ORIGINAL RESEARCH

Arterial Stiffness and Central Hemodynamics are Associated with Low Diurnal Urinary Sodium Excretion

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Background: Excessive salt intake is an important determinant of cardiovascular (CV) health, impacting arterial stiffness and central blood pressure. However, sodium exhibits several patterns of excretion in urine during day- and night-time, which could differently affect CV risk. Here, we sought to explore the relationship between the day:night urinary sodium excretion ratio and arterial stiffness and central hemodynamics in the general population.

Methods: Cross-sectional analysis in 1062 subjects. Arterial stiffness (pulse-wave velocity, PWV), central blood pressure (central systolic blood pressure, cSBP; central diastolic blood pressure, cDBP), and other hemodynamic parameters were noninvasively assessed. Day- and night-time urinary sodium were separately detected. Analyses were performed according to the day:night urinary sodium excretion ratio tertiles (T1–T3).

Results: Low day-time excretors (T1) showed significantly higher values of arterial stiffness when compared with high day-time excretors (T3) (cf-PWV 7.6 ± 1.9 vs 6.9 ± 1.5 m/sec; p ≤ 0.001), and higher central BP parameters (cSBP: 111.6 ± 12.1 vs 109.0 ± 11.1 mmHg, p ≤ 0.001; cDBP, 76.9 ± 9.2 vs 75.1 ± 9.3 mmHg, p ≤ 0.001). In multivariate linear-regression models (β, CI), the day:night ratio of sodium excretion was significantly associated with arterial stiffness (cf-PWV –0.386, –0.559, –0.213, p ≤ 0.001) and with central hemodynamic parameters (cSBP –1.655, –2.800, –0.510; p ≤ 0.001; cDBP –1.319, –2.218, –0.420, p ≤ 0.001). Associations persisted after controlling for multiple confounding factors. In logistic-regression models, the risk of increased arterial stiffness was significantly reduced as the day:night ratio of urinary sodium excretion increased (OR 0.40, 95% CI 0.25–0.65, p ≤ 0.001).

Conclusion: The individual, intra-daily pattern of urinary sodium excretion, characterised by low daytime excretion, is associated with increased arterial stiffness and central blood pressure. Further studies are advocated to clarify the clinical utility of assessing the daily pattern of sodium excretion.

Keywords: night-time urinary-sodium excretion, day-time urinary-sodium excretion, arterial stiffness, pulse-wave velocity, central hemodynamics, central blood pressure

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Background

Salt intake is one of the most important environmental determinants of cardiovascular health.[1] Previous robust evidence highlighted the role of excessive sodium intake in promoting structural and functional pressure-independent vascular damage through the remodelling of central and peripheral arterial walls.[2–4]

It was postulated that high salt intake could promote oxidative stress on arterial walls, resulting in wall hypertrophy, endothelial dysfunction, and arterial-vessel

contractility impairment, lastly increasing arterial stiffness.[5,6] As a consequence, increased arterial stiffness could produce an increasing amplitude of forward and reflected waves, and an anticipated comeback to the proximal aorta of the reflected wave, as well as a central systolic blood pressure elevation (cSBP).[7]

Central blood pressure (cBP) is a major element able to predict target organ (such as brain, heart, and kidney) damage, and it is therefore conceivable that it could be more predictive of CVD than peripheral blood pressure (BP). A cumulative amount of evidence suggests the pivotal role of cBP in target organ damage and, more recently, metaregression analysis has revealed the higher power of cBP compared with peripheral BP in predicting preclinical organ damage.[8–10]

Moreover, evidence from previous studies on multiple populations suggested that central blood pressure is a better predictor of cardiovascular events than brachial pressure.[11,12]

Normally, central BP is lower than brachial values, as a consequence of a physiological phenomenon of amplification, for which an increase in arterial stiffness moving from the highly elastic central arteries of the heart away to the stiffer brachial artery.[13]

Elevated cSBP can, indeed, induce increased heart workload, with consequent left ventricular hypertrophy, decreased perfusion during the diastolic phase, and reduced coronary blood flow.[14]

Previous studies investigated the relationship between salt intake, central BP and arterial stiffness.[7,15] To date, the gold-standard method to quantify salt intake is the determination of 24-hour urinary sodium excretion.[16] However, daily variability in the sodium excretion rhythm is a debated field of research. A circadian rhythm of sodium excretion in urine exists and, in physiological conditions, it is characterised by an increased rate of excretion during daytime and a decreased rate during night-time.[17]

Moreover, the daily rate of sodium excretion in the urine showed inter-individual variability, and some evidence suggested the existence of different patterns of day- and night-time sodium excretion. In addition, the daily pattern of sodium excretion could have a different impact on cardiovascular (CV) risk. Higher risk was documented in nondippers and in subjects with increased night-time BP values showing lower day-time urinary sodium excretion.[18,19]

Recently, it was found that an abnormal circadian rhythm of urinary sodium excretion was independently associated with hypertension and target-organ damage in a selected population affected by chronic kidney disease.[20]

Although a number of studies suggested that daily sodium intake is related to arterial stiffness and central blood pressure, there have been no studies until now exploring whether a difference in the rhythm of sodium excretion could impact arterial-stiffness and central BP components.

In the present study, we sought to elucidate the relationship existing between the day:night urinary sodium excretion ratio, arterial stiffness and central hemodynamics in a general sample of an adult population.

Methods
Study Participants

The present analysis was based on a cross-sectional study of a sample of general-population residents in southern Switzerland (Ticino), conducted between 2017 and 2018. A detailed description of the study design and the main characteristics of the population were published elsewhere.[21] Briefly, the study aimed to explore vascular ageing and cardiovascular risk factors in the resident population. At the end of the recruitment period, the data of 1202 participants were collected. The local Swiss ethics committee (Comitato etico cantonale Ticino) approved the research protocol, and all participants signed their written consent before data collection. The study protocol adhered to the Declaration of Helsinki. In the present analysis, we excluded 76 individuals on the basis of incomplete urine collection in either the day- or night-time, and 64 individuals for incomplete data from the 24-hour ambulatory blood pressure (ABPM). The present analyses are, therefore, based on 1062 individuals.

Clinical Assessment and Urine Collection

The study protocol included two consecutive visits with an examination performed during a weekday on the participants' usual diet. Examinations were performed at the research unit of the internal medicine department of the regional hospital of Bellinzona (Switzerland). During the first visit, demographic, comorbidity, traditional cardiovascular risk factors, and medication information were collected. Anthropometric characteristics were assessed: height (cm), weight (kg), waist circumference (cm), hip circumference (cm), and body-mass index (BMI; kg/m^2). Peripheral blood pressure (BP) and heart rate (m/sec) were measured during the first examination using the Mobil-O-Graph and a validated automatic oscillometric

device (Dinamap model Pro 100 automated sphygmoman-ometer, Critikon, Tampa, Florida). For consistency, only results of peripheral blood pressure obtained with the Mobil-O-Graph were shown.

Patients were asked to make the first visit after at least 8 hours of fasting, and the following parameters in serum were determined: blood glucose, total cholesterol, trigly-ceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatinine and cystatin, magne-sium, and calcium.

During the first day, tonometric assessment of arterial stiffness was also performed following the procedure described below, and a 24-hour ambulatory-blood-pressure monitoring recording started. At the end of the first examina-tion, participants were given two containers for urine collec-tion, marked as "day-time urine" and "night-time urine", with a beaker to transfer the urine in the collection containers. Day- and night-time periods were defined according to self-reported bed- and wake-up time. A diary was also provided in order to mark (i) the starting diurnal hour of urine collec-tion, (ii) the starting hour of night-time urine collection, and (iii) the hour of the last collected urine sample. All urine voided during the next 24 hours was collected. The next day, the second study/examination day, the collected urine con-tainers were transferred to the Biochemistry Laboratory of Ente Ospedaliero Cantonale, at the regional hospital of Bellinzona, for analyses. In the collected urine, the following parameters were measured: sodium and potassium concen-trations, albumin concentration, and creatinine. All urine assessments of day- and night-time periods were separately performed. Self-reported urine loss and 24-hour urine volume were excluded in cases of insufficient urine collec-tion (ie, urine volume <500 mL/24 h, self-reported loss of a urine sample of more than 100 mL, or more than one time). The amount of excreted 24-hour urine sodium and potassium was calculated by multiplying the total volume of the col-lected urine by the concentration of measured sodium.

Central Hemodynamics and Arterial Stiffness Assessment

Estimates of central hemodynamics were noninvasively obtained using a 24-hour ambulatory blood pressure (ABPM) device (Mobil-O-Graph, IEM; Stolberg, Germany) that was able to record pulse waveforms from the brachial artery for 24 hours with an integrated ARC solver algorithm (Austrian Institute of Technology, Vienna). Recorded and analysed (more than 75% of readings) hemodynamics were

central systolic blood pressure (cSBP), central diastolic blood pressure (cDBP), augmentation pressure (AP), augmentation index standardised to a heart rate of 75 bpm (AIx75), cardiac output (CO), cardiac index (CI), peripheral vascular resistance (PVR), and reflection magnitude percentage (Ref %). Every study participant underwent 24-hour BP monitoring during the first study visit. Arm circumferences were first measured and recorded to allow for the correct choice of cuff size. The ABPM device consisted of a brachial cuff-based oscillometric monitor, approved and validated for brachial BP monitoring.[22] The device was programmed to obtain BP recordings every 30 minutes during the day-time and every hour during night-time.

The algorithm used for the oscillometric central BP estimation has already been largely described. Briefly, after standard oscillometric BP assessment, the brachial cuff reinflated, acquiring brachial pressure waveforms for about 10 seconds. Thereafter, a generalised transfer-function algorithm (ARC Solver) produced the aortic-pulse waveform after a process of calibration based on brachial SBP and DBP.[22] Computerised point-and-area-based analysis was further realised to derive different cardiovascular parameters. Analysis of the aortic-pulse waveform was therefore performed, with separate analysis of the incident and reflected waves using an uncalibrated triangular aortic-flow waveform. Pulse-wave velocity was estimated from the time difference between the derived forward and reflected waves. Central hemodynamics para-meters provided by the Mobil-O-Graph device were vali-dated in comparative studies with other noninvasive devices (Sphygmocor, ArtCor, Sydney, Australia), as well as with gold-standard invasive intra-aortic techniques.[23,24] High levels of reproducibility and accuracy were found under both static and ambulatory conditions.

Arterial stiffness was estimated by analysing the gold-standard parameter of pulse-wave velocity (PWV). PWV was noninvasively assessed in each participant with both an oscillometric and a tonometric method. Tonometric cf-PWV measurements were performed during the first day of the examination, following a standard operational proce-dure in a quiet, stable temperature room. After 10 minutes of participants resting in the supine position, as recom-mended by ARTERY Society guidelines, arterial wave-forms at the subject's dominant carotid and femoral sites were recorded by applanation tonometry using a SphygmoCor device (AtCor Medical, Sydney, Australia; Model MM3, Software version 7.01 S). Participants were instructed to abstain from caffeine and tobacco use for four hours before the examination. Measurements with

a standard deviation of less than 10% were used for analysis. After cf-PWV measurement, oscillometric pulse-wave-velocity estimation was acquired, and ABPM was applied to each participant.

The oscillometric parameters of PWV were assessed with the ABPM in use, able to simultaneously perform BP and PWV measurements. All PWV and central hemodynamic measurements were performed on a weekday. PWV assessment was first conducted with the tonometric method, and then by the o-PWV device following the described standardised procedures. Considering arterial stiffness as a consequence of a chronic stress of the arterial wall, and the well-documented association between the 24h-ABPM measurements and specific target organ damage (ie left ventricular hypertrophy),[25,26] the mean 24-hour estimates of PWV and central hemodynamic were used for data analysis.

Statistical Analysis

Continuous variables were expressed as mean ± SD, and categorical variables as a percentage. According to the day:night ratio of urinary sodium excretion distribution in the study population, tertile categories were defined as follows: T1 < 0.85; 0.85 ≤ T2 < 1.56 ≤ T3. Categorical variables were compared using the χ^2 test. Variables were compared by tertile group with analysis of variance (ANOVA) for multiple comparisons and Tukey post hoc test or Games–Howell post hoc test were used as appropriate for the comparison of PWVs and hemodynamic parameters among the three groups of day:night ratio of urinary sodium excretion.

The association of day:night ratio of urinary sodium excretion with hemodynamic parameters and arterial stiffness was explored using cSBP, cDBP, cPP, AP, AIx, CI, PVR, Ref %, o-PWV, and cf-PWV as dependent variables. Both a crude (Model 1) and an adjusted model (Model 2) were provided to examine potential confounding effects. All traditional cardiovascular-risk factors and variables potentially affecting the dependent variables were selected: sex, age, diabetes, hypertension, hypercholesterolemia, current smoking, body-mass index, hip circumference, systolic and diastolic blood pressure, heart rate, cholesterol LDL and HDL, cystatin C, creatinine, magnesium, calcium, pulse pressure, urine potassium; β-coefficient and confidence interval (CI) are shown. Each adjusted regression model was separately examined for multicollinearity using the variance inflation factor (VIF) statistic; VIF > 4.0 was an indicator of multicollinearity. To explore the association between the day:night ratio of urinary sodium excretion and the risk of increased arterial stiffness, logistic-regression models were also produced. Associations were expressed as odds ratios (OR) with 95% confidence interval (CI). Increased arterial stiffness was defined as that with values ≥10 m/sec. Both crude and adjusted models are shown.

Restricted cubic regression spline analyses with three knots located at the 25th, 50th, and 75th percentiles were performed to test the linearity of the relationship between the day:night ratio of urinary sodium excretion and PWV. Values were plotted for values of day:night ratio of urinary sodium excretion until 4, considering that the low amount of individuals with higher values (n. 13).

All statistical analyses were conducted using SPSS (version 18.0, SPSS Inc, IBM, US) and STATA. P ≤ 0.05 was considered statistically significant; all P-values were two-tailed.

Results

Patient characteristics, blood pressure, sodium excretion, and humoral variables for the whole study group and between tertiles of day:night ratio of urinary sodium excretion are presented in Table 1. The subjects in T1 of sodium excretion could be considered as low day-time sodium excretors, excreting an amount of sodium during the day-time of more than 30% lower compared with subjects in T3.

However, even if a different intra-daily pattern of urinary sodium excretion was evident, no significant differences in the 24-h urinary sodium excretion were present across tertiles (p-value 0.281).

Mean age ± SD for the entire sample population was 51.4 ± 13.6 years, and it significantly increased as day:night ratio of urinary sodium excretion decreased. Subjects in the lowest tertiles of the day:night ratio of urinary sodium excretion also showed significantly higher BMI values (p-value 0.042). Creatinine values reduced and eGFR significantly increased as tertiles decreased (p-value ≤ 0.001). Considering BP parameters, no differences across day:night ratio of urinary sodium excretion for the in-office and daytime BP values for both SBP and DBP were found. Low day-time sodium excretors (T1) showed significantly higher nighttime values of both systolic and diastolic BP, compared with high daytime sodium excretors (p-value ≤0.001). No difference in the rate of hypertension across tertiles was detected.

Comparison of baseline characteristics among the three groups revealed no significant differences in other parameters.

Table 1 Participants' Characteristics by Tertiles of Day:Night Ratio of Urinary Sodium Excretion

Variables	Overall	T1 Ratio Day:Night UrinSodExc	T2 Ratio Day:Night UrinSodExc	T3 Ratio Day:Night UrinSodExc	p-value
Age, years	51.4±13.6	54.4±14.2	51.3±13.6	48.8± 12.4	≤0.001*
Females. (%)	591 (55.7)	182 (52)	204 (58.3)	205 (56.6)	0.221
BMI, kg/m^2	25.0±4.4	25.4±4.6	25.2±4.4	24.6± 4.1	0.042*
Current Smoking, (%)	192 (18.2)	47 (13.5)	58 (16.7)	86 (23.9)	≤0.001*
Diabetes, (%)	22 (2.1)	8 (2.3)	5 (1.5)	9 (2.5)	0.582
Hypertension, (%)	162 (15.4)	63 (18.1)	55 (15.9)	45 (12.5)	0.119
SBP, mmHg	130 ± 19	131 ± 21	130 ± 19	129 ±18	0.417
DBP, mmHg	85 ± 13	86 ± 13	86 ± 13	85 ± 13	0.493
Daytime SBP, mmHg	122 ± 12	123 ± 13	122± 12	121 ± 12	0.1471
Daytime DBP, mmHg	77 ± 9	77 ± 8	77 ± 9	77 ± 9	0.385
Nighttime SBP, mmHg	112 ± 13	114 ± 14	111 ± 12	109 ± 11	≤0.001*
Nighttime DBP, mmHg	67 ± 9	69 ± 10	67 ± 9	66 ± 9	≤0.001*
Heart Rate, beats/min	69 ± 11	68 ±11	68 ± 10	69 ± 10	0.247
Fasting blood Glucose, mmol/L	5.92 ± 0.77	5.99 ± 0.88	5.89 ± 0.73	5.87 ± 0.69	0.064
Magnesium, mmol/L	0.83 ± 0.06	0.83 ± 0.06	0.83 ± 0.06	0.8 2± 0.05	0.295
Total Cholesterol, mmol/L	5.35 ± 1.06	5.28 ± 1.05	5.37 ± 1.05	5.39 ± 1.08	0.305
HDL, mmol/L	1.57 ± 0.43	1.59 ± 0.44	1.57 ± 0.45	1.57 ± 0.41	0.741
LDL,mmol/L	3.60 ±1.03	3.53±1.00	3.61±1.04	3.66±1.03	0.223
Triglycerides, mmol/L	1.18±1.37	1.14±0.67	1.20±1.14	1.18±1.96	0.839
Creatinine, μmol/L	75.5±19.7	79.3±25.6	75.4±16.5	71.8±14.5	≤0.001*
eGFR,mL/min/1.73m2	95.4±16.9	92.8± 18.1	95.8 ± 16.6	97.6± 15.6	≤0.001*
24 hour Na excretion, mmol	138.3 ± 61.8	142.2± 69.3	139.3±57.3	134.7±62.1	0.281
Sodium Excretion daytime, mmol	73.6 ± 36.8	57.3 ± 27.1	74.2 ± 30.3	88.8± 43.4	≤0.001*
Sodium Excretion nighttime, mmol	65.1 ± 36.4	84.9 ± 49.7	65.1 ± 27.5	45.9 ± 22.8	≤0.001*

Note: *p-value <0.05.
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; UrinSodExc, urinary sodium excretion; eGFR, glomerular filtration rate.

Hemodynamic parameters are shown in Table 2. Compared with Group T3, Group T1 displayed higher values of cSBP and cDBP. Low day-time excretors showed significantly higher values of cSBP (111.6 ± 12.1) compared with high day-time excretors (110.0 ± 10.8, p-value ≤ 0.001), and of cDBP (76.9 ± 9.2 vs 75.1 ± 9.3 mmHg, p-value ≤ 0.001). No significant differences were observed between tertiles for other hemodynamic parameters. No remarkable differences were observed between any of the three groups with respect to cPP, AP grades, AIx, cardiac output, cardiac index, peripheral vascular resistance, and reflection magnitude percentage (Ref %). Comparisons between groups revealed significant differences in cSBP (T1 vs T3) and in cDBP (T1 vs T3). All other comparisons showed no significant differences.

Associations between the day:night ratio of urinary -sodium excretion and central hemodynamic parameters were also explored in multivariate-regression models (Table 3). Central BP was significantly associated with the day:night ratio of sodium excretion in both crude (Model 1) and adjusted models (Model 2). Specifically, for the cSBP (β-coefficient, CI) of Models 1 and 2, they were,

respectively, –1.655 (–2.800, –0.510), p-value ≤ 0.001, and –0.767 (–1.520, –0.014) p-value 0.046; for cDBP, they were –1.319 (–2.218, –0.420) p-value ≤ 0.001; and –0.819 (–1.539, –0.099), p-value 0.026. In a similar manner, a significant decrease of cardiac output and peripheral resistances as the day:night ratio of sodium excretion increased was also found in linear-regression models.

Mean ± SD by tertiles of day:night ratio of sodium excretion (T1 vs T2 vs T3) for cf-PWV were respectively, 7.6 ± 1.9 vs 7.3 ± 1.8 vs 6.9 ± 1.5 m/sec, p ≤ 0.001, as shown in Figure 1A. Low day-time excretors showed significantly higher T1 values of arterial stiffness, also measured using the oscillometric method (oPWV), which was 7.7 ± 1.9 compared with 7.3 ± 1.7 and 6.9 ± 1.5 m/sec, respectively, in T2 and in T3 (Figure 1B).

Multivariate-regression models confirmed, in both crude and adjusted models, significantly reduced arterial stiffness as day-time urinary sodium excretion increased. More specifically, cf-PWV in Model 1 showed a β-coefficient (CI) of –0.386 (–0.559, –0.213), p-value ≤ 0.001, with an association that significantly persisted after controlling for multiple confounding factors in Model 2: 0.164 (–0.307, –0.022),

Table 2 Comparison of Central BP and Hemodynamic Parameters by Tertiles of Day:Night Ratio of Urinary Sodium Excretion

Central Aortic Pressure Parameters	T1 Ratio Day:Night UrinSodExc	T2 Ratio Day:Night UrinSodExc	T3 Ratio Day:Night UrinSodExc	F/χ2	p-value
cSBP	112 ± 12[¥]	110 ± 11	109 ± 11[¥]	4.403	0.012
cDBP	77 ± 9[¥]	76 ± 9	75 ± 9[¥]	3.823	0.022
cPP	35.7 ± 12.5	34.6 ± 11.3	35.3 ± 11.5	0.880	0.415
AP	10.1 ± 7.7	9.6 ± 6.9	9.9 ± 7.1	0.509	0.601
Cardiac Index	2.5 ± 0.5	2.6 ± 0.6	2.6 ± 0.8	0.602	0.548
Cardiac Output	4.5 ± 0.51	4.4 ±0.48	4.4 ± 0.49	0.990	0.372
Peripheral resistances	1.30 ± 0.12	1.29 ± 0.12	1.29 ± 0.11	0.919	0.399
Refl. Coef	66.0 ± 4.5	66.1 ± 4.0	65.8 ± 4.8	0.540	0.583
AIx(HR75)	24.6 ± 7.8	24.7 ± 8.1	24.0 ± 8.2	0.720	0.487

Notes: [¥]p-value <0.05 according to post hoc testing comparisons T1 vs T3 and T3 vs T1. Comparisons between groups revealed significant differences in cSBP (T1 vs T3) and in cDBP (T1 vs T3). All other comparisons were not significant.
Abbreviations: cSBP, central systolic blood pressure; cDBP, central diastolic blood pressure; cPP, central pulse pressure; AP, augmented pressure.

p-value 0.024. A similar significant association was also found for o-PWV.

In logistic regression models, the risk of increased arterial stiffness was significantly reduced as the day:night ratio of urinary sodium excretion increased (Table 4). Specifically, for Models 1 and 2 (OR, 95% CI), the risk of cf-PWV ≥10 m/

sec for the day:night ratio of sodium excretion was, respectively, 0.40 (0.25–0.65, p≤0.001) and 0.60 (0.37–0.98, p-value 0.039). The day:night ratio of sodium excretion was also significantly associated with a reduced risk of increased o-PWV in both logistic models. Restricted cubic spline analysis suggested that the relationship between day:

Table 3 Estimates in Arterial Stiffness Parameters and Central Hemodynamics According to Tertiles of the Urinary Daytime: Nighttime Sodium Excretion Ratio

Arterial Stiffness Parameters					
	Unadjusted Model	**p-value**	**Adjusted Model**		**p-value**
	β-Coefficient (95%, Confidence Interval)		β-Coefficient (95%, Confidence Interval)		
Cf-PWV	−0.386 (−0.559,-0.213)	≤0.001*	−0.164 (−0.307,-0.022)		0.024*
o-PWV	−0.501 (−0.671,-0.332)	≤0.001*	−0.045 (−0.089,-0.001)		0.044*
Central Aortic Pressure Parameters					
	Unadjusted model	**p-value**	**Adjusted Model**		**p-value**
	β-coefficient (95%, confidence interval)		β-coefficient (95%, confidence interval)		
cSBP, mmHg	−1.655 (−2.800,-0.510)	≤0.001*	−0.767 (−1.520,-0.014)		0.046*
cDBP, mmHg	−1.319 (−2.218,-0.420)	≤0.001*	−0.819 (−1.539,-0.099)		0.026*
cPP, mmHg	0.577 (−0.654,1.808)	0.358	0.217 (−0.915–1.349)		0.707
AP, mmHg	0.136 (−0.610–0.882)	0.676	0.312 (−0.422–1.046)		0.404
Cardiac Index, l/min*1/m^2	−0.025 (−0.031–0.081)	0.378	−0.029 (−0.03–0.026)		0.303
Cardiac Output, l/min	−0.054 (−0.105,-0.004)	0.034*	−0.070 (−0.109,-0.032)		≤0.001*
Peripheral resistances, mmHg/mL	−0.002 (−0.014–0.010)	0.779	0.012 (0.001–0.023)		0.033*
Refl. Coef, %	−0.231 (−0.705–0.243)	0.339	0.012 (−0.416–0.439)		0.957
AIx(HR75), %	−0.442 (−1.252–0.367)	0.284	0.162 (−0.390–0.713)		0.565

Notes: Model 1 unadjusted; Model 2 adjusted for sex, age, diabetes, hypertension, hypercholesterolemia, current smoking, body mass index, hip circumference, systolic blood pressure, diastolic blood pressure, heart rate, cholesterol LDL, cholesterol HDL, triglycerides, cystatin C, creatinine, magnesium, calcium, pulse pressure, fasting plasma glucose. *p value<0.05.
Abbreviations: cf-PWV, carotid-femoral pulse wave velocity; o-PWV, oscillometric pulse wave velocity; cSBP, central systolic blood pressure, cDBP, central diastolic blood pressure, cPP central pulse pressure, AP, augmented pressure, AIx(HR75), augmentation index corrected for heart rate 75 beat per minute.

night ratio and PWV prolongation was not linear (nonlinearity $p < 0.001$) ([Figure 2]).

Discussion

The novel finding of the present study is that the pattern of urinary sodium excretion, characterised by low day-time excretion, is associated with increased arterial stiffness and augmented central hemodynamic parameters such as cSBP, cDBP, and cardiac output in the general population. In addition, the risk of documented vascular target-organ damage significantly decreased as day-time sodium excretion increased. These results provide observational evidence that the intraindividual pattern of urinary sodium excretion is associated with central blood pressure and arterial ageing.

The close relationship between high sodium intake with diet and cardiovascular health has been well explored, and several previous studies have highlighted its negative effects on cardiovascular outcomes.[27,28]

However, it is also important to identify factors that could affect CVD risk at the individual level, considering that CVD is still globally one of the most frequent causes of death. From this perspective, a better understanding of renal sodium-handling mechanisms could contribute to providing prevention measures with individualised programmes of salt intake that also could take into account the subject's pattern of intradaily urinary sodium excretion.

Excessive sodium intake negatively impacts blood pressure, and significantly increases the risk of stroke and renal dysfunction.[29,30] Moreover, findings from both epidemiological and clinical studies indicated an association between habitual dietary-salt intake and PWV.[31,32]

The salt-mediated BP increase is a multifactorial phenomenon in which complex inter-related mechanisms are implied, ranging from the action of sodium on small-artery resistance to a direct effect on the structure and function of large arteries.[33] Considering the above-mentioned salt-induced mechanisms, increased arterial stiffness represents a BP-independent consequence of mean increased salt intake which also partially contributes to BP increase.

However, BP and PWV are two factors that are strictly interdependent, and a robust number of cardiovascular-physiology studies have highlighted this association in which complex and inter-related mechanisms are involved. This hypothesis is also corroborated by recent meta-analysis of available randomised controlled trials in which direct association between the reduction of dietary-salt intake and a decrease in arterial stiffness was found.[32] It was highlighted that an average weighed difference of 89.3 mmol of sodium per day corresponded, in the short term (1–6 weeks), to a 2.8% reduction in arterial stiffness. It was also shown that PWV reduction was independent from BP reduction.[15] Furthermore, experimental evidence confirmed also the BP-independent nature of salt-induced vascular alterations.[34] It was identified that vascular damage consequent to salt intake could be linked to an abnormal activation of the renin–angiotensin system, and with reduced bioavailability of nitric oxide.[35] Even if the relationship between salt consumption and arterial
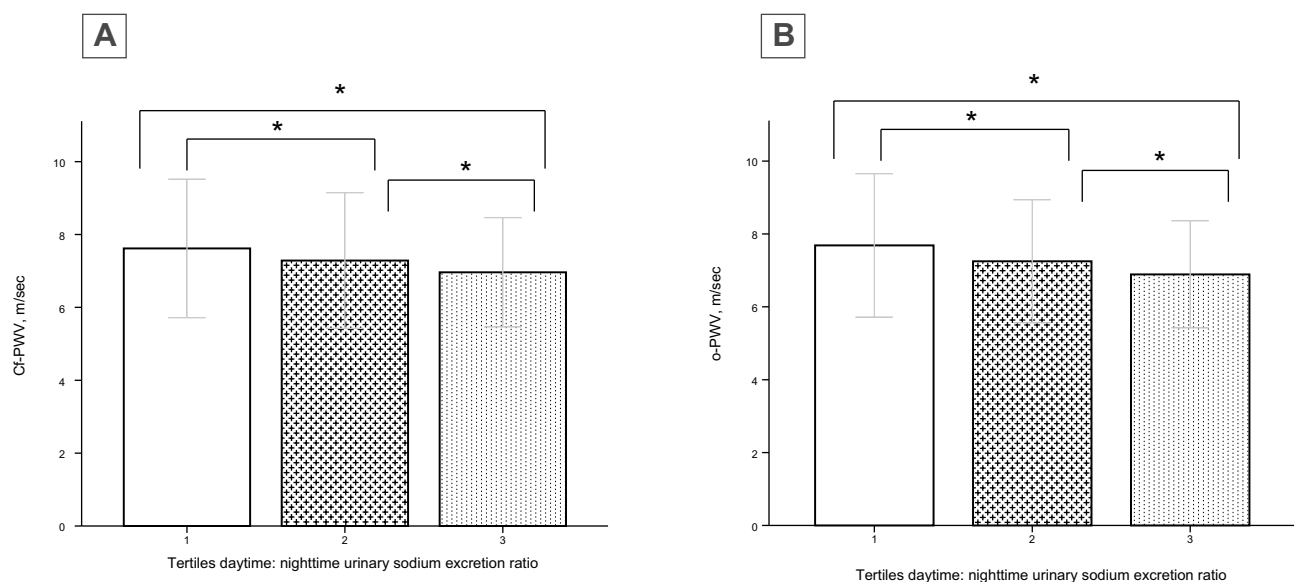
Figure 1 Comparison of oscillometric and carotid-femoral pulse wave velocity (o-PWV and cf-PWV) among the tertiles of day:night ratio of urinary sodium excretion. Cf-PWV (**A**) and o-PWV (**B**) means ± SD by tertiles of daytime: nighttime urinary sodium excretion ratio. *Indicates p-value <0.05 according to post hoc testing comparison.

Table 4 Logistic Regression Models Exploring the Risk of Increased Arterial Stiffness and Day:Night Ratio of Urinary Sodium Excretion

	Risk of Increased cf-PWV		
	OR	95% CI	p-value
	Model 1		
Day:night ratio of urinary sodium excretion	0.40	0.25–0.65	≤0.001
	Model 2		
Day:night ratio of urinary sodium excretion	0.60	0.37–0.98	0.041
	Risk of increased o-PWV		
	Model 1		
Day:night ratio of urinary sodium excretion	0.25	0.14–0.43	≤0.001
	Model 2		
Day:night ratio of urinary sodium excretion	0.27	0.072–0.99	0.048

Abbreviations: cf-PWV, carotid-femoral pulse wave velocity; o-PWV, oscillometric pulse wave velocity. Model 1, unadjusted; Model 2, adjusted for sex, age, previous cardiovascular disease, diabetes, hypertension, hypercholesterolemia, current smoking, body mass index, hip circumference, systolic blood pressure, diastolic blood pressure, heart rate, cholesterol LDL, cholesterol HDL, triglycerides, cystatin C, creatinine.

stiffness has been previously investigated, no studies examined the association between the daily pattern of urinary sodium excretion and arterial stiffness.

As previous studies showed, the low day-time pattern of sodium excretion is significantly associated with increased CV risk by affecting the nondipping pattern in hypertensive and nonhypertensive subjects.[17] Here, we strove to corroborate the compelling hypothesis that the individual pattern of intradaily sodium excretion could affect CV risk, influencing arterial ageing and central BP parameters.
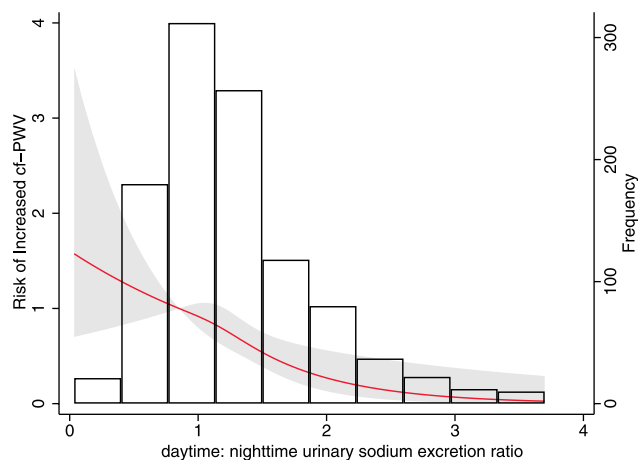

Figure 2 Association between the risk of increased arterial stiffness and the day:night ratio of urinary sodium excretion based on restricted cubic spline model. The bar plots show the day:night ratio of urinary sodium excretion distribution in the population.

In our study, the association between arterial stiffness, measured with PWV, and sodium excretion was significant using two different assessment techniques, aspect which further strengthen the association found.

Moreover, the absence of a significant difference in the 24-h urinary sodium excretion across tertiles, confirms the pivotal role-played by the circadian rhythm of sodium excretion in vascular damage.

As in previous studies, our analysis found no association between augmentation index and sodium excretion. As in previous studies, our analysis found no association between augmentation index and sodium excretion. This aspect could, in part, be explained by the fact that augmentation index strongly depends on many factors beyond vascular-wall properties (ie, systolic ejection duration, HR, and vasoconstriction of peripheral arteries), which can vary without any alteration of aortic stiffness. The reliability of AI as a specific marker of arterial stiffness is still debated.[36–38] On the other hand, central pressure is significantly associated with the day:night ratio of urinary sodium excretion, with values significantly decreasing as day-time sodium excretion increases. Very few previous studies investigated the association between central BP and hemodynamic parameters, and sodium excretion, and none explored the relationship between the daily pattern of sodium excretion and central BP parameters; even if cBP is more relevant than peripheral BP in CVD pathogenesis. Here, we found that the peculiar pattern of

low day-time sodium excretors was negatively associated with central BP. Moreover, it is important to note that the association between central pressure values and the day-time pattern of sodium excretion persisted also after correction for peripheral BP measurements in the multivariate analysis. However, due to the observational nature of the present study, we could not identify the exact mechanisms underlying this association. It was previously postulated that sodium loading is associated with an increased level of reactive oxygen species and with a reduced bioavailability of nitric oxide, which is a regulator of the arterial diameter. The impairment of nitric oxide releasing could result in increased wave reflection; it was also shown that sodium loading could affect artery and microvascular function.[38]

The present study should be interpreted within the context of its limitations. The first limitation, as stated above, is the observational cross-sectional nature of the design; not allowing us to establish the cause–effect relationship between the rhythm of urinary sodium excretion, arterial stiffness, central BP, and hemodynamic parameters, and to answer the causality dilemma. A large number of subjects in our study as well as controlling for several potential confounders in multivariate-regression analyses improved result reliability. Lastly, difference in the measured and calculated parameters between the groups was quantitatively small, raising the question of clinical relevance. Moreover, we did not evaluate the long-term influence of sodium intake on central BP and arterial stiffness.

The urine collection was performed on a single day for practical reasons of feasibility. However, even if the 24-hour urine sodium excretion is more precise in assessing salt intake, compared with questionnaires and urine overnight samples, we did not perform repeated collections or verify results with questionnaires and therefore, we cannot quantify the inter-daily variability, which could have impacted the results.

The duration of urine collection was not standardised for day- and night-time-period collection, but adapted to intraindividual subject habits, and a variation in collection hours might have also affected the results.

Moreover, an increasing body of studies has highlighted that low sodium and high potassium intake exerts a synergistic effect on BP and related aspects, and that this could be more relevant than the effects of sodium or potassium taken individually.[39] In the present study, we primarily aimed to investigate the association between the intra-daily variation of sodium excretion, arterial stiffness and central hemodynamics; however, even if beyond our scope, a role of potassium excretion in the association found can be postulated.

Last but not least, the central BP determined with the oscillometric device used in the present study, was based on brachial waveforms calibrated with SBP and DBP. This aspect could limit the reliability of our results, considering the amount of evidence which has currently shown that calibration with mean arterial pressure and DBP provides a more accurate assessment of central BP.[40]

In conclusion, the present findings shed light on an important aspect of the complex relationship between salt intake, arterial ageing, central BP and hemodynamics: not only could the level of sodium intake have significant impact on this relationship but also individual intradaily sodium handling, determining different risk profiles. Possibly the individual daily pattern of sodium excretion should not be disregarded when cardiovascular assessment is performed. However, for deeper insight, further mechanistic and epidemiological investigations in other populations, as well as randomised controlled trials, are advocated to clarify the utility of assessing the daily pattern of sodium excretion in modelling the individual's CV risk.

Abbreviations
PWV, pulse wave velocity; BP, blood pressure; cSBP, central systolic blood pressure; cDBP, central diastolic blood pressure; CV, cardiovascular; ABPM, 24-hour ambulatory blood pressure monitoring; BMI, body mass index; AP, augmentation pressure; AIx75, augmentation index standardised to heart rate of 75 bpm; CO, cardiac output; CI, cardiac index; PVR, peripheral vascular resistance; Ref %, reflection magnitude percentage; OR, odds ratios; SD, standard deviation.

Ethics Approval
The study was carried out in accordance with the Helsinki Declaration and was approved by the local Swiss ethics committee (Comitato etico cantonale Ticino). All participants provided informed written consent.

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Author Contributions

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Disclosure

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