

Salt-Sensitivity Trait and Coronary Microvascular Function in New-Onset Hypertension

Ayşe Paralı Ak

Istanbul Medeniyet University Goztepe Süleyman Yalcın City Hospital

Fatma Betül Çelik

Istanbul Medeniyet University Goztepe Süleyman Yalcın City Hospital

Tolga Sinan Güvenç

Memorial Goztepe Hospital

Ahmet Eren Caliskan

Bezmialem Vakıf University Faculty of Medicine

Merve Kaptık

Istanbul Medeniyet University Goztepe Süleyman Yalcın City Hospital

Narmin İsmayilzade

Istanbul Medeniyet University Goztepe Süleyman Yalcın City Hospital

Yusuf Yılmaz

Istanbul Medeniyet University Goztepe Süleyman Yalcın City Hospital

Seref Kul

Istanbul Medeniyet University Goztepe Süleyman Yalcın City Hospital

Ahmet Seyda Yılmaz

`ahmetseyda.yilmaz@erdogan.edu.tr`

Recep Tayyip Erdoğan University

Mustafa Caliskan

Istanbul Medeniyet University Goztepe Süleyman Yalcın City Hospital

Article

Keywords: Hypertension, salt-sensitive, coronary microvascular dysfunction, coronary flow reserve

Posted Date: October 11th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10120214/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background

Salt sensitivity is a trait observed in up to 50% of hypertensive patients. This study examined the link between salt sensitivity and coronary microvascular dysfunction in new-onset hypertension to clarify its broader cardiovascular impact.

Methods

54 individuals with hypertension were included. Patients consumed a high-salt diet followed by a low-salt diet, and those with a greater than 5 mmHg change in mean blood pressure or systolic blood pressure were classified as having salt-sensitive hypertension. Coronary flow reserve was measured using echocardiography.

Results

Patients with salt-sensitive (2.51 ± 0.42) and salt-resistant (2.61 ± 0.47) hypertension had a lower Coronary flow reserve compared to controls (3.12 ± 0.33 , $p < 0.001$). However, there were no statistically significant differences between the two hypertensive groups in crude or adjusted analyses. When the alternative definition was applied, patients with salt-sensitive systolic hypertension had a lower Coronary flow reserve (2.41 ± 0.31) compared to both controls (3.12 ± 0.33 , $p < 0.001$) and patients with salt-resistant hypertension (2.71 ± 0.51 , $p = 0.017$). These findings remained consistent after covariate adjustment.

Conclusions

Coronary microvascular function was altered in new-onset hypertensive patients with salt sensitivity; however, the magnitude was similar to salt-resistant patients. In systolic BP salt sensitivity, dysfunction was more pronounced.

Highlights

- The salt sensitivity (SS) trait is present in approximately half of all patients with hypertension.
- It remains unclear whether the SS trait itself is associated with cardiovascular disease independent of hypertension.
- The conventionally defined SS trait was not associated with coronary microvascular dysfunction beyond what is expected from hypertension alone.

- Hypertensive patients with systolic blood pressure (BP) salt sensitivity had a lower coronary flow reserve than those without this trait.
- Systolic BP salt sensitivity may be a more important determinant of long-term cardiovascular outcomes than the conventional SS trait.

Introduction

Hypertension is a widespread healthcare problem, with an estimated 1.4 billion people living with the condition worldwide (1). Excessive salt intake is a major preventable risk factor for chronic hypertension. It was initially described in case series dating back to 1904, and the first large-scale study associating salt intake with hypertension was reported by Dahl and Love in 1954 (2–4). Approximately 33% of the overall population and 50% of patients with hypertension have an exaggerated response to salt intake, a trait known as salt sensitivity (SS) (5). Several studies conducted since the 2000s have associated SS with endothelial dysfunction, albuminuria, and microvascular dysfunction in individuals with or without hypertension. This suggests that the SS trait could be a risk marker for accelerated atherosclerosis and major adverse cardiovascular events (MACE), independent of the presence or absence of hypertension (6–10).

Coronary microvascular dysfunction is considered a precursor to atherosclerotic coronary artery disease (CAD) and is independently associated with death and MACE, even in the absence of manifest CAD (11, 12). Given that most cardiovascular morbidity and mortality are related to myocardial ischemia, alterations in the coronary microvascular bed represent an ominous prognostic sign. Although there is some data to suggest that SS trait may be associated with endothelial dysfunction and microvascular dysfunction in peripheral arteries, the embryonic origins of the peripheral and coronary microvasculature differ; therefore, changes in skin microvasculature or brachial vasoreactivity may not fully reflect microvascular function in the coronary arteries (6, 7). Thus, direct data on the effects of SS trait on coronary microvasculature should be more instructive for the mechanisms linking SS trait with the lifelong risk of adverse cardiovascular outcomes.

Therefore, the aim of the present study was to investigate whether non-invasively measured coronary flow reserve (CFR)—an index of coronary microvascular function—differed among patients with new-onset hypertension depending on the presence of the SS trait, and whether these differences were independent of other factors associated with CFR.

Methods

Patient selection

This was a cross-sectional observational study conducted at a single academic institution. Individuals presenting to the cardiology outpatient clinic with complaints of high blood pressure (BP) and an office BP $\geq 130/80$ mmHg were included in the study. Individuals were excluded if they were under 18 years of

age, were taking vasoactive medications (such as alpha-blockers for prostatic hyperplasia), or had known chronic metabolic or cardiac disorders that could affect CFR. These excluded disorders comprised diabetes; hyper- or hypothyroidism; chronic kidney or liver disease; a history of coronary artery disease with any degree of stenosis; heart failure; any type of cardiomyopathy; more than mild valvular regurgitation; any degree of valvular stenosis; and persistent arrhythmias. Additionally, patients with known hypertension, a history of medical treatment for hypertension, or excessive BP elevation ($\geq 180/110$ mmHg) were excluded.

A total of 83 individuals were initially screened, of whom 63 were deemed eligible for further screening and potential inclusion. All patients underwent exercise testing with imaging to rule out significant coronary artery disease, and a screening echocardiogram was performed prior to inclusion to rule out the aforementioned cardiac disorders. Thirty-four healthy volunteers were enrolled to serve as the control group. All individuals in the control arm underwent the exact same screening procedures to ensure they did not meet any of the exclusion criteria.

The study was conducted in accordance with the principles outlined in the 1975 Declaration of Helsinki and its subsequent revisions, and all patients provided written informed consent prior to inclusion. The study protocol was approved by the institutional Clinical Research Ethics Committee (approval date: 31.07.2025; approval no: 2025/0073) prior to commencement.

Power analysis

Based on our prior experience and available data, we expected a mean CFR of 2.5 ± 0.5 in hypertensive patients. Assuming a 20% lower CFR in patients with salt-sensitive (SS) hypertension, we calculated that 27 individuals per group would be required to detect a difference between the groups with an alpha of 0.05 and a statistical power ($1-\beta$) of 0.95. Enrollment was concluded once the target sample size was achieved in each group.

Determination of salt sensitivity

During the screening phase, individuals were instructed to consume a high-salt diet (> 12 g/day) for one week, and 24-hour ambulatory BP monitoring was used to determine the mean BP during this period. Individuals with either a systolic BP > 135 mmHg or a diastolic BP > 85 mmHg on this initial measurement were then instructed to consume a low-salt diet (< 5 g/day, with strict avoidance of salty foods) for one week. A repeat 24-hour ambulatory BP monitoring was performed to observe the change in BP following the low-salt diet. Individuals exhibiting a > 5 mmHg change in mean BP were classified as salt-sensitive, while the remainder were classified as salt-resistant (11). A secondary classification, utilizing an alternative definition of a > 5 mmHg change in systolic (rather than mean) BP, was also applied to analyze whether individuals with systolic BP salt sensitivity differed from those identified

using the conventional definition. The screening and enrollment phase was terminated once both groups reached the required 27 individuals.

To verify dietary compliance, spot urine samples for sodium and chloride were obtained from each participant during both phases. Measurements for flow-mediated vasodilatation (FMD) and CFR were performed at the end of the low-salt diet period.

Transthoracic echocardiography

All transthoracic echocardiographic examinations were performed by a single expert cardiologist who was blinded to the participants' clinical data. To maintain objectivity, any repeat assessments were performed independently of prior records. Imaging was carried out using a Philips EPIQ 7G ultrasound system (Bothell, WA, USA) equipped with an S5-1 broadband sector array transducer (transmit frequency: 1.7 MHz; receive frequency: 3.4 MHz).

For all quantitative echocardiographic variables, three consecutive cardiac cycles were recorded from standard imaging planes, and their arithmetic means were calculated. Left ventricular (LV) internal dimensions, along with septal and posterior wall thicknesses, were measured in the parasternal long-axis view. The biplane modified Simpson's method was applied to the apical four- and two-chamber views to determine the LV ejection fraction. Furthermore, LV mass was calculated from end-diastolic dimensions and wall thicknesses using the Devereux formula (12). All other echocardiographic measurements were performed in accordance with current standard guidelines (13).

Measurement of flow-mediated vasodilatation

Endothelium-dependent FMD was assessed in the non-dominant brachial artery. To ensure stable baseline hemodynamics, all participants were required to abstain from vigorous physical exertion for a minimum of 12 hours prior to the assessment. All ultrasound imaging was performed by an experienced operator using a GE Vivid S6 system (GE Vingmed Ultrasound, Horten, Norway) equipped with a 12.5-MHz linear-array vascular transducer.

The artery was visualized longitudinally through an optimal acoustic window located 2 to 4 cm above the antecubital fossa. Under continuous electrocardiographic monitoring, the resting baseline diameter was determined by calculating the mean of three consecutive end-diastolic measurements. To induce reactive hyperemia, a pneumatic sphygmomanometer cuff was inflated to a pressure at least 50 mmHg above the participant's resting systolic BP, producing complete arterial occlusion for exactly 5 minutes. Following rapid deflation of the cuff, the hyperemic vessel diameter was recorded at the exact same anatomical site 60 seconds post-release. FMD was calculated as the maximum percentage change in the internal diameter of the brachial artery relative to its baseline resting state (14).

Measurement of coronary flow reserve

Coronary flow reserve was evaluated using the aforementioned echocardiography equipment. Transducer settings were specifically adjusted for B-mode (8 MHz) and Doppler (1.00 to 2.50 kHz) imaging, with manual titration of color gain to optimize signal resolution. Prior to testing, all patients were required to abstain from caffeine for at least 12 hours to prevent interference with coronary vasoreactivity.

With the patient in the left lateral decubitus position, the mid-to-distal portion of the left anterior descending coronary artery was visualized. This was achieved by placing the transducer at the midclavicular line over the fourth or fifth intercostal space to obtain modified two- or four-chamber views. Coronary flow within the target LAD segment was identified using color Doppler, and flow velocities were recorded using pulsed-wave Doppler. The baseline, pharmacological stress, and recovery phases were conducted under continuous BP and electrocardiographic monitoring.

After acquiring baseline resting coronary flow velocities, hyperemia was provoked via a continuous intravenous infusion of adenosine (0.84 mg/kg administered over 4 to 6 minutes) to record peak hyperemic velocities. Final values for both the resting and stress phases were derived by averaging the measurements from the three highest-quality Doppler spectral envelopes (15). Repeat measurements were obtained if the variance among the averaged flows exceeded 20%. The final CFR value was calculated as the ratio of hyperemic peak diastolic flow velocity to baseline resting peak diastolic flow velocity.

Laboratory analysis

Prior to any ultrasound assessments, morning venous blood samples were drawn from all participants in a seated position. All samples were delivered to the institutional laboratory within 30 minutes of collection. Hematologic parameters were quantified using a Beckman Coulter LH 780 automated analyzer (Beckman Coulter Ireland Inc., Mervue, Galway, Ireland). Standard biochemical indices, including fasting plasma glucose and a comprehensive lipid profile (total cholesterol, triglycerides, high-density lipoprotein [HDL], and low-density lipoprotein [LDL] cholesterol), were measured according to established protocols. These standardized enzymatic analyses were performed on a Roche Cobas 8000 modular system (c702 and e801 modules; Roche Diagnostics, Mannheim, Germany) utilizing the manufacturer's specified reagents. LDL cholesterol concentrations were determined via a direct enzymatic measurement technique. Aldosterone and plasma renin activity were assessed by enzyme-linked immunosorbent assays with compatible reagent kits on the aforementioned modular system. For the measurement of urinary catecholamines, a first-morning spot urine sample was obtained. Prior to collection, patients were instructed to abstain from coffee, tea, chocolate, and other substances known to interfere with the assay. These samples were also transported to the laboratory within 30 minutes of collection and analyzed using a high-performance liquid chromatography (HPLC) system. Plasma renin activity, aldosterone and urinary catecholamines were measured only in the two study groups with hypertension.

Statistical analysis

Continuous variables were expressed as the mean $\pm$ standard deviation (SD) or as the median [interquartile range], depending on the data distribution. Categorical variables were presented as percentages. The normality of continuous variables was assessed using the Shapiro-Wilk test and visual inspection of histograms and Q-Q plots. For analyses involving two independent groups, the Mann-Whitney U test was used, while the paired t-test was utilized for comparisons involving dependent samples. When three groups were present, analysis of variance (ANOVA) was used to evaluate between-group differences, with Tukey's HSD or Games-Howell tests applied for post-hoc analyses. Correlation analyses were performed using the Pearson product-moment correlation.

Two analysis of covariance models were constructed to evaluate whether salt-sensitive (SS) hypertension or systolic BP salt sensitivity was independently associated with coronary flow reserve. In these models, age, sex, diastolic BP, rate-pressure product, and hypercholesterolemia were included as covariates, as these variables were previously shown to be associated with CFR in an analysis of two large registries comprising patients with ischemia and normal coronary arteries (16). Partial η^2 and Cohen's d were used to determine effect sizes.

P-values were calculated using robust Welch's test for ANOVA models, and a P-value < 0.05 was considered statistically significant. All statistical analyses were performed using jamovi (The jamovi project, 2025; Version 2.7 for macOS), a graphical user interface for the R programming language (R Core Team, 2025; Version 4.5 for macOS).

Results

Baseline demographic, clinical, echocardiographic, and laboratory findings for the study groups are summarized in Table 1. Aside from expected differences in systolic and diastolic blood pressures, the only significant difference between the two hypertensive groups and the control group was a higher hemoglobin A1c level in both hypertensive groups. Notably, there were no significant differences in any baseline variables between the salt-sensitive (SS) and salt-resistant (SR) patients.

Table 1

Baseline demographic, clinical, echocardiography and laboratory findings for the study groups.

Aldosterone, plasma renin activity and urinary catecholamines were only analyzed in the two hypertension groups and no data were available for controls. BP: Blood pressure, HT: Hypertension, LA: Left atrium, LDL: Low-density lipoprotein.

Characteristic	Healthy volunteers (n = 34)	Salt-resistant HT (n = 27)	Salt-sensitive HT (n = 28)	P value
Age (y)	48.5 ± 9.5	49.4 ± 9.4	49.8 ± 8.2	0.847
Gender (%Female)	11 (32.4%)	12 (44.4%)	16 (57.1%)	0.346
Body mass index (kg/m ²)	28.6 ± 3.7	29.6 ± 3.4 ^a	28.1 ± 4.8 ^b	0.332
Smoking (%)	11 (32.4%)	9 (33.3%)	9 (32.1%)	0.925
Office systolic BP (mmHg)	122.0 ± 7.8	139.0 ± 16.0 ^a	142.0 ± 14.5 ^b	< 0.001
Office diastolic BP (mmHg)	80.6 ± 4.3	86.1 ± 12.2 ^a	92.9 ± 12.8 ^b	< 0.001
Heart rate (bpm)	77.0 ± 9.6	79.9 ± 11.6	84.4 ± 13.6	0.062
LV end-diastolic volume (ml)	97.8 ± 15.5	98.2 ± 16.1	95.5 ± 15.9	0.796
LV end-systolic volume (ml)	30.1 ± 6.6	27.4 ± 8.1	28.7 ± 7.2	0.370
LV ejection fraction (%)	69.2 ± 4.8	72.2 ± 6.6	69.7 ± 7.1	0.151
LV mass index (g/m ²)	79.1 ± 13.3	80.3 ± 15.1	80.9 ± 15.9	0.989
Left atrial diameter (mm)	34.8 ± 4.4	34.6 ± 3.5	34.0 ± 4.3	0.639
Hemoglobin (g/dl)	14.4 ± 1.2	14.7 ± 1.7	14.5 ± 1.5	0.703
Fasting glucose (mg/dl)	91.8 ± 9.2	98.9 ± 24.0	93.1 ± 11.1	0.339
HbA1c (%)	5.4 ± 0.3	5.8 ± 0.6 ^a	5.7 ± 0.4 ^b	< 0.001
Total cholesterol (mg/dL)	207.0 ± 29.6	215.0 ± 49.6	209.0 ± 39.0	0.776
LDL-cholesterol (mg/dl)	123.0 ± 28.1	135.0 ± 43.6	128.0 ± 38.5	0.486
Creatinine (mg/dl)	0.85 ± 0.14	0.84 ± 0.19	0.83 ± 0.17	0.915
Aldosterone (ng/dL) (n = 55)	-	15.8 [10.1–20.6]	14.1 [10.9–17.9]	0.396
Plasma renin activity (ng/mL/h) (n = 55)	-	1.68 [0.66–2.79]	1.62 [0.56–2.62]	0.946
Urinary catecholamines (ng/L) (n = 55)	-	219.0 [140.0–264.0]	252.0 [165.0–407.0]	0.341

Urinary sodium and creatinine levels were higher during the high-salt phase compared to the low-salt phase in both groups, indicating good adherence to the dietary recommendations. As expected, both systolic and diastolic BP were higher in the SS group during the high-salt phase; however, systolic BP was also significantly higher in the SR group during the high-salt phase compared to the low-salt phase (Table 2).

Table 2

Spot urinary sodium and chloride measurements, and mean ambulatory 24-hours systolic and diastolic blood pressure measurements in salt-sensitive and salt-resistant hypertension groups and changes in these parameters during high- and low-salt intake phases. P values denote changes within groups.

Parameters	High salt intake	Low salt intake	P _{change}
Urinary sodium (mEq/L)			
Salt-resistant hypertension	116.0 ± 25.6	42.8 ± 20.9	< 0.001
Salt-sensitive hypertension	115.0 ± 30.1	45.5 ± 20.2	< 0.001
Urinary chloride (mEq/L)			
Salt-resistant hypertension	148.0 ± 35.4	57.8 ± 27.8	< 0.001
Salt-sensitive hypertension	146.0 ± 35.1	65.3 ± 32.4	< 0.001
Ambulatory 24 hours systolic blood pressure			
Salt-resistant hypertension	133.0 ± 9.4	132.0 ± 7.2	0.296
Salt-sensitive hypertension	139.0 ± 11.1	128.0 ± 13.4	< 0.001
Ambulatory 24 hours diastolic blood pressure			
Salt-resistant hypertension	76.8 ± 11.8	79.9 ± 10.3	0.034
Salt-sensitive hypertension	90.1 ± 9.9	80.7 ± 12.0	< 0.001

Measurements of FMD and CFR for the study groups are presented in Table 3. Both FMD and CFR were significantly lower in the two hypertensive groups compared to controls, but there were no differences in either parameter between the SR and SS groups. Additionally, there were no significant differences between the control group and the two hypertensive groups regarding basal coronary flow velocity (CFV) and peak hyperemic CFV, although SS patients trended toward a higher basal CFV and SR patients exhibited a numerically lower peak CFV compared to controls (Fig. 1).

Table 3

Flow-mediated vasodilatation, coronary flow reserve and individual components of coronary flow reserve in salt-resistant and salt-sensitive hypertensive patients. HT: Hypertension.

Characteristic	Healthy volunteers (n = 34)	Salt resistant HT (n = 27)	Salt sensitive HT (n = 28)	P value
Flow-mediated vasodilatation (%)	12.7 ± 1.9	10.0 ± 2.5 ^a	10.5 ± 2.4 ^b	< 0.001
Coronary flow reserve	3.12 ± 0.33	2.61 ± 0.47 ^a	2.51 ± 0.42 ^b	< 0.001
Basal coronary flow velocity (cm/s)	26.0 ± 4.4	27.4 ± 6.1	30.7 ± 8.7	0.091
Peak coronary flow velocity (cm/s)	81.4 ± 15.8	70.7 ± 17.6	76.0 ± 20.6	0.059

Following multivariable adjustment, CFR remained significantly lower in both hypertensive groups compared to controls (estimated marginal mean [EMM]: 2.91 [2.76–3.07] in controls vs. 2.53 [2.36–2.71] in the SR group vs. 2.52 [2.36–2.71] in the SS group; $P_{\text{adj}} = 0.002$, partial $\eta^2 = 0.148$). However, there remained no difference between the SS and SR patients ($P_{\text{adj}} = 0.871$, Cohen's d: 0.047 [-0.522 to 0.615]) (Fig. 2).

Correlations between CFR and BP, urinary electrolytes, and biochemical measurements in hypertensive patients

Coronary flow reserve (CFR) exhibited negative correlations with mean BP measurements derived from ambulatory BP readings obtained during the high-salt phase; however, no such correlations were observed with the same measurements during the low-salt phase (Fig. 3). Notably, the correlation between CFR and mean systolic BP was slightly stronger than the correlation between CFR and overall mean BP, whereas the correlation between CFR and diastolic BP did not reach statistical significance. Furthermore, there were no correlations between CFR and urinary sodium or chloride levels during either the high-salt or low-salt phases, nor were there correlations with aldosterone, plasma renin activity, or spot urinary catecholamines ($p > 0.05$ for all).

Associations between CFR and salt-sensitive systolic hypertension

As in the main analysis, both systolic and diastolic BP, as well as hemoglobin A1c levels, were significantly higher in both hypertensive groups compared to controls (Table 1). Similarly, both FMD and CFR were significantly lower in the salt-sensitive and salt-resistant systolic hypertension (SS S-HT and SR S-HT) groups compared to controls; however, CFR was also lower in the SS S-HT group compared to the SR S-HT group. This difference was driven by a numerically higher basal CFV in the SS S-HT group, rather than a difference in peak hyperemic CFV (Fig. 4).

After adjusting for covariates, CFR remained significantly lower in both S-HT groups compared to controls (estimated marginal mean [EMM]: 2.94 [2.79–3.08] in controls vs. 2.64 [2.47–2.81] in the SR S-HT group vs. 2.39 [2.19–2.59] in the SS S-HT group; $P_{\text{adj}} < 0.001$, partial $\eta^2 = 0.204$). Furthermore, CFR was significantly lower in the SS S-HT group compared to the SR S-HT group, demonstrating a moderate effect size ($P_{\text{adj}} = 0.019$, Cohen's d : 0.670 [0.103–1.240]) (Fig. 5).

Discussion

Although the close association between the SS trait and hypertension in susceptible individuals has been known for decades, it remains unclear whether the SS trait per se confers an additional risk for MACE independent of hypertension. The main takeaways from the present study are as follows: i) Both CFR and FMD were significantly lower in patients with SS hypertension than in controls, but neither parameter differed from those observed in patients with SR hypertension; ii) CFR exhibited a significant negative correlation with BP (particularly systolic BP) during the high-salt phase, but not with BP measurements taken during the low-salt phase; and iii) patients with systolic BP salt sensitivity had a significantly lower CFR (but not FMD) compared to both controls and hypertensive patients without this trait. Thus, systolic BP salt sensitivity may serve as a better marker for abnormal CFR, although the effect size (compared to patients without systolic BP salt sensitivity) was moderate, suggesting that most of the reduction in CFR is attributable to hypertension itself rather than the SS trait. A summary of study design and main results can be found in the Graphical Abstract.

Several lines of evidence suggest that salt intake, either in isolation or in the context of hypertension, is associated with microvascular dysfunction in the subcutaneous tissue and kidneys, with the latter typically evidenced by microalbuminuria (17–20). What remains less certain is whether the presence of the SS trait has an additive deleterious effect on cardiovascular outcomes beyond that expected from the established negative effects of salt intake and hypertension. Two retrospective studies have suggested that the SS trait, assessed via dietary intervention or sodium infusion, is associated with increased cardiovascular mortality in both normotensive and hypertensive individuals (9, 10). These findings are further supported by data from various human studies demonstrating associations between the SS trait and biomarkers of inflammation, atherosclerosis, endothelial dysfunction, and target-organ damage. Consequently, it is reasonable to hypothesize that a similar association might exist between the SS trait and coronary microvascular dysfunction (21–24).

Nonetheless, the present results do not support an independent association between the SS trait and CFR or FMD in individuals with new-onset hypertension beyond the alterations already attributable to hypertension. Regarding FMD, findings similar to those of the present study were reported previously by Matthews and colleagues, who noted that FMD did not differ between hypertensive patients with or without the SS trait, regardless of the diet's salt content (25). Of note, the present measurements were obtained during the low-salt phase of the study and do not necessarily reflect what coronary microvascular function would be during continued high-salt intake. However, given that most patients with hypertension and the SS trait are advised to reduce their salt intake, the present findings are

reassuring: the conventionally defined SS trait does not appear to confer an additional deterioration in microvascular function when salt intake is appropriately limited.

Indeed, secondary findings from the present study suggest that patients with a higher mean BP during the high-salt phase—but not during the low-salt phase—had a correspondingly lower CFR. This makes it plausible that continued high-salt intake could exert a more profound effect on the coronary microvasculature. Previous observations demonstrating impaired endothelial or microvascular function following salt intake in healthy volunteers or individuals with the SS trait were predominantly conducted while participants were on a high-salt diet. Thus, it is reasonable to hypothesize that CFR would be lower in SS hypertensive patients had the measurements been taken during the high-salt phase (6, 26). Although direct causality cannot be inferred from the present findings, the data suggest that avoiding a high-salt diet should be strictly prioritized in individuals with the SS trait, given its potential association with the progression of coronary microvascular dysfunction and subsequent adverse cardiovascular sequelae.

An interesting observation in the present study is that although a conventionally-defined SS trait was not associated with worse coronary microvascular dysfunction, we found that patients with salt-sensitive systolic hypertension had lower CFR as compared to those without this trait. Although the relative importance of systolic and diastolic BP in predicting cardiovascular outcomes has long been debated, more emphasis has been placed on systolic BP in recent years, as it appears to have a greater predictive value for these outcomes (27, 28). Thus, it may be reasonable to consider that a definition of salt-sensitivity based on the changes in systolic BP (rather than MAP) may be more informative for prognosis, given that present results suggest that coronary microvascular dysfunction was more profound in the subset of patients with SS S-HT. Nevertheless, we emphasize that the present findings should not be over-interpreted. The observed effect size was moderate, and the primary driver for the difference in CFR was a higher basal flow rather than a reduction in recruitable flow, suggesting that the vasodilatory response to adenosine remained intact in patients with systolic BP salt sensitivity. Of note, the present results do not support an association between systolic BP salt sensitivity and FMD, suggesting a comparable degree of alteration in endothelium-dependent vasodilation across hypertensive patients regardless of SS trait.

The present study has several strengths and limitations. The sample size was adequate to detect a prespecified difference in CFR between groups, and our laboratory has a long track record of conducting studies on the echocardiographic measurement of CFR with acceptable intra- and inter-observer variability (29, 30). Although a separate power analysis was not performed for the alternative definition based on systolic BP, the means and expected differences between groups aligned well with our assumptions for the primary analysis; therefore, the study was adequately powered to detect a difference between groups when this alternative definition was applied.

Because the results were obtained during a low-salt diet, no extrapolations can be made regarding coronary microvascular function if individuals were to continue consuming a high-salt diet. Furthermore,

although we monitored adherence to dietary recommendations using spot urinary sodium and chloride concentrations—and the mean changes in these parameters suggested that the vast majority of patients adhered to the study protocol—these concentrations could not be used to explicitly exclude non-adherent participants, as definitive cut-off values do not exist to confirm high- or low-salt intake. The definition of SS trait varies between studies, and present results are not adequate to rule out an association between SS trait and CFR when an alternative definition (i.e. ≥ 10 mmHg change in MAP during high-salt intake) is used. Finally, the present findings are only applicable to individuals with new-onset grade < 3 hypertension (and are predominantly confined to those with grade 1 hypertension). Consequently, generalizations cannot be made regarding individuals with the SS trait in the absence of hypertension or patients with established hypertension receiving medical treatment.

Conclusions

In patients with new-onset hypertension, CFR was reduced in all patients regardless of the presence or absence of the SS trait. However, patients with an increased systolic BP response to a high-salt diet had a lower CFR compared to those with systolic BP salt resistance, suggesting a more pronounced coronary microvascular dysfunction in this subgroup. Further work is needed to ascertain whether this finding translates into an increased frequency of adverse cardiovascular events in the subset of patients with systolic BP salt sensitivity.

Declarations

Funding: This study has been supported by the Recep Tayyip Erdogan University Development Foundation.

Conflict of Interest: None.

Previous Presentations: None

ACKNOWLEDGEMENTS

Informed consent form for publication was obtained from all authors.

COMPETING INTERESTS STATEMENT

The authors (AP.A., FB.C., TS.G., AE.E., M.K., N.I., Y.Y., S.K., AS.Y., and M.C.) declare no competing financial or non-financial interests.

AUTHOR CONTRIBUTIONS

Ayşe Paralı Ak: Conceptualization (supporting); data curation (lead); formal analysis (equal); funding acquisition (supporting); investigation (equal); methodology (equal); project administration (lead); supervision (equal); validation (equal); visualization (equal); writing—original draft (lead); writing—review

and editing (lead). **Fatma Betul Celik:** Conceptualization (equal); data curation (supporting); formal analysis (equal); funding acquisition (equal); investigation (supporting); methodology (equal); project administration (supporting); resources (supporting); software (lead); writing—original draft (equal); writing—review and editing (equal). **Tolga Sinan Guvenc:** Conceptualization (equal); formal analysis (supporting); funding acquisition (equal); methodology (equal); writing—review and editing (equal). **Ahmet Eren Caliskan:** Conceptualization (equal); formal analysis (equal); funding acquisition (equal); methodology (equal); writing—review and editing (equal). **Merve Kapcik:** Conceptualization (equal); formal analysis (equal); funding acquisition (equal); methodology (equal); writing—review and editing (equal). **Nermin Ismailzade:** Conceptualization (equal); formal analysis (equal); funding acquisition (equal); methodology (equal); writing—review and editing (equal). **Yusuf Yilmaz:** Conceptualization (equal); formal analysis (equal); funding acquisition (equal); methodology (equal); writing—review and editing (equal). **Seref Kul:** Conceptualization (equal); formal analysis (equal); funding acquisition (equal); methodology (equal); writing—review and editing (equal). **Ahmet Seyda Yilmaz:** Conceptualization (equal); data curation (supporting); formal analysis (equal); funding acquisition (equal); investigation (supporting); methodology (equal); project administration (supporting); resources (supporting); software (lead); writing—original draft (equal); writing—review and editing (equal). **Mustafa Caliskan:** Conceptualization (lead); data curation (equal); formal analysis (lead); funding acquisition (lead); investigation (lead); methodology (lead); project administration (equal); supervision (lead); validation (lead); visualization (lead); writing—original draft (lead); writing—review and editing (lead).

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study was ethically approved by the Medeniyet University Faculty of Medicine Clinical and Pharmaceutical Research Local Ethics Committee with the recommendation of the Ministry of Health Istanbul Medeniyet University Göztepe Training and Research Hospital Research Board (Decision no: 2025/0073). Written informed consent was obtained from all participants before participating in the study.

References

1. Farrar, J. & Frieden, T. WHO global report on hypertension 2025. *Lancet* **406** (10517), 2318–2319. 10.1016/S0140-6736(25)02208-1 (2025).
2. Ambard, L. & Beujard, E. Asynopsis in English of Causes de l'hypertension arterielle. In: (ed Swales, J. D.) *Classic Papers in Hypertension: Blood Pressure and Renin*. Science Press Ltd; :139–151. (1904).

3. Dahl, L. K. & Love, R. A. Evidence for relationship between sodium (chloride) intake and human essential hypertension. *AMA Arch. Intern. Med.* **94**, 525–531. 10.1001/archinte.1954.00250040017003 (1954).
4. Hunter, R. W., Dhaun, N. & Bailey, M. A. The impact of excessive salt intake on human health. *Nat. Rev. Nephrol.* **18** (5), 321–335. 10.1038/s41581-021-00533-0. (2022). Epub 2022 Jan 20. PMID: 35058650.
5. Bailey, M. A. & Dhaun, N. Salt Sensitivity: Causes, Consequences, and Recent Advances. *Hypertension* **81** (3), 476–489. 10.1161/HYPERTENSIONAHA.123.17959. (2024). Epub 2023 Sep 18. PMID: 37721034; PMCID: PMC10863664.
6. Barić, L. et al. Seven-Day Salt Loading Impairs Microvascular Endothelium-Dependent Vasodilation without Changes in Blood Pressure, Body Composition and Fluid Status in Healthy Young Humans. *Kidney Blood Press. Res.* **44** (4), 835–847. 10.1159/000501747. (2019). Epub 2019 Aug 20. PMID: 31430746.
7. Rorije, N. M. G. et al. High-salt intake affects sublingual microcirculation and is linked to body weight change in healthy volunteers: a randomized cross-over trial. *J Hypertens.* ;37(6):1254–1261. (2019). 10.1097/HJH.0000000000002015. PMID: 30575682.
8. Imanishi, M. et al. Sodium sensitivity related to albuminuria appearing before hypertension in type 2 diabetic patients. *Diabetes Care.* ;24(1):111-6. (2001). 10.2337/diacare.24.1.111. PMID: 11194215.
9. Morimoto, A. et al. Sodium sensitivity and cardiovascular events in patients with essential hypertension. *Lancet.* ;350(9093):1734-7. (1997). 10.1016/S0140-6736(97)05189-1. PMID: 9413464.
10. Weinberger, M. H., Fineberg, N. S., Fineberg, S. E. & Weinberger, M. Salt sensitivity, pulse pressure, and death in normal and hypertensive humans. *Hypertension.* ;37(2 Pt 2):429 – 32. (2001). 10.1161/01.hyp.37.2.429. PMID: 11230313.
11. Weinberger, M. H., Miller, J. Z., Luft, F. C., Grim, C. E. & Fineberg, N. S. Definitions and characteristics of sodium sensitivity and blood pressure resistance. *Hypertension.* ;8(6 Pt 2):II127-34. (1986). 10.1161/01.hyp.8.6_pt_2.ii127. PMID: 3522418.
12. Foppa, M., Duncan, B. B. & Rohde, L. E. Echocardiography-based left ventricular mass estimation. How should we define hypertrophy? *Cardiovasc. Ultrasound.* **3**, 17. 10.1186/1476-7120-3-17. (2005). PMID: 15963236; PMCID: PMC1183230.
13. Lang, R. M. et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J. Am. Soc. Echocardiogr.* **28** (1), 1–39e14. 10.1016/j.echo.2014.10.003 (2015).
14. Maruhashi, T. et al. Diagnostic Criteria of Flow-Mediated Vasodilation for Normal Endothelial Function and Nitroglycerin-Induced Vasodilation for Normal Vascular Smooth Muscle Function of the Brachial Artery. *J. Am. Heart Assoc.* **9** (2), e013915. 10.1161/JAHA.119.013915 (2020).

15. S. I. Coronary Flow Velocity Reserve Assessment with Transthoracic Doppler Echocardiography. *Eur. Cardiol.* **10** (1), 12–18. 10.15420/ecr.2015.10.01.12. (2015). PMID: 30310417; PMCID: PMC6159450.
16. Stegehuis, V. E. et al. Impact of clinical and haemodynamic factors on coronary flow reserve and invasive coronary flow capacity in non-obstructed coronary arteries: a patient-level pooled analysis of the DEBATE and ILIAS studies. *EuroIntervention* **16** (18), e1503–e1510. 10.4244/EIJ-D-19-00774. (2021). PMID: 31951205; PMCID: PMC9724860.
17. Cavka, A. et al. Short-term high salt intake reduces brachial artery and microvascular function in the absence of changes in blood pressure. *J. Hypertens.* **34** (4), 676–684 (2016). PMID: 26848993; PMCID: PMC6711169.
18. Jablonski, K. L. et al. Dietary sodium restriction reverses vascular endothelial dysfunction in middle-aged/older adults with moderately elevated systolic blood pressure. *J. Am. Coll. Cardiol.* **61** (3), 335–343. 10.1016/j.jacc.2012.09.010. (2013). Epub 2012 Nov 7. PMID: 23141486; PMCID: PMC3549053.
19. Konta, T. et al. Prevalence and risk factor analysis of microalbuminuria in Japanese general population: the Takahata study. *Kidney Int.* ;70(4):751-6. (2006). 10.1038/sj.ki.5001504. PMID: 16807548.
20. Ekin, E. I. et al. Effects of salt supplementation on the albuminuric response to telmisartan with or without hydrochlorothiazide therapy in hypertensive patients with type 2 diabetes are modulated by habitual dietary salt intake. *Diabetes Care.* **32** (8), 1398–1403. 10.2337/dc08-2297. (2009). Epub 2009 Jun 23. PMID: 19549737; PMCID: PMC2713627.
21. Larrousse, M. et al. Increased levels of atherosclerosis markers in salt-sensitive hypertension. *Am J Hypertens.* ;19(1):87–93. (2006). 10.1016/j.amjhyper.2005.06.019. PMID: 16461197.
22. Fujiwara, N. et al. Study on the relationship between plasma nitrite and nitrate level and salt sensitivity in human hypertension: modulation of nitric oxide synthesis by salt intake. *Circulation.* ;101(8):856 – 61. (2000). 10.1161/01.cir.101.8.856. PMID: 10694524.
23. Cubeddu, L. X. et al. Nitric oxide and salt sensitivity. *Am J Hypertens.* ;13(9):973-9. (2000). 10.1016/s0895-7061(00)00283-1. PMID: 10981546.
24. Bihorac, A., Tezcan, H., Ozener, C., Oktay, A. & Akoglu, E. Association between salt sensitivity and target organ damage in essential hypertension. *Am J Hypertens.* ;13(8):864 – 72. (2000). 10.1016/s0895-7061(00)00253-3. PMID: 10950394.
25. Matthews, E. L. et al. High dietary sodium reduces brachial artery flow-mediated dilation in humans with salt-sensitive and salt-resistant blood pressure. *J. Appl. Physiol.* (1985). **118** (12), 1510–1515. 10.1152/japplphysiol.00023.2015. (2015). Epub 2015 Apr 2.
26. de Zeeuw, R. T., Serné, E. H., IJzerman, R. G. & Stehouwer, C. D. Microvascular function: a potential link between salt sensitivity, insulin resistance and hypertension. *J Hypertens.* ;25(9):1887-93. (2007). 10.1097/HJH.0b013e32825e1db7. PMID: 17762653.

27. Flint, A. C. et al. Effect of Systolic and Diastolic Blood Pressure on Cardiovascular Outcomes. *N Engl J Med.* ;381(3):243–251. (2019). 10.1056/NEJMoa1803180. PMID: 31314968.
28. Vishram-Nielsen, J. K. K. et al. Predictive Importance of Blood Pressure Characteristics With Increasing Age in Healthy Men and Women: The MORGAM Project. *Hypertension* **77** (4), 1076–1085. 10.1161/HYPERTENSIONAHA.120.16354. (2021). Epub 2021 Mar 1. PMID: 33641358.
29. Kul, Ş. et al. Combined past preeclampsia and gestational diabetes is associated with a very high frequency of coronary microvascular dysfunction. *Microvasc Res.* **134**, 104104 (2021). Epub 2020 Nov 13. PMID: 33189732.
30. Çalışkan, M. et al. Coronary microvascular dysfunction is common in patients hospitalized with COVID-19 infection. *Microcirculation* **29** (4–5), e12757. 10.1111/micc.12757. (2022). Epub 2022 May 3. PMID: 35437863; PMCID: PMC9115225.

Figures

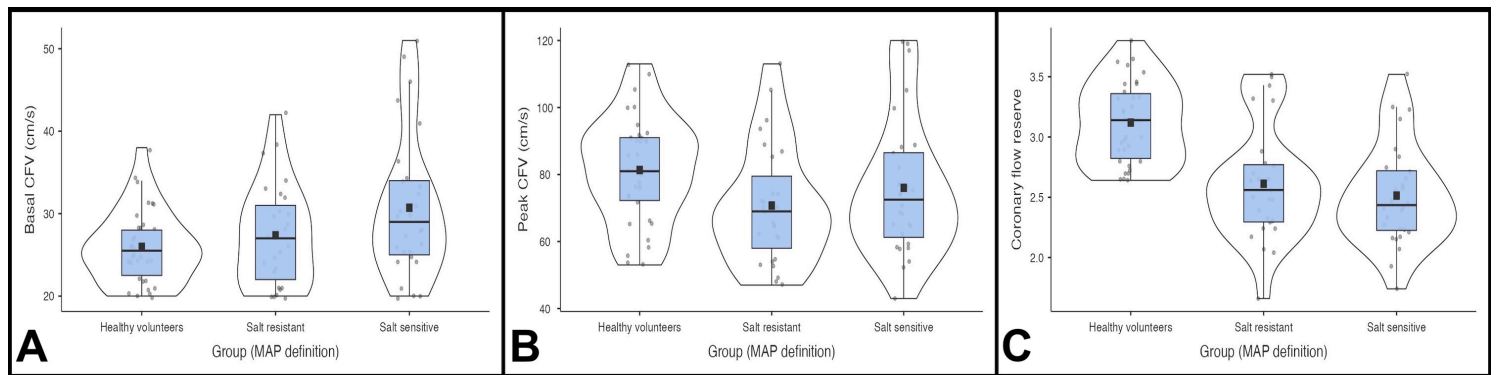


Figure 1

Violin plots showing basal coronary flow velocity, peak coronary flow velocity, and coronary flow reserve in the study groups and controls. Salt sensitivity is defined conventionally using the change in mean arterial blood pressure between the high- and low-salt diets. Blue boxes represent medians and interquartile ranges, small black squares represent means, and dots represent individual measurements. CFV: Coronary flow velocity; MAP: Mean arterial pressure.

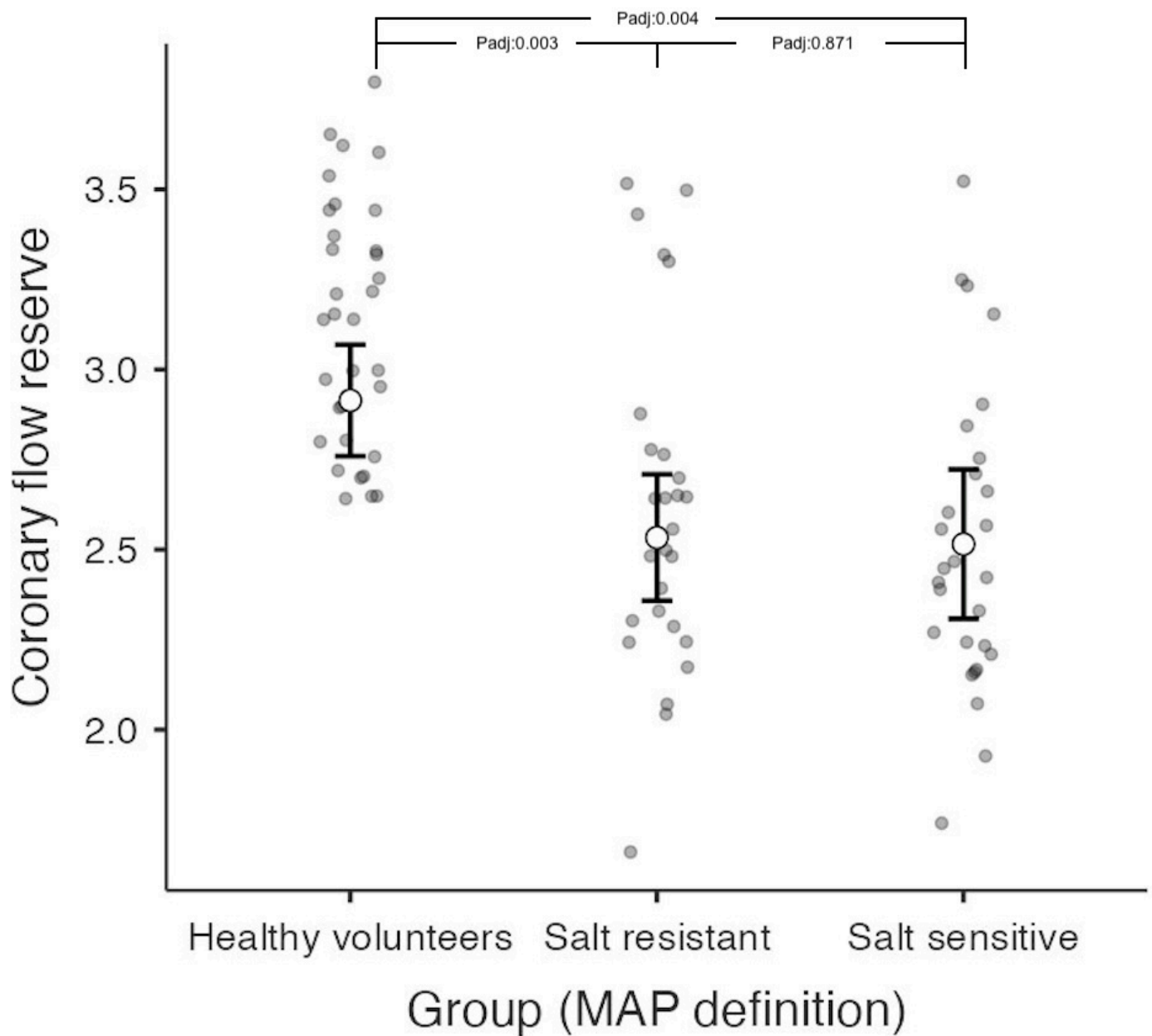


Figure 2

Estimated marginal means for coronary flow reserve in the study groups and controls after adjustment for covariates. Salt sensitivity is defined conventionally using the change in mean arterial blood pressure between the high- and low-salt diets. Error bars represent standard errors, and dots represent individual measurements. MAP: Mean arterial pressure.

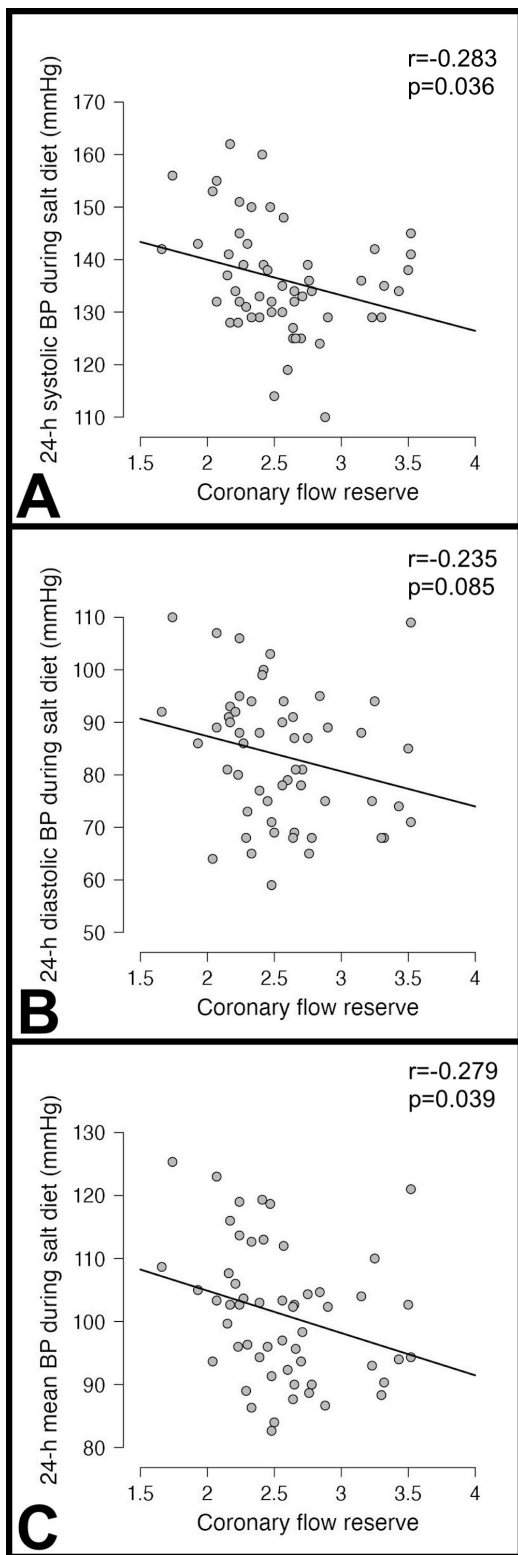


Figure 3

Correlations between coronary flow reserve and average 24-hour systolic (A), diastolic (B), and mean (C) ambulatory blood pressures obtained during the high-salt phase. BP: Blood pressure.

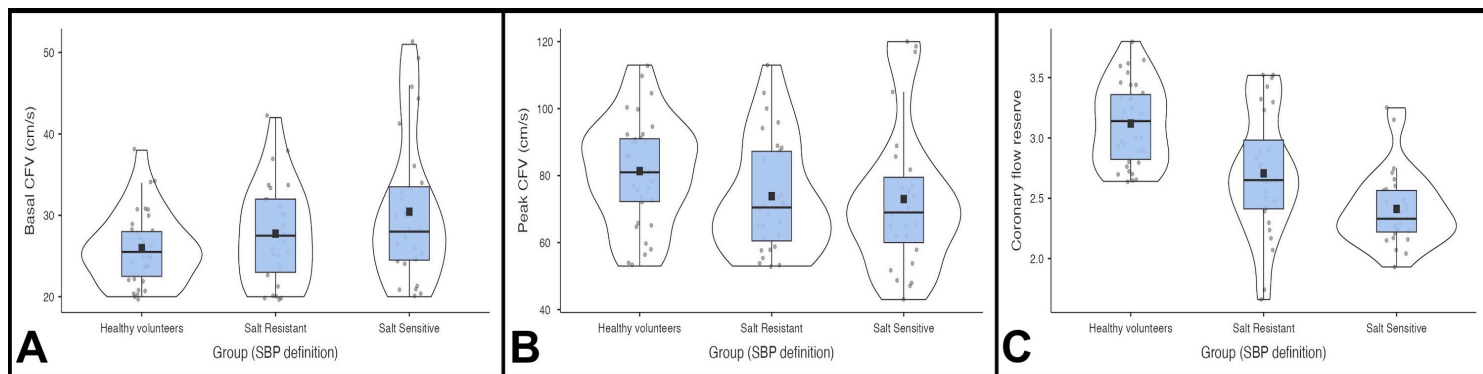


Figure 4

Violin plots showing basal coronary flow velocity, peak coronary flow velocity, and coronary flow reserve in the study groups and controls. Salt sensitivity is defined based on the change in systolic blood pressure between the high- and low-salt diets. Blue boxes represent medians and interquartile ranges, small black squares represent means, and dots represent individual measurements. CFV: Coronary flow velocity; SBP: Systolic blood pressure.

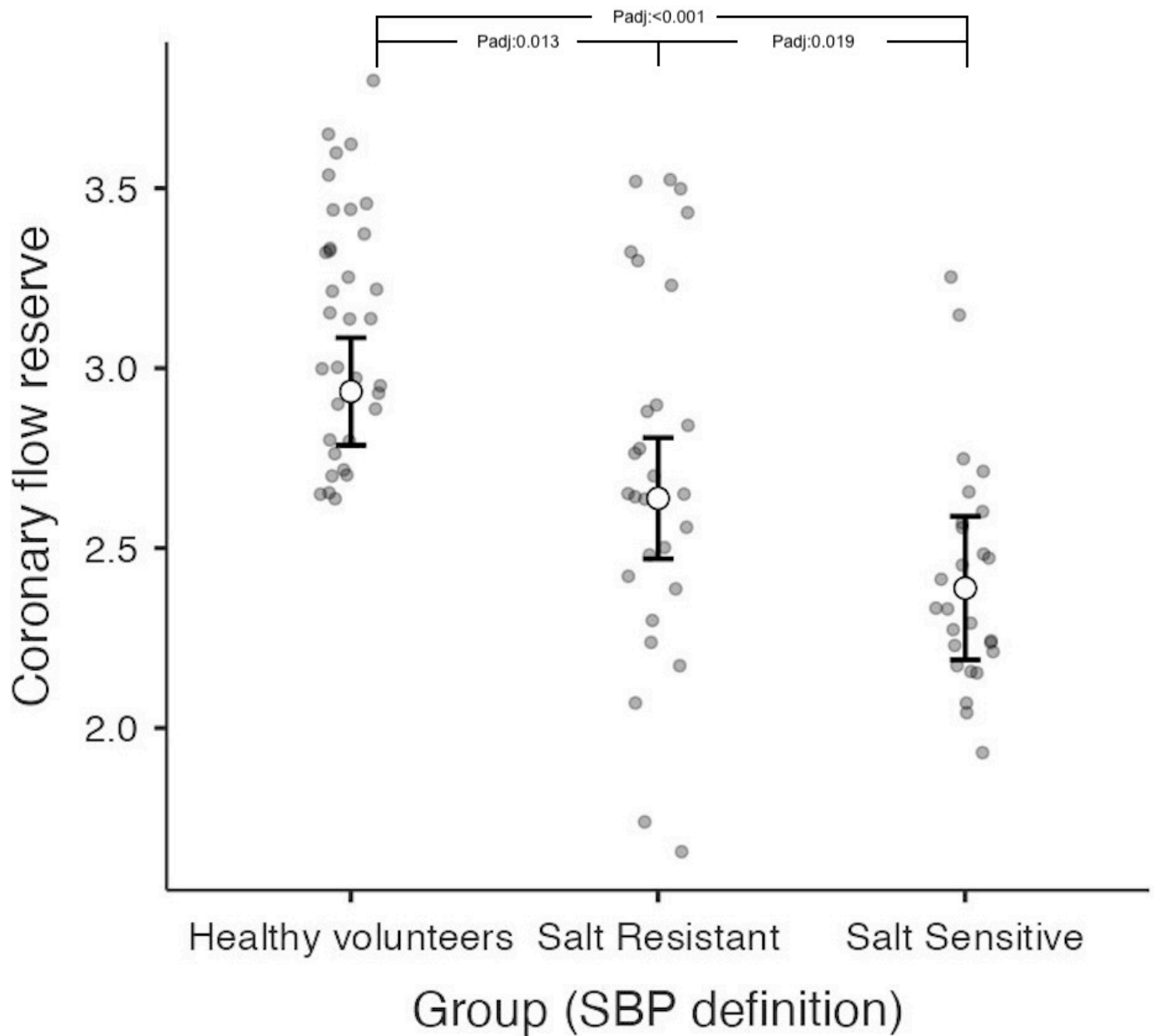


Figure 5

Estimated marginal means for coronary flow reserve in the study groups and controls after adjustment for covariates. Salt sensitivity is defined based on the change in systolic blood pressure between the high- and low-salt diets. Error bars represent standard errors, and dots represent individual measurements. SBP: Systolic blood pressure.