-restricted diet ($n = 19$, 163.2 ± 59.2 mEq/24 hr). Since the U-Na in this study was measured on the day of admission, it reflected the daily sodium intake of the subjects and was not affected by the salt restriction on the day of admission. Patients might need to be on a low salt diet before the measurement of cardiac function to avoid the potential bias of varying daily salt intake. However, we could not control the salt intake because we could not spend the time and effort. For the same reasons, we could not stop the use of diuretics and other medications during measurement of U-Na, but we did not find that the medication made a difference on cardiac function even though we included the kinds of medication in the multivariate regression analysis. Dietary salt restriction enhances an antihypertensive effect of renin-angiotensin system blockade,[27] and it has been reported that the reduction of proteinuria by angiotensin-converting enzyme inhibition was decreased by high sodium intake.[28] We did not observe any difference between U-Na and BP or the drugs which the subjects were currently taking. It might be because this study was not designed to control for drug administration.

Cardiac function was evaluated from the direct cardiac catheterization in this study because direct cardiac pressure monitoring is a first-line method for evaluating cardiac diastolic function in the case of a diagnosis of diastolic heart failure.[29] Although echocardiography is widely used for noninvasive assessment of cardiac diastolic function due to its low cost and convenience,[8] we did not examine the relationship between echocardiographic findings and

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direct cardiac pressure monitoring in the present study. Future studies are needed to examine the relationship between cardiac function evaluated from echocardiography and urinary sodium excretion.

A recent clinical study has indicated that diastolic dysfunction is related to increased mortality[30] and that a sodium-restricted diet improves mortality.[31] The present study was limited by its observational design and the lack of follow-up examinations. Obviously, further studies are needed to explore the possible improvement of cardiac diastolic function by salt restriction.

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