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ORIGINAL RESEARCH

Effects of a Low-Salt and High-Potassium Diet on Arterial Stiffness and Left Ventricular Function in Indigenous Papuans

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BACKGROUND: A sodium-restricted diet represents a potential non-pharmacological strategy for improving blood pressure, arterial stiffness, and left ventricular (LV) diastolic function. We investigated age-related differences in LV structure and function and the relationship between LV function and central hemodynamics in an indigenous Papuan population, who maintain a traditional lifestyle, including a low-salt and high-potassium diet.

METHODS AND RESULTS: We measured LV dimensions, transmitral blood flow, and mitral annular tissue velocities through echocardiography and Doppler imaging. Blood pressure and brachial-ankle pulse wave velocity were measured using an automatic device (Omron). Central blood pressure and wave reflection parameters were estimated via oscillometry (Mobil-O-Graph, using European calibrations). A total of 82 native Papuans (median age, 42 years; 38 women; no blood pressure treatment) were enrolled. Age-related difference in brachial systolic pressure was modest but significant, and brachial-ankle pulse wave velocity significantly increased with age; however, LV mass index remained unchanged. LV ejection fraction and global longitudinal strain were preserved; mitral A-wave velocity and average E/e´ increased; and e´ and E/A decreased with age. Brachial-ankle pulse wave velocity and spot urine Na/K were positively and independently correlated with E/e´. Age and heart rate were inversely associated with E/A. In conclusion, LV systolic function was preserved; however, LV diastolic function decreased with age in Papuans. Moreover, age-related arterial stiffening, but not wave reflections, was inversely related to LV diastolic function.

CONCLUSIONS: Our results suggest that arterial and LV stiffness may not be altered by sodium restriction. Longitudinal studies are warranted to elucidate the effects of diet on arterial and LV function.

Key Words: aging ■ arterial stiffness ■ left ventricular function ■ potassium ■ salt intake

Left ventricular (LV) systolic function is relatively preserved through an individual's lifetime in the general population, whereas LV diastolic function decreases with age.[1–3] Heart failure with preserved ejection fraction (HFpEF) is a significant public health problem with increasing prevalence, high morbidity and mortality, and lack of proven effective therapies.[4] Several factors are implicated in the pathogenesis of HFpEF, including LV diastolic dysfunction, LV hypertrophy, and ventricular-arterial stiffening. Ventricular-arterial interactions constitute an important element of dynamic cardiovascular circulation.[5] Ideal coupling of the left ventricle and systemic arterial system maintains optimal cardiac output and blood pressure. Arterial stiffening is a common feature of aging. Increased arterial stiffness causes earlier and amplified wave

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CLINICAL PERSPECTIVE

What Is New?

- Among indigenous Papuan populations who have maintained a lifelong low-salt and high-potassium diet, left ventricular systolic function was preserved, whereas left ventricular diastolic function decreased with age.
- Age-related arterial stiffening was inversely related to left ventricular diastolic function, but wave reflections and mean arterial pressure were not.

What Are the Clinical Implications?

- Age-related arterial and cardiac changes may share pathophysiological mechanisms.
- Further studies are needed to elucidate whether prevention or reduction of arterial stiffness might have additional value to prevent or delay subclinical alterations in left ventricular diastolic function.

Nonstandard Abbreviations and Acronyms

baPWV	brachial-ankle pulse wave velocity
HFpEF	heart failure with preserved ejection fraction

reflections, augmented central systolic pressure, pulse pressure (PP), and LV afterload, and contributes to LV remodeling and diastolic dysfunction. In animal models, dietary sodium restriction or supplementation with potassium reduced blood pressure and cardiovascular damage.[6,7] Similarly, in patients with hypertensive HFpEF, a sodium-restricted and potassium-rich diet (sodium-restricted Dietary Approaches to Stop Hypertension diet) for 21 days reduced brachial and central systolic pressure and produced favorable changes in diastolic function, arterial elastance, and ventricular-arterial coupling.[8,9] However, no significant changes were observed in standard diastolic function parameters, such as E/e´, because of diet therapy, likely because of a short observation period. Studies with longer observation periods are needed to identify changes in cardiac and arterial structure and function; however, continuing a dietary intervention in a study cohort is difficult owing to the modern lifestyle.

Indigenous populations, including Yanomamo and Xingu Indians in Brazil and the highlanders of Papua New Guinea, are known to have low blood pressure. Moreover, an age-related increase of systolic blood pressure (SBP) is not observed in this population partly because of low salt intake.[10] We had conducted a field survey of the indigenous population of the Dani tribe living in the Soroba village in the central highlands of Papua in Indonesia.[11,12] The inhabitants of Soroba maintained a traditional way of life, particularly a traditional dietary habit; sweet potato and taro were their staple food and accounted for ≈80%–90% of their diet. Median sodium and potassium intakes of the 6 inhabitants assessed by a 24-hour recall method were 0.8 g/day and 6.6 g/day, respectively.[12] The World Health Organization recommendation for sodium intake is <2.0 g/day and for potassium intake is >3.5 g/day, whereas current average sodium and potassium intakes of the global population are estimated at 4.0 g/day and 2.0 g/day, respectively.[13–15] The spot urine Na/K of the 126 inhabitants was low (median 1.1; interquartile range, 0.49–2.40).[12] An age-related increase in brachial SBP was absent in this population, whereas brachial-ankle pulse wave velocity (baPWV) increased with age. LV structure and function assessed by using echocardiography have not yet been examined in such indigenous populations, who maintain a lifelong low-salt and high-potassium diet. This study aimed to investigate the age-related differences in LV structure and function and the relationship with central hemodynamics and arterial stiffness in an indigenous Papuan population. Because central hemodynamics and incidence of HFpEF generally vary with sex, we assessed sex differences in central hemodynamics and LV geometry and function.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participants

Soroba is a small village located in the central highlands of Papua, situated at an altitude of 1500 m, ≈10 km from the city of Wamena, Republic of Indonesia. Sweet potato and taro are the staple foods in this region; however, the diet and lifestyle of indigenous Papuans are rapidly changing with social globalization. Alcohol consumption is prohibited by the government and no villagers take any regular medications.

In March 2017, as part of health promotional activities, we conducted a field survey of the indigenous population of the Dani tribe in Soroba. With the help of the village leader, we recruited volunteers who could participate in medical checkups. A total of 112 native Papuans participated in the survey and 90 participants voluntarily underwent transthoracic echocardiography. Participants with missing data on Mobil-O-Graph (n=3), baPWV (n=1), and tissue Doppler imaging recordings

(n=2) were excluded. A 39-year-old woman with apparent combined valvular disease and a 30-year-old pregnant woman were also excluded. After application of the exclusion criteria, a total of 82 participants were enrolled in this study. Indonesian collaborators and co-authors who spoke both English and Indonesian, local people who spoke both Indonesian and the local language of Soroba village, and the co-author E.G., who spoke English, Indonesian, and Japanese, served as interpreters. For participants who could not read/write, verbal communication was performed with the support of their family members and the translators. Informed consent was obtained from all study participants. The study was approved by the Ethics Committee of the Center for Southeast Asian Studies of the Kyoto University and the Ethics Committee of the University of the Ryukyus and was performed with the permission of the Department of Health of the Papua Provincial Government in cooperation with Cenderawasih University.

Echocardiography

An experienced European Association of Cardiovascular Imaging certified echocardiologist (A. Isotani) performed the ultrasound examinations following the American Society of Echocardiography and European Association of Echocardiography recommendations using a Vivid iq (GE Healthcare) interfaced with a 2.50 to 3.5 MHz phased array probe.[16] With the participants in a partial left decubitus position, the observer obtained images along the parasternal long and short axes and from the apical 4- and 2-chamber long-axis views, together with a simultaneous ECG signal. All recordings included at least 5 cardiac cycles and were digitally stored for offline analysis. Left atrial volume and LV mass were estimated using the ellipse model formula[17] and the Devereux formula,[18] respectively, and were normalized for body surface area. The cut-off points for diagnosing LV hypertrophy were 95 g/m^2 for women and 115 g/m^2 for men. Concentric LV remodeling was diagnosed when relative wall thickness (RWT) was >0.42. LV ejection fraction (EF) was calculated by biplane modified Simpson rule (n=81) or the Teichholz formula (n=1). LV diastolic function was assessed using pulsed-wave Doppler and tissue Doppler indices. Transmitral Doppler flow signals were used to measure peak early (E) and late (A) diastolic velocities and E/A which is an index of myocardial relaxation. From pulsed-wave tissue Doppler indices recordings, we measured the early (e´) diastolic peak velocities of the septal and lateral mitral annulus. We calculated E/e´ by dividing the transmitral E peak by the average value of septal and lateral e´. Speckle-tracking echocardiography procedures were performed according to standardized procedures. LV global longitudinal strain, a comprehensive parameter of LV systolic function, was determined using 2D speckle-tracking echocardiography.

Spot Urine Sodium-Potassium Ratio

Spot urine sodium-potassium (Na/K) molar ratio was measured using a handy-sized urinary Na/K ratio monitor (HEU-001F, Omron Healthcare Co., Ltd, Kyoto, Japan).

Brachial-Ankle Pulse Wave Velocity and Supine Blood Pressure

The baPWV was measured using a validated automatic apparatus (BP-203RPE, III form PWV/ABI: Omron Healthcare Co., Ltd, Kyoto, Japan), which simultaneously measured pulse volume in the brachial and ankle arteries using an oscillometric method, and bilateral arm and ankle blood pressure.[19] The participants were examined at resting in the supine position for at least 5 minutes. Electrocardiographic electrodes were placed on both wrists, and cuffs were wrapped on the bilateral brachia and ankles. Hypertension was defined as a supine SBP ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg. PP was calculated as SBP - DBP.

Oscillometric Pulse Wave Analysis

Central blood pressure was estimated using a validated cuff-based oscillometric device (Mobil-O-Graph; I.E.M., Stolberg, Germany) in the sitting position. An appropriate cuff size was selected according to arm size. After brachial blood pressure was measured, pulse wave analysis and wave separation analysis were performed. The central blood pressure, and measures of forward (amplitude of forward wave; Pf) and reflected waves (augmentation index; Aix, augmentation pressure; Pa, amplitude of backward wave; Pb), and their ratio (reflection magnitude; RM) were calculated based on the mathematical transformation (ARCsolver algorithm).[20–22] The brachial pressure waveform was calibrated using brachial mean arterial pressure (MAP) and DBP. The augmentation index was adjusted to a heart rate of 75 bpm (Aix@75).

Statistical Analysis

Continuous variables are presented as median (interquartile range) and categorical variables are presented as absolute and relative frequencies (%). Data for groups according to sex were compared using the Wilcoxon rank-sum test for continuous variables. Categorical variables were compared using the Fisher exact test. Spearman simple correlation analyses were

performed to determine the relationship between the variables of interest. Multivariate linear regression analyses were used to evaluate which factors were independently associated with LV diastolic function. Age, sex, body mass index (BMI), current cigarette smoking, MAP, heart rate, LV mass index (LVMI), baPWV, and urine Na/K were included as independent variables. Statistical analyses were performed using JMP Pro (version 14.1). A 2-sided *P* value <0.05 was considered statistically significant.

RESULTS

Characteristics of the Participants

Among the 82 participants, 38 (46%) were women (Table 1). Women were shorter and had lower BMI than men. The prevalence of hypertension was significantly higher in women than that in men. Brachial PP was higher in women than that in men; however, central BPs and PWVs were comparable between men and women. Women had higher Pa and Aix@75 than men. All participants had a sinus rhythm. Women had a smaller aorta, left atrial and LV dimensions, and LVMI, yet larger RWT, higher EF, and lower (better) global longitudinal strain than men (Table 2). Concentric LV remodeling was observed in 15 participants (18%), but no participant had LV hypertrophy. Three (4%) participants, all of whom were men, had mildly reduced EF (40%–50%). No participant had a reduced EF <40%. Median left atrial volume index was 23.8 mL/m^2. Three (4%) participants had an increased left atrial volume index (>34 mL/m^2). Indices of diastolic function, including E/A, E/e´, and isovolumic relaxation time, were comparable between men and women.

Clinical Characteristics by Hypertension

Thirteen (15%) participants had hypertension (Table S1). Participants with hypertension were found to be older; women; and shorter in height. They also had higher urine Na/K, higher brachial and central BPs, PWVs, Pa, Aix@75, Pf, and Pb than participants with normotension. Participants with hypertension had a smaller aorta, higher mitral E and A wave velocities, shorter deceleration time, slower lateral and average e´, and higher E/e´ (Table S2) than participants with normotension. LVMI and RWT were comparable between participants with hypertension and participants with normotension.

Associations of Hemodynamic and Echocardiography Indices With Age and Urine Na/K

BMI inversely correlated with age (Table S3). Median urine Na/K was 1.60 (Figure S1); participants aged >50 years had lower urine Na/K than those aged <50 years, but the difference was not significant (0.93 versus 1.76, *P*=0.107). Brachial BPs positively correlated with age. Central SBP, Pa, Aix@75, and Pb were positively associated with age, but neither DBP nor PP

Table 1. Clinical and Hemodynamic Characteristics by Sex

Variables	Men (n=44)	Women (n=38)	*P* value
Age, y	42 (37–54)	43 (38–50)	0.78
Height, cm	162 (157–165)	152 (149–156)	<0.001
Weight, kg	58.5 (53.0–64.8)	46.5 (42.8–55.0)	<0.001
BMI, kg/m^2	22.9 (20.7–24.9)	20.2 (19.0–22.3)	0.001
Abdominal circumference, cm	82 (80–87)	80 (74–86)	0.062
Current smoking (%)	32 (73)	21 (55)	0.111
Urine Na/K, mol/mol	1.5 (0.8–2.3)	1.7 (0.6–2.3)	0.93
Brachial BP			
SBP, mm Hg	117 (110–129)	123 (110–143)	0.23
DBP, mm Hg	72 (67–76)	71 (65–81)	0.78
MAP, mm Hg	88 (83–98)	91 (85–106)	0.137
PP, mm Hg	45 (42–54)	52 (44–62)	0.045
Heart rate, bpm	62 (52–71)	62 (55–73)	0.33
Hypertension (%)	3 (7)	10 (26)	0.031
Central BP			
SBP, mm Hg	126 (115–137)	122 (109–145)	0.42
DBP, mm Hg	78 (75–86)	79 (72–90)	0.81
PP, mm Hg	46 (36–56)	43 (32–56)	0.44
PPA	1.4 (1.3–1.4)	1.4 (1.3–1.5)	0.65
PWA/WSA			
Pa, mm Hg	5.0 (2.0–8.8)	8.5 (5.0–16.3)	0.001
Aix@75 (%)	7 (3–15)	20 (14–31)	<0.001
Pf, mm Hg	29.3 (25.8–34.9)	27.9 (21.2–36.0)	0.39
Pb, mm Hg	18.2 (14.7–24.5)	17.7 (13.2–24.6)	0.78
RM (%)	61 (54–67)	64 (57–73)	0.25
PWV			
oPWV, m/s	6.4 (5.5–7.5)	6.2 (5.5–7.0)	0.54
baPWV, cm/s	1396 (1284–1535)	1383 (1290–1581)	0.64

Data are median with an interquartile range or number (%). Continuous variables were compared using the Wilcoxon rank-sum test, and categorical variables were compared using the Fisher exact test. ABI indicates ankle–brachial index; Aix@75, augmentation index normalized to 75 bpm; baPWV, brachial–ankle pulse wave velocity; BMI, body mass index; DBP, diastolic blood pressure; MAP, mean arterial pressure; oPWV, oscillometric pulse wave velocity; Pa, amplitude of augmented pressure; Pb, amplitude of backward wave pressure; Pf, amplitude of forward wave pressure; PP, pulse pressure; PPA, pulse pressure amplification; PWA, pulse wave analysis; RM, reflection magnitude; SBP, systolic blood pressure; and WSA, wave separation analysis.

Table 2. Echocardiographic Characteristics by Sex

Variables	Men (n=44)	Women (n=38)	*P* value
Aortic root diameter, mm	31 (29 to 33)	28 (26 to 30)	<0.001
LA dimension, mm	31 (29 to 33)	29 (27 to 33)	0.027
LV septal wall, mm	8 (7 to 9)	8 (7 to 9)	0.35
LV posterior wall, mm	8 (7 to 8)	8 (7 to 8)	0.133
LV end-diastolic dimension, mm	46 (43 to 49)	40 (38 to 42)	<0.001
LV end-systolic dimension, mm	31 (28 to 33)	27 (25 to 28)	<0.001
Ejection fraction (%)	59 (56 to 62)	62 (60 to 66)	0.002
LV mass index, g/m^2	72 (62 to 81)	63 (56 to 72)	0.013
LV mass index, g/height$^{1.7}$	52 (44 to 59)	43 (39 to 52)	0.006
Relative wall thickness	0.35 (0.32 to 0.38)	0.37 (0.34 to 0.44)	0.008
Relative wall thickness >0.42	4 (9)	11 (29)	0.025
E, cm/s	71 (62 to 82)	74 (62 to 92)	0.25
A, cm/s	62 (51 to 67)	62 (53 to 82)	0.166
E/A	1.19 (1.04 to 1.47)	1.22 (0.88 to 1.60)	0.94
Deceleration time, msec	220 (184 to 249)	208 (174 to 238)	0.28
IVRT, msec	100.3 (86.5 to 107.3)	96.9 (85.6 to 103.8)	0.33
Septal e′, cm/s	8.5 (6.8 to 11.0)	8.4 (7.2 to 9.7)	0.55
Lateral e′, cm/s	11.4 (9.2 to 14.0)	10.3 (9.1 to 13.6)	0.43
Average e′, cm/s	9.9 (8.4 to 12.6)	9.4 (8.2 to 11.1)	0.47
Average E/e′	7.6 (5.9 to 8.8)	7.8 (6.6 to 9.9)	0.24
LA volume index, mL/m^2	23.5 (18.7 to 27.6)	24.2 (20.5 to 28.9)	0.44
Global longitudinal strain (%)	−19.7 (−20.8 to −17.9)	−20.5 (−23.0 to −19.6)	0.008

Data are median with an interquartile range or number (%). Continuous variables were compared using the Wilcoxon rank-sum test, and categorical variables were compared using the Fisher exact test. A indicates late diastolic mitral inflow; ABI, ankle–brachial index; baPWV, brachial-ankle pulse wave velocity; E, early diastolic mitral inflow; e′, mitral annular early diastolic velocity; IVRT, isovolumic relaxation time; LA, left atrial; LV, left ventricle; MAP, mean arterial pressure; and PP, pulse pressure.

were not. Estimated aortic PWV using the Mobil-O-Graph and baPWV increased with age, but the variance was greater in baPWV. BMI positively correlated with urine Na/K. Brachial and central DBP positively correlated with urine Na/K; however, neither wave reflection parameters nor PWVs correlated with urine Na/K. Left atrial and LV dimensions correlated inversely with age (Table S4). RWT increased with age, but not LVMI. The EF positively correlated with age; however, global longitudinal strain, which is a sensitive marker of early LV dysfunction, did not correlate with age. Mitral E-wave velocity did not correlate with age, whereas mitral A-wave velocity increased with age, revealing an inverse correlation between E/A and age. The deceleration time was not prolonged with age. The e´ wave velocity showed a linear decline with age and revealed a positive association of E/e´ with age. The isovolumic relaxation time was prolonged with age. Left atrial and LV dimensions were positively associated with urine Na/K, whereas RWT correlated inversely with urine Na/K. Mitral E-wave velocity and E/A were positively associated with urine Na/K.

Associations of Hemodynamic Load Components With Indices of Echocardiography

In multivariate analyses, LVMI was not associated with any hemodynamic load component (Tables S5 and S6). RWT was positively associated with Pa after adjustment for several covariates. None of the indices of wave reflections was associated with average e´ and E/e´ after adjustment for covariates. The baPWV positively correlated with E/e´ and mitral A-wave velocity and inversely correlated with average e´ and E/A (Figure). Multivariate analyses showed that a faster baPWV was associated with higher E/e´ and lower e´ (Table 3). Older age was associated with lower e´ and lower E/A after adjustment for covariates. Urine Na/K was positively associated with E/e´ in multivariate analysis. LVMI was not associated with LV diastolic function indices, but RWT, when used as an independent factor instead of LVMI, was independently associated with E/e´ in multivariate analysis. Age and heart rate, but not baPWV, were inversely associated with E/A.

DISCUSSION

This study showed that age-related differences of brachial BPs and indices of wave reflections were modest but significant, and there was a marked age-related difference of baPWV was marked in indigenous highland Papuan populations. LV dimensions decreased, LVMI remained unchanged, and RWT increased with advancing age. LV systolic function was preserved or increased with age, whereas LV diastolic function significantly decreased with age. Neither PP nor baPWV was associated with LV geometry. Increased urine Na/K was related to increased LV filling pressure. Increased arterial stiffening, but not wave reflections, was associated with impaired LV relaxation and increased LV filling pressure in indigenous highland Papuan populations.

In our previous survey of 126 native Papuan individuals conducted in 2014, the median urine Na/K (1.10) was much lower than in this study.[12] The prevalence of hypertension was higher in 2017 than in 2014 (16% versus 5%). SBP measured in the supine position did not correlate with age or urine Na/K in 2014

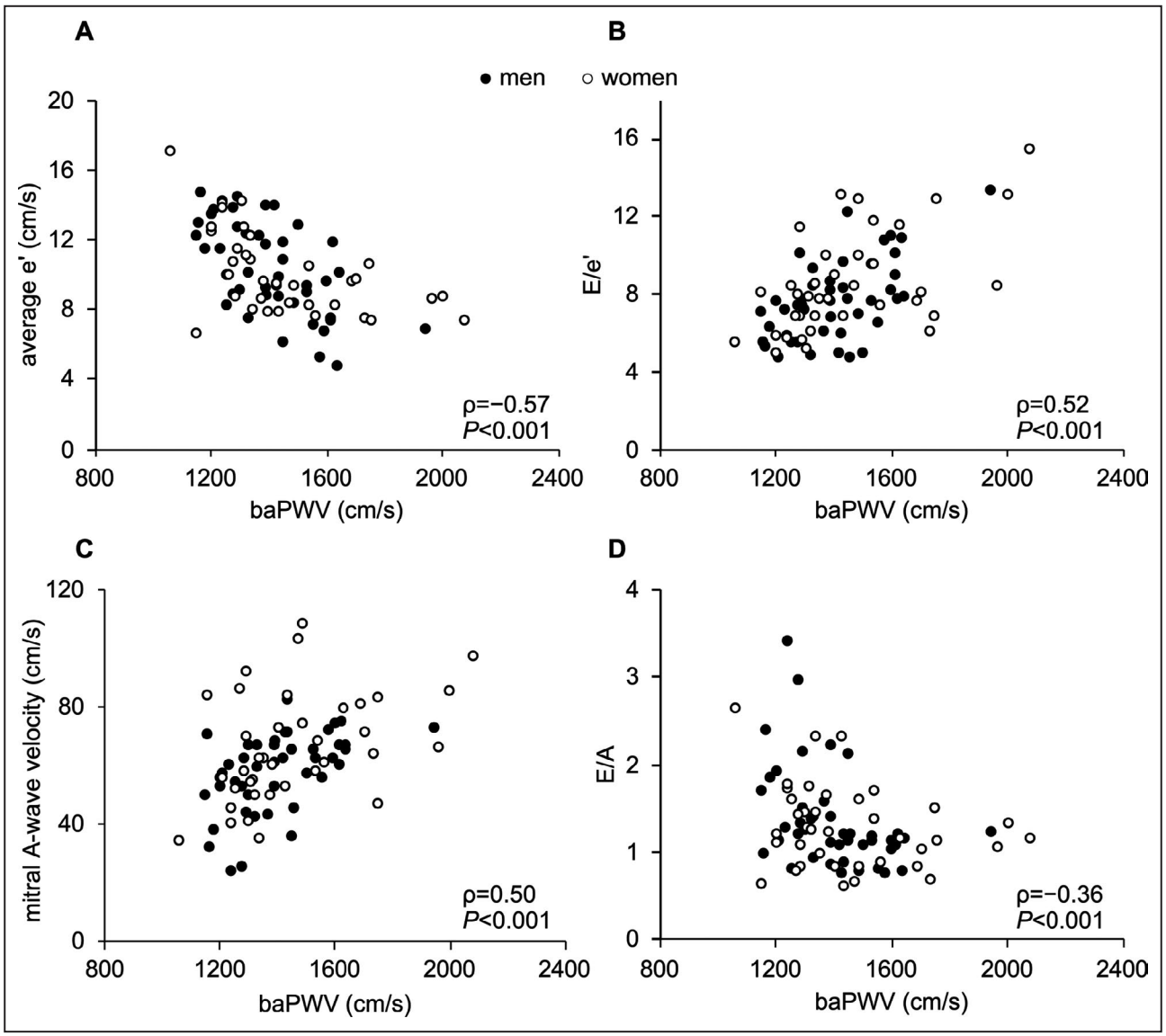

Figure. Correlations between brachial-ankle pulse wave velocity and indices of left ventricular diastolic function. Correlation of baPWV with average e´ (A), E/e´ (B), mitral A-wave velocity (C), and E/A (D). A indicates late diastolic mitral inflow; baPWV, brachial-ankle pulse wave velocity; E, early diastolic mitral inflow; and e´, mitral annular early diastolic velocity.

but significantly correlated with age in this study. Urine Na/K independently and positively correlated with the supine brachial SBP, after adjustment for age, sex, and BMI (β=0.27; 95% CI, 0.96–6.53), but did not correlate with the sitting brachial SBP. Urine Na/K was positively associated with left atrial and LV dimensions and mitral E-velocity and E/e´. These results suggest that an increased salt intake and/or decreased potassium intake increases the stroke volume and supine SBP by increasing the LV preload that influences LV filling pressure.[23]

Little is known about the effects of diet on LV diastolic function and previous studies provide inconsistent results. A cross-sectional study showed that a higher salt intake, assessed by 24-hour urinary sodium excretion, was associated with impaired LV diastolic function in patients with early essential hypertension.[24] Contrastingly, in participants with normotension, spot urine-estimated sodium excretion was positively associated with SBP but not with LV structure or with LV systolic and diastolic functions.[25] In a prospective study of young Native Americans aged ≤40 years, the questionnaire-estimated Na/K was modestly related to an increased atrial filling fraction in participants with normotension but not to other LV diastolic functions.[23] The sodium-restricted and potassium-rich Dietary Approaches to Stop Hypertension diet for 21 days in patients with hypertensive HFpEF improved LV diastolic function, global contractility, and arterial elastance, and reduced brachial and central SBP.[8,9] However, E/A

Table 3. Multivariate Regression Analyses for LV Diastolic Function

	E/e'				Average e'				E/A			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	β	*P* value	β	*P* value	β	*P* value	β	*P* value	β	*P* value	β	*P* value
Variables	R^2=0.42		R^2=0.49		R^2=0.47		R^2=0.47		R^2=0.43		R^2=0.45	
Age, y	0.10	0.36	0.17	0.132	−0.46	<0.001	−0.46	<0.001	−0.50	<0.001	−0.47	<0.001
Sex (men)	−0.13	0.23	−0.13	0.20	0.07	0.49	0.07	0.49	−0.01	0.91	−0.01	0.90
BMI	0.003	0.98	−0.01	0.94	−0.06	0.60	−0.06	0.61	0.01	0.92	0.01	0.95
Current smoking	−0.08	0.39	−0.11	0.25	−0.06	0.49	−0.06	0.51	−0.14	0.15	−0.15	0.12
MAP	0.24	0.121	0.04	0.82	0.12	0.41	0.13	0.42	0.14	0.35	0.05	0.78
Heart rate	−0.11	0.29	−0.15	0.132	−0.08	0.39	−0.08	0.41	−0.29	0.006	−0.31	0.003
LV mass index	0.09	0.35	0.07	0.49	−0.10	0.31	−0.10	0.32	0.11	0.28	0.09	0.34
baPWV	0.38	0.017	0.51	0.001	−0.43	0.005	−0.44	0.007	−0.12	0.44	−0.06	0.71
Urine Na/K	…	…	0.31	0.003	…	…	−0.02	0.87	…	…	0.14	0.165

Model 1, adjusted for age, sex, body mass index, current smoking, mean arterial pressure, heart rate, left ventricular mass index, and brachial-ankle pulse wave velocity; model 2, adjusted as model 1 and additionally for urine Na/K. A indicates late diastolic mitral inflow; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; E, early diastolic mitral inflow; e', mitral annular early diastolic velocity; LV, left ventricle; and MAP, mean arterial pressure.

and E/e´ did not change significantly with the diet, likely because of the short observation period. Urine Na/K increased in 2017 compared with 2014, likely because of lifestyle changes attributable to social globalization, but it was still low, especially in participants older than 50 years, when compared with other populations in the INTERSALT (mean, 3.24).[10] In such populations, we found that LV diastolic function significantly decreased with age. Further long-term comparative studies are needed to elucidate the effects of diet on LV diastolic function.

In line with our findings, previous studies showed that LV diastolic function deteriorates throughout adulthood.[1–3] Several studies indicated that increased arterial stiffness is associated with diastolic dysfunction and is independent of age.[26,27] As indices of wave reflections were less affected by physiological aging than those of arterial stiffness,[28] age-related arterial stiffening mitigates age-related LV diastolic dysfunction more than wave reflections. Accordingly, Weber et al reported that the strength of the association between carotid-femoral PWV and diastolic function was substantially greater than that of the augmentation index.[26]

Fundamentally, in normal arterial aging, increased stiffening leads to earlier wave reflections from peripheral reflection sites and, consequently, to increased SBP and LV afterload, thereby promoting increased LV mass.[2,26] However, we found that LV wall thickness and LVMI did not increase with age despite the age-related increase in arterial stiffness, wave reflections, and SBP. Multivariate analysis revealed that BMI was positively associated with LVMI and heart rate was inversely associated with LVMI, but baPWV, wave reflection parameters, and BPs were not associated with LVMI. Previous studies indicated that LV mass and wall thickness increased with age and were important risk factors for the development of diastolic dysfunction.[29] In this study, however, LVMI was not associated with any LV diastolic function indices. In contrast, RWT was associated with E/e´, independent of age, sex, BMI, MAP, heart rate, and urine Na/K. Low salt and high potassium intake resulted in activation of the renin-angiotensin-aldosterone system and increased sympathetic nervous activity.[30,31] These neurohormonal changes may affect arterial stiffening, RWT, and LV diastolic function. Further studies are needed to explore the relationship between dietary effects on arterial stiffness and LV geometry and functions.

Although women have lower blood pressure than men in most populations, women in this population had higher blood pressure than men despite their lower BMI. Selection bias and residual confounding are inevitable in such an observational study; however, hypertension was more prevalent in women than in men in both 2014 and 2017, and hence, selection bias is unlikely. Thirty-one out of 32 women in this study

had at least 1 child. Unfortunately, no data were available on the history of hypertensive disorders of pregnancy and preeclampsia. Further studies are needed to determine why women had a higher prevalence of hypertension than men in this population.

Indices of diastolic function were comparable between men and women; however, previous epidemiological studies showed that diastolic dysfunction and HFpEF are more prevalent among elderly women.[32] As previously reported, women had higher peripheral PP, increased indices of wave reflections, such as Pa and Aix@75, and a higher prevalence of hypertension than men, despite their lower BMI, than men. These results suggest that an increased pulsatile afterload may contribute to LV concentric remodeling. Correspondingly, a higher Pa was independently associated with a higher RWT after adjustment for age, sex, BMI, MAP, heart rate, and urine Na/K. Although the higher prevalence of obesity in women is thought to be associated with their higher prevalence of HFpEF, our results suggest that the different arterial and cardiac effects of sex were attributable to factors other than obesity. Regarding LV diastolic function, we found no significant differences in most clinical parameters between men and women. Similar results have been reported previously.[33]

Epidemiologically, hypertension is the most common risk factor for HFpEF.[32] Although peripheral and central BPs were not associated with LV diastolic function in this study, LV diastolic function assessed by lateral e´ and E/e´ was impaired in participants with hypertension. Hypertension was associated with increased E/e´ after adjustment for age, sex, BMI, and urine Na/K.

As recently reported, estimated aortic PWV using the Mobil-O-Graph was largely driven by the participants' age and measured SBP. The coefficients of determination (R^2) of estimated aortic PWV and baPWV were 97% and 54%, respectively. Hence, we did not use the estimated aortic PWV in this study.[22,34]

This study must be interpreted within the context of its potential limitations and strengths. We were unable to confirm all the participants' exact ages from their national identity cards, which is the major limitation of this study. However, the values of BMI, SBP, baPWV, wave reflection indices, and LV diastolic function provide reasonable results. We used spot urine samples to determine Na/K. Repeated measurements on different days or multiple 24-hour urine collections would be ideal[35]; however, such an approach was impractical for this region. The urinary Na/K monitor does not provide individual concentrations of sodium and potassium. Echocardiographic measurements are prone to measurement errors because of signal noise, acoustic artifacts, and angle dependency. However, a single experienced echocardiologist recorded measurements in this study. The study had a small sample size and a cross-sectional design; accordingly, it did not allow for the detection of a cause-effect relationship but only of associations between the studied variables. This study had an observational design and was therefore subject to potential residual confounding effects. Thirteen villagers had participated in both surveys conducted in 2014 and 2017. However, echocardiographic measurements, central BP, and wave reflection parameters were only obtained in 2017. Future longitudinal studies are warranted to prove a causal relationship between arterial stiffness and LV diastolic function. Several studies reported that women were more vulnerable than men to the deleterious effects of arterial stiffness and wave reflections on LV diastolic function.[27,36] Here, the indices of wave reflections, such as Pa and Aix@75, were significantly higher in women than in men, even after adjustment for age, BMI, MAP, and heart rate. We could not find a sex-dependent difference in the relationship between wave reflection and diastolic function in this study, and this was likely attributable to the small sample size. Previous validation studies conducted in Western populations have shown acceptable agreement between Mobil-O-Graph-derived parameters (central BP and wave reflections) and invasive and non-invasive measurements.[37] A short height is associated with shorter wave traveling distance and earlier arrival of wave reflections to the proximal aorta causing an increase in Pa, augmentation index, and central SBP. Here, height was inversely associated with Pa and Aix@75 but not with central SBP; however, the relationship of height with Pa and Aix@75 disappeared after adjustment for sex. Accuracy of the central BP by Mobil-O-Graph has been validated against invasive measurements in Japanese children and adolescents, who were shorter than the participants in the study[38]; however, inconsistent results have been reported.[39] Hence, more studies are needed to verify whether Mobil-O-Graph-derived parameters are acceptable in a range of body height, ethnicities, and ages.

No patients used any medications, particularly antihypertensive medicines and medicines which affect the urine sodium and potassium excretion. Therefore, the effect of medications on the relationships can be completely excluded.

To our knowledge, this study provides the first evidence of an age-related decline in LV diastolic function in indigenous Papuan populations despite lifelong low-salt and high-potassium dietary habits. Arterial and LV stiffness might be biological processes and may not be altered by a sodium-restricted and potassium-rich diet. Additional comparative studies are needed to elucidate the effects of diet on arterial and LV structure and function. Strategies to reduce arterial stiffness might have additional value to prevent or delay subclinical alternations in LV diastolic function.

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Disclosures

None.

Supplementary Material

Tables S1–S6
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Clinical and hemodynamic characteristics by hypertension

Variables	Hypertension (n=13)	Normotension (n=69)	*P*
Sex (women)	10 (77)	28 (41)	0.031
Age (years)	46 (43–55)	41 (37–50)	0.033
Height (cm)	153 (148–157)	157 (152–163)	0.040
Weight (kg)	54.0 (45.0–56.0)	54.0 (47.0–60.5)	0.34
BMI (kg/m^2)	22.2 (19.2–24.3)	21.6 (20.1–24.1)	0.92
Abdominal circumference (cm)	87.0 (75.5–90.3)	81.0 (78.5–85.0)	0.20
Current smoking (%)	6 (46)	47 (68)	0.20
Urine Na/K (mol/mol)	1.97 (1.78–3.39)	1.37 (0.72–2.20)	0.028
Brachial BP			
SBP (mmHg)	148 (143–154)	116 (110–127)	<0.001
DBP (mmHg)	82 (77–88)	70 (65–75)	<0.001
MAP (mmHg)	113 (104–116)	88 (83–95)	<0.001
PP (mmHg)	67 (63–72)	46 (41–53)	<0.001
Heart rate (bpm)	60 (52–68)	63 (54–72)	0.47
Central BP			
SBP (mmHg)	152 (146–173)	122 (111–130)	<0.001
DBP (mmHg)	98 (85–106)	77 (72–82)	<0.001
PP (mmHg)	63 (56–78)	42 (35–52)	<0.001
PPA	1.4 (1.3–1.6)	1.4 (1.3–1.4)	0.36
PWA/WSA			
Pa (mmHg)	23.0 (7.5–32.5)	6.0 (3.0–9.5)	<0.001
Aix@75 (%)	22 (15–39)	11 (5–20)	0.014
Pf (mmHg)	38.7 (36.3–51.1)	27.6 (22.3–31.5)	<0.001
Pb (mmHg)	27.7 (25.0–32.3)	17.0 (13.3–21.5)	<0.001
RM (%)	67 (63–75)	61 (56–69)	0.05
PWV			
oPWV (m/s)	7.3 (6.3–9.3)	6.1 (5.5–6.8)	0.004
baPWV (cm/s)	1633 (1464–1959)	1353 (1281–1491)	<0.001

Data are median with an interquartile range or number (%). ABI, ankle–brachial index; Aix@75, augmentation index normalized to 75bpm; baPWV, brachial–ankle pulse wave velocity; BMI, body mass index; DBP, diastolic blood pressure; MAP, mean arterial pressure; oPWV, oscillometric pulse wave velocity; Pa, amplitude of augmented pressure; Pb, amplitude of backward wave pressure; Pf, amplitude of forward wave pressure; PP, pulse pressure; PPA, pulse pressure amplification; PWA, pulse wave analysis; RM, reflection magnitude; SBP, systolic blood pressure; WSA, wave separation analysis.

Table S2. Echocardiographic characteristics by hypertension

Variables	Hypertension (n=13)	Normotension (n=69)	*P*
Aortic root diameter (mm)	27 (25–29)	30 (27–32)	0.014
LA dimension (mm)	31 (28–35)	31 (28–33)	0.71
LV septal wall (mm)	8 (7–9)	8 (7–9)	0.66
LV posterior wall (mm)	8 (7–9)	8 (7–8)	0.32
LV end-diastolic dimension (mm)	42 (40–46)	44 (40–48)	0.43
LV end-systolic dimension (mm)	27 (25–31)	29 (26–32)	0.30
Ejection fraction (%)	62 (60–65)	61 (57–65)	0.37
LV mass index (g/m^2)	70 (62–77)	69 (60–77)	0.60
LV mass index (g/height$^{1.7}$)	51 (42–57)	47 (41–56)	0.56
Relative wall thickness	0.37 (0.35–0.45)	0.36 (0.33–0.39)	0.158
Relative wall thickness>0.42	4 (31)	11 (16)	0.24
E (cm/s)	91 (84–105)	70 (60–82)	<0.001
A (cm/s)	73 (62–84)	60 (50–68)	0.004
E/A	1.20 (1.09–1.46)	1.19 (0.91–1.55)	0.75
Deceleration time (msec)	177 (168–214)	220 (193–248)	0.024
IVRT (msec)	96.9 (86.5–102.1)	96.9 (84.8–105.6)	0.57
Septal e’ (cm/s)	7.6 (6.9–9.7)	8.5 (7.2–10.8)	0.28
Lateral e’ (cm/s)	9.4 (8.4–11.5)	11.1 (9.5–14.1)	0.030
Average e’ (cm/s)	9.2 (7.7–9.8)	9.9 (8.3–12.5)	0.094
Average E/e’	9.9 (8.4–13.1)	7.4 (5.9–8.3)	<0.001
LA volume index (ml/m^2)	26.2 (21.8–29.1)	23.1 (19.1–28.4)	0.23
Global longitudinal strain (%)	-19.9 (-22.2–-19.7)	-19.9 (-21.5– -18.7)	0.34

Data are median with an interquartile range or number (%). A, late diastolic mitral inflow; baPWV, brachial–ankle pulse wave velocity; E, early diastolic mitral inflow; e’, mitral annular early diastolic velocity; IVRT, isovolumic relaxation time; LA, left atrial; LV, left ventricle; MAP, mean arterial pressure; PP, pulse pressure.

Table S3. Simple correlations to age and urine Na/K

Variables	Correlation to age		Correlation to Na/K	
	Spearman's ρ	*P*	Spearman's ρ	*P*
BMI	-0.43	<0.001	0.23	0.038
Abdominal circumference	-0.06	0.61	0.14	0.21
Urine Na/K	-0.16	0.150	-	-
Brachial BP				
SBP	0.38	<0.001	0.19	0.086
DBP	0.40	<0.001	0.28	0.012
MAP	0.30	0.006	0.18	0.106
PP	0.32	0.003	0.08	0.50
Central BP				
SBP	0.25	0.023	0.17	0.138
DBP	0.13	0.24	0.34	0.002
PP	0.22	0.051	0.04	0.73
PPA	0.13	0.25	-0.09	0.44
PWA/WSA				
Pa	0.26	0.016	0.05	0.68
Aix@75	0.22	0.042	-0.02	0.85
Pf	0.19	0.090	0.07	0.55
Pb	0.24	0.027	0.06	0.59
RM	0.16	0.144	0.01	0.91
PWV				
oPWV	0.89	<0.001	-0.05	0.66
baPWV	0.54	<0.001	-0.10	0.37

Aix@75, augmentation index normalized to 75bpm; baPWV, brachial–ankle pulse wave velocity; BMI, body mass index; DBP, diastolic blood pressure; MAP, mean arterial pressure; oPWV, oscillometric pulse wave velocity; Pa, amplitude of augmented pressure; Pb, amplitude of backward wave pressure; Pf, amplitude of forward wave pressure; PP, pulse pressure; PPA, pulse pressure amplification; PWA, pulse wave analysis; RM, reflection magnitude; SBP, systolic blood pressure; WSA, wave separation analysis.

Table S4. Simple correlations to age and urine Na/K

	Correlation to age		Correlation to Na/K	
Variables	Spearman's ρ	*P*	Spearman's ρ	*P*
Aortic root diameter	0.002	0.99	-0.18	0.107
LA dimension	-0.32	0.004	0.29	0.009
LV end-diastolic dimension	-0.34	0.002	0.34	0.002
LV end-systolic dimension	-0.31	0.005	0.35	0.001
Ejection fraction	0.27	0.014	-0.06	0.60
Global longitudinal strain	-0.16	0.158	0.26	0.022
LV mass index	-0.12	0.27	0.18	0.100
Relative wall thickness	0.23	0.037	-0.23	0.038
E	-0.12	0.28	0.29	0.008
A	0.59	<0.001	-0.07	0.54
E/A	-0.51	<0.001	0.25	0.022
Deceleration time	0.12	0.29	-0.21	0.061
IVRT	0.36	0.001	-0.15	0.175
Septal e'	-0.60	<0.001	0.10	0.36
Lateral e'	-0.52	<0.001	0.10	0.37
Average E/e'	0.44	<0.001	0.19	0.096
LA volume index	-0.23	0.037	0.19	0.096

A, late diastolic mitral inflow; baPWV, brachial–ankle pulse wave velocity; E, early diastolic mitral inflow; e', mitral annular early diastolic velocity; IVRT, isovolumic relaxation time; LA, left atrial; LV, left ventricle; MAP, mean arterial pressure; PP, pulse pressure; RWT, relative wall thickness.

Table S5. Associations of LV diastolic and systolic function and structure with central hemodynamics

	Peripheral PP		Central PP		Peripheral MAP		baPWV	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate[a]	Univariate	Multivariate[b]
Component	ρ	β	ρ	β	ρ	β	ρ	β
LV diastolic function								
E peak (cm/s)	0.47**	0.41**	0.36**	0.18	0.24*	0.20	0.03	0.12
A peak (cm/s)	0.31**	0.10	0.15	0.10	0.36**	0.06	0.50**	0.17
E/A	0.08	0.24	0.13	0.11	-0.12	0.04	-0.36**	-0.07
Average e’	-0.13	0.29*	-0.05	0.22	-0.39**	0.14	-0.57**	-0.43**
Average E/e’	0.45**	0.06	0.30**	-0.01	0.56**	0.04	0.52**	0.50**
LV systolic function								
Ejection fraction (%)	0.31**	0.35*	0.16	0.26	0.19	0.13	0.17	-0.17
LV structure								
RWT	0.13	0.26	0.001	0.16	0.10	0.03	0.19	0.12
LV mass index (g/m^2)	0.08	0.26	0.05	-0.001	-0.10	-0.02	-0.21	-0.09

Multivariate analyses were adjusted for age, sex, body mass index, current smoking, MAP, heart rate, urine Na/K, and baPWV.
[a]Multivariate analyses were adjusted for age, sex, body mass index, current smoking, heart rate, urine Na/K, and baPWV. [b]Multivariate analyses were adjusted for age, sex, body mass index, current smoking, MAP, heart rate, and urine Na/K.*P<0.05, **P<0.01.
A, late diastolic mitral inflow; baPWV, brachial–ankle pulse wave velocity; E, early diastolic mitral inflow; e’, mitral annular early diastolic velocity; LV, left ventricle; MAP, mean arterial pressure; PP, pulse pressure; RWT, relative wall thickness.

Table S6. Associations of LV diastolic and systolic function and structure with central hemodynamics

	Pa		Aix@75		Pf		Pb		RM	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Component	ρ	β	ρ	β	ρ	β	ρ	β	ρ	β
LV diastolic function										
E peak (cm/s)	0.40**	0.09	0.08	0.17	0.35**	0.09	0.35**	0.16	0.20	0.08
A peak (cm/s)	0.20	-0.01	0.29**	0.01	0.07	-0.002	0.18	0.18	0.23*	0.23*
E/A	0.15	0.13	-0.13	0.13	0.18	0.10	0.09	0.03	-0.05	-0.12
Average e’	-0.09	0.14	-0.20	0.07	-0.02	0.18	-0.11	0.13	-0.17	-0.10
Average E/e’	0.36**	-0.02	0.19	0.11	0.28*	-0.05	0.36**	0.03	0.30**	0.13
LV systolic function										
LVEF (%)	0.34**	0.13	0.30**	0.12	0.15	0.16	0.16	0.27	0.10	0.08
LV structure										
RWT	0.18	0.29*	0.35**	0.21	0.02	0.07	0.01	0.16	-0.02	-0.02
LVMI (g/m^2)	-0.15	-0.03	-0.25*	-0.11	0.07	-0.05	0.11	0.07	0.12	0.11

Multivariate analyses were adjusted for age, sex, body mass index, current smoking, MAP, heart rate, and urine Na/K. *P<0.05, **P<0.01.
A, late diastolic mitral inflow; Aix@75, augmentation index normalized to 75bpm; baPWV, brachial–ankle pulse wave velocity; E, early diastolic mitral inflow; e’, mitral annular early diastolic velocity; LVEF, left ventricle ejection fraction; LVMI, left ventricle mass index; MAP, mean arterial pressure; Pa, amplitude of augmented pressure; Pb, amplitude of backward wave pressure; Pf, amplitude of forward wave pressure; PP, pulse pressure; RM, reflection magnitude; RWT, relative wall thickness.

Figure S1. Distribution of urine Na/K molar ratio.