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Sex difference in sympathetic nervous system activity and blood pressure in hypertensive patients

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Abstract

Increased sympathetic nervous system (SNS) activity leads to increased risk of cardiovascular morbidity and mortality. This study investigated whether there were sex differences in SNS activity among Chinese patients with hypertension. Ethnic Chinese non-diabetic hypertensive patients aged 20–50 years were enrolled in Taiwan. A total of 970 hypertensive patients (41.0 ± 7.2 years) completed the study, 664 men and 306 women. They received comprehensive evaluations including office blood pressure (BP) measurement, 24-h ambulatory BP monitoring, and 24-h urine sampling assayed for catecholamine excretion. Compared to women, men were younger, had higher body mass index (BMI), office systolic BP (SBP), office diastolic BP (DBP), 24-h ambulatory BP, and 24-h urine catecholamine excretion. In men, 24-h urine total catecholamine levels were correlated with 24-h SBP (r = 0.103, p = .008) and 24-h DBP (r = 0.083, p = .033). In women, however, there was no correlation between 24-h urine total catecholamine levels and 24-h

ambulatory BP. Multivariate linear regression indicated that being male (β = 1.65, 95% confidence interval [CI] 0.01–3.29, p = .048) and 24-h urine total catecholamine (β = 5.03, 95% CI 0.62–9.44, p = .025) were both independently associated with 24-h SBP; being male was independently associated with 24-h DBP (β = 3.55, 95% CI 2.26–4.85, p < .001). In conclusion, Chinese men with hypertension had higher SNS activity than women, and SNS activity was independently associated with 24-h ambulatory BP in men rather than in women. These findings suggest that different hypertensive treatment strategies should be considered according to patient sex.

1 | INTRODUCTION

Hypertension is one of the most important traditional risk factors for cardiovascular disease (CVD), and the most common cause of death worldwide.[1] Over the past decades, hypertension prevalence has continually increased, with a corresponding increase in disease burden and deaths.[2] The control rates have improved, but not consistently in all hypertensive subgroups.[3,4] These findings suggest the need for a more detailed understanding of hypertension etiologies and more efficient antihypertensive strategies.

The cardiac autonomic nervous system is a crucial component in physiological and pathological responses of the cardiovascular system. Pronounced alterations in the autonomic nervous system have been noted in hypertension and other CVDs.[5–7] Sympathetic nervous system (SNS) activity is increased in essential hypertension.[7] Increased out-of-clinic SNS activity is also noted in patients with masked uncontrolled hypertension.[8] For hypertension management, it is important to clarify the impacts of SNS activity on blood pressure (BP) in different hypertension populations.

There are well-described differences in CVD clinical manifestations, management, and outcomes between men and women.[9] There are still conflicting results by sex on SNS activity and the impact of sex differences on BP. Furthermore, the study of sex differences in SNS activity among Chinese populations is still lacking. The current study aimed to investigate whether there were sex differences in SNS activity and BP in a cohort of Chinese hypertensive patients.

2 | METHODS

2.1 | Study cohort

Non-diabetic hypertensive patients have been prospectively recruited from six Taiwan medical centers, including Taipei Veteran General Hospital, Taichung Veteran General Hospital, National Cheng Kung University Medical Center, Kaohsiung Medical University Chung-Ho Memorial Hospital, Cheng Hsin Rehabilitation Medical Center, and Min Sheng General Hospital since 2005. The subject inclusion criteria included: age 20–50 years, met one of the following hypertension criteria: (i) systolic BP (SBP) ≥ 140 mm Hg or diastolic BP (DBP) ≥90 mm Hg in at least two consecutive visits in 2 months, (ii) was taking one or more antihypertensive medication for 2 months and had a body mass index (BMI) ≤35 kg/m^2, fasting glucose level <126 mg/dL with no diabetes mellitus, no history of severe diseases, no acute disease within 2 weeks, and no secondary hypertension. The detailed inclusion criteria and exclusion criteria were mentioned in our previous study.[10]

The study protocol was approved by the ethics committee of Academia Sinica and six medical centers. All patients agreed to participate and provided informed consent for the study. This study was conducted in accordance with the principles of the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, revised November 13, 2001, effective December 13, 2001.

2.2 | Study design

This was a cross-sectional study. All patients were evaluated at the hypertension clinics of the six medical centers, prospectively. A comprehensive history and physical examination were performed by a hypertension specialist. Patients were also evaluated with respect to weight, height, office BP, 24-h ambulatory BP monitoring (ABPM), and blood and urine samples. Weight and height were recorded with patients barefoot and wearing only light, indoor clothes. BMI was defined as weight in kilograms divided by the square of height in meters.

2.3 | BP measurement

Office BP was measured, according to a standardized protocol, by a well-trained nurse with an electronic BP monitor in the morning hours, after the patients were instructed to sit in a quiet room for 10 min. Three consecutive BP measurements were taken on the same upper arm. Each measurement was separated by a 30-s interval. The average of the last two measurements was recorded as BP.

Patients were connected to an ABPM device between 0800 h and 1000 h The device was programmed to record BP every 20 min from

0600 h until 2300 h and 30 min from 2300 h until 0600 h. All patients were asked to record the time they went to sleep and woke up.

2.4 | Measuring SNS activity

Sympathetic nervous system activity was measured using 24-h urine catecholamine. Twenty-four-hour urine samples were collected during the ABPM session. A standard protocol was used for collection and participants were instructed by well-trained nursing staff. Each urine sample container had a preservative to prevent urine deterioration and was stored in a portable cooler. The samples were sent to a central laboratory for evaluation. Urinary norepinephrine and epinephrine were measured using high-pressure liquid chromatography with electrochemical detection.[11]

2.5 | Statistical analysis

Patient characteristics were summarized with descriptive statistics. All continuous variables were expressed as mean ± standard deviation. Non-normally distributed variables were expressed as median (interquartile range), including norepinephrine, epinephrine, and total catecholamine (sum of norepinephrine and epinephrine). Parametric continuous data between the different sexes were compared using unpaired Student's t test, and nonparametric data using Mann–Whitney U test. Categorical variables were expressed as frequencies (percentages) and analyzed by chi-square test or Fisher's exact tests. Urine catecholamine was normalized for further analysis by log-transformation of the original values because of their skewed distributions. Pearson's correlation coefficient was used to evaluate the correlation between 24-h urine catecholamine and BP parameters. Multiple linear regression and general linear model were performed to assess interactions and effects of sex and 24-h urine catecholamine on 24-h BP parameters in the total cohort. To examine whether the effect of sex and SNS activity on 24-h ambulatory BP was independent, sex effect in model 1, 24-h urine catecholamine effect in model 2, and join effect of sex and 24-h urine catecholamine in model 3 were analyzed with adjustment for age, BMI, and antihypertensive drugs. Because of the interaction between sex and 24-h urine catecholamine, receiver operating characteristic curve analysis was performed for optimal cut-off value to stratify total 24-h urine catecholamine into high- and low-level groups.

In order to minimize possible confounding factors of SNS activity, we created a propensity model to compare the characteristics of hypertensive men and women who were not taking antihypertensive medications. The model included age, BMI, office SBP, and office DBP. Men with untreated hypertension were then matched with women with untreated hypertension in a 1:1 ratio using the propensity-matching algorithm. Parametric continuous data between different sex groups were compared using paired Student's t test, and nonparametric data were compared using Mann–Whitney test. Categorical variables were analyzed by Chi-Square test or Fisher's Exact test. Pearson's correlation coefficient was used to evaluate the relationship between 24-h urine catecholamine and BP parameters. Multivariate analysis was evaluated with linear regression. Statistical significance was inferred with a two-sided p value <.05. Statistical analysis was performed using SPSS software (version 18.0, SPSS Inc).

3 | RESULTS

3.1 | Total cohort

A total of 970 hypertensive patients (41.0 ± 7.2 years) completed the study, including 664 men and 306 women. Men were younger ($p < .001$), had higher BMI ($p < .001$), office SBP ($p = .002$), office DBP ($p < .001$), 24-h SBP ($P < .001$), 24-h DBP ($p < .001$), awake SBP ($p < .001$), awake DBP ($p < .001$), asleep SBP ($p = .027$), and asleep DBP ($p = .006$), compared to women. The 24-h heart rate (HR) and awake HR were similar in men and women; the asleep HR was lower in men than in women ($p = .033$). When comparing patient 24-h urine catecholamine excretion, men had higher epinephrine ($p < .001$), norepinephrine ($p < .001$), and total catecholamine ($p < .001$) than women (Table 1).

To test whether there were sex differences in the association between SNS activity and 24-h ambulatory BP, we analyzed the correlation between 24-h urine catecholamine levels (log-transformed) and ambulatory BP parameters in the total cohort and different sexes, separately. In the total cohort, 24-h urine total catecholamine levels were correlated with 24-h SBP ($r = 0.113$, $p < .001$), 24-h DBP ($r = 0.106$, $p = .001$), awake SBP ($r = 0.129$, $p < .001$), awake DBP ($r = 0.121$, $p < .001$), 24-h HR ($r = 0.175$, $p < .001$), awake HR ($r = 0.176$, $p < .001$), and asleep HR ($r = 0.130$, $p < .001$) (Table 2). In the hypertensive men, 24-h urine total catecholamine levels were correlated with 24-h SBP ($r = 0.103$, $p = .008$), 24-h DBP ($r = 0.083$, $p = .033$), awake SBP ($r = 0.117$, $p = .003$), awake DBP ($r = 0.091$, $p = .019$), 24-h HR ($r = 0.213$, $p < .001$), awake HR ($r = 0.211$, $p < .001$), and asleep HR ($r = 0.183$, $p < .001$) (Table 2). In the hypertensive women, however, there was no correlation between 24-h urine total catecholamine levels and 24-h ambulatory BP (Table 2).

To examine whether the effect of sex and SNS activity on 24-h ambulatory BP was independent, multivariate linear regression was performed. In model 1, sex was independently associated with 24-h SBP ($\beta = 2.04$, 95% confidence interval [CI] 0.44–3.64, $p = .013$), 24-h DBP ($\beta = 3.78$, 95% CI 2.51–5.04, $p < .001$), awake SBP ($\beta = 2.21$, 95% CI 0.55–3.87, $p = .009$), awake DBP ($\beta = 4.28$, 95% CI 2.97–5.59, $p < .001$), and asleep DBP ($\beta = 1.74$, 95% CI 0.39–3.10, $p = .012$) (Table 3). In model 2, 24-h urine total catecholamine was independently associated with 24-h SBP ($\beta = 5.94$, 95% CI 1.62–10.26, $p = .007$), 24-h DBP ($\beta = 5.14$, 95% CI 1.67–8.61, $p = .004$), awake SBP ($\beta = 7.79$, 95% CI 3.31–12.26, $p = .001$), and awake DBP ($\beta = 6.31$, 95% CI 2.71–9.91, $p = .001$) (Table 3). In model 3, both sex ($\beta = 1.65$, 95% CI 0.01–3.29, $p = .048$) and 24-h urine total catecholamine

TABLE 1 Baseline characteristics of the patients according to sex in the total cohort

	All (*n* = 970)	Men (*n* = 664)	Women (*n* = 306)	*p*-value
Age, years	41.0 ± 7.2	40.4 ± 7.5	42.4 ± 6.2	<.001
BMI, kg/m^2	26.5 ± 3.4	26.9 ± 3.2	25.9 ± 3.8	<.001
Office SBP, mm Hg	126.1 ± 14.5	127.1 ± 13.8	124.0 ± 15.7	.002
Office DBP, mm Hg	84.9 ± 11.7	86.7 ± 11.5	81.1 ± 11.4	<.001
24-h SBP, mm Hg	123.2 ± 12.2	124.3 ± 12.4	121.0 ± 11.4	<.001
24-h DBP, mm Hg	82.6 ± 9.5	83.8 ± 9.5	79.8 ± 9.0	<.001
24-h HR, bpm	72.1 ± 9.4	72.3 ± 9.5	71.6 ± 9.0	.325
Awake SBP, mm Hg	126.1 ± 12.7	127.2 ± 12.9	123.7 ± 11.9	<.001
Awake DBP, mm Hg	84.9 ± 9.9	86.4 ± 9.8	81.8 ± 9.4	<.001
Awake HR, bpm	75.2 ± 10.3	75.5 ± 10.5	74.4 ± 9.9	.114
Asleep SBP, mm Hg	114.0 ± 12.8	114.6 ± 12.9	112.7 ± 12.3	.027
Asleep DBP, mm Hg	74.7 ± 10.0	75.3 ± 10.1	73.5 ± 9.5	.006
Asleep HR, bpm	61.9 ± 8.1	61.5 ± 8.4	62.7 ± 7.4	.033
ACEI/ARB, *n* (%)	410(42.3%)	293(44.1%)	117(38.2%)	.084
BB, *n* (%)	437(45.1%)	292(44.0%)	145(47.4%)	.321
CCB, *n* (%)	405(41.8%)	272(41.0%)	133(43.5%)	.463
Thiazide, *n* (%)	157(16.2%)	103(15.5%)	54(17.6%)	.401
Spironolactone, *n* (%)	7(0.7%)	5(0.8%)	2(0.7%)	1.000
Urine catecholamine[a]				
Epinephrine, μg/24 h	7.4(5.4)	8.1(5.9)	6.2(4.4)	<.001
Norepinephrine, μg/24 h	41.6(25.7)	44.4(27.8)	36.7(18.9)	<.001
Total catecholamine, μg/24 h	49.4(27.2)	53.6(29.2)	43.2(20.6)	<.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BMI, body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

[a]Expressed as median and interquartile range.

TABLE 2 The association between 24-h urine total catecholamine and ambulatory blood pressure in the total cohort

	All (*n* = 970)		Men (*n* = 664)		Women (*n* = 306)	
	r	*p*-value	*r*	*p*-value	*r*	*p*-value
24-h SBP	0.113	<.001	0.103	.008	0.058	.309
24-h DBP	0.106	.001	0.083	.033	0.029	.608
24-h HR	0.175	<.001	0.213	<.001	0.070	.221
Awake SBP	0.129	<.001	0.117	.003	0.079	.169
Awake DBP	0.121	<.001	0.091	.019	0.045	.432
Awake HR	0.176	<.001	0.211	<.001	0.066	.249
Asleep SBP	0.034	.289	0.042	.277	−0.029	.612
Asleep DBP	0.034	.294	0.041	.290	−0.040	.481
Asleep HR	0.130	<.001	0.183	<.001	0.063	.273

Note: Abbreviations: DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

24-h urine total catecholamine concentrations were log-transformed.

r = Pearson's correlation coefficients.

(β = 5.03, 95% CI 0.62–9.44, p = .025) were independently associated with 24-h SBP. Sex was independently associated with 24-h DBP (β = 3.55, 95% CI 2.26–4.85, p < .001). Twenty-four-hour urine total catecholamine was independently associated with awake SBP (β = 6.86, 95% CI 2.30–11.43, p = .003). Both sex (β = 3.97, 95% CI 2.63–5.31, p < .001) and 24-h urine total catecholamine (β = 4.11,

TABLE 3 The independent effect of sex and 24-h urine total catecholamine on 24-h ambulatory blood pressure in the total cohort

	Model 1		Model 2		Model 3	
	β (95% CI)	*p*-value	β (95% CI)	*p*-value	β (95% CI)	*p*-value
24-h SBP						
Men	2.04 (0.44, 3.64)	.013	-		1.65 (0.01, 3.29)	.048
Log (Total catecholamine)	-		5.94 (1.62, 10.26)	.007	5.03 (0.62, 9.44)	.025
24-h DBP						
Men	3.78 (2.51, 5.04)	.001	-		3.55 (2.26, 4.85)	<.001
Log (Total catecholamine)	-		5.14 (1.67, 8.61)	.004	3.18 (−0.32, 6.67)	.075
Awake SBP						
Men	2.21 (0.55, 3.87)	.009	-		1.67 (−0.02, 3.36)	.053
Log (Total catecholamine)	-		7.79 (3.31, 12.26)	.001	6.86 (2.30, 11.43)	.003
Awake DBP						
Men	4.28 (2.97, 5.59)	<.001	-		3.97 (2.63, 5.31)	<.001
Log (Total catecholamine)	-		6.31 (2.71, 9.91)	.001	4.11 (0.50, 7.73)	.026
Asleep SBP						
Men	0.93 (−0.79, 2.65)	.289	-		1.02 (−0.75, 2.79)	.257
Log (Total catecholamine)	-		−0.19 (−4.85, 4.47)	.937	−0.75 (−5.52, 4.01)	.756
Asleep DBP						
Men	1.74 (0.39, 3.10)	.012	-		1.80 (0.41, 3.19)	.011
Log (Total catecholamine)	-		1.07 (−2.61, 4.76)	.567	0.08 (−3.67, 3.83)	.967

Note: Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure.
Model 1, Model 2, Model 3: Adjusted for age, body mass index, and antihypertensive drugs.
Total catecholamine concentrations were log-transformed.
β = Unstandardized coefficients.

95% CI 0.50–7.73, p = .026) were independently associated with awake DBP. Sex was independently associated with asleep DBP (β = 1.80, 95% CI 0.41–3.19, p = .011) (Table 3).

Receiver operating characteristic curve analysis was conducted to find the optimal cut-off value of 24-h urine total catecholamine. The cut-off value 63.9 μg/24 h was used to stratify 24-h urine total catecholamine into high- and low-level groups. Table 4 presents the estimated change (β) of 24-h BP parameters for 24-h urine total catecholamine and sex. The β values for 24-h SBP, 24-h DBP, awake SBP, and awake DBP were significantly increased in men and high-level 24-h urine total catecholamine group, in unadjusted and adjusted models. Although asleep DBP was significantly associated with sex and 24-h urine total catecholamine in the unadjusted model (p = .0387), it became insignificant in the adjusted model. Overall, sex and 24-h urine total catecholamine have a synergic effect on increases in the 24-h BP parameter, especially awake BP.

Considering interactions between sex and 24-h urine total catecholamine for 24-h BP parameters, there were significant interactions for 24-h SBP (p = .0601) and awake SBP (p = .0393) in the unadjusted model at p-value ≤.10 significance level. There were still interactions for awake SBP after adjustment for age, BMI, and all antihypertensive drugs (p = .0725).

3.2 | Propensity-matched cohort

Among 970 hypertensive patients, 801 took at least 1 antihypertensive drug and 169 did not take any antihypertensive drugs. Among 169 untreated hypertensive patients, men were younger (p = .005), had higher 24-h SBP (p = .013), 24-h DBP (p = .012), awake SBP (p = .012), and awake DBP (p = .006), compared to women. When comparing patient 24-h urine catecholamine excretion, men had higher epinephrine (p = .021), norepinephrine (p = .002), and total catecholamine (p = .008) than women (Table S1). In order to minimize possible confounding factors of SNS activity, propensity matching was performed in untreated hypertensive patients. In total, 43 men and 43 women were selected from 169 untreated hypertensive patients. All baseline characteristics were similar among the different sex groups, including age, BMI, office BP, and ambulatory BP. We consistently found that men had higher total catecholamine than women (p = .013) (Table 5).

We further analyzed the association between 24-h urine catecholamine levels (log-transformed) and 24-h ambulatory BP parameters. In men with untreated hypertension, 24-h urine total catecholamine levels were correlated with 24-h SBP (r = 0.308, p = .044), 24-h DBP (r = 0.410, p = .006), awake SBP (r = 0.330, p = .031), awake DBP (r = 0.436, p = .003), 24-h HR (r = 0.391,

TABLE 4 The interactions and synergic effects of sex and 24-h urine total catecholamine on 24-h ambulatory blood pressure in the total cohort

		24-h SBP		24-h DBP		Awake SBP		Awake DBP		Asleep SBP		Asleep DBP	
Sex	**Catecholamine**	**Estimate (β)**	***p*-value**	**Estimate (β)**	***p*-value**	**Estimate (β)**	***p*-value**	**Estimate (β)**	***p*-value**	**Estimate (β)**	***p*-value**	**Estimate (β)**	***p*-value**
Unadjusted model													
Women	Low	1.00	<.0001*	1.00	<.0001	1.00	<.0001**	1.00	<.0001	1.00	.075	1.00	.0387
Women	High	2.48		2.59		2.66		2.85		1.67		1.61	
Men	Low	3.96		4.19		4.33		4.70		2.34		2.21	
Men	High	5.44		5.78		5.99		6.56		3.01		2.82	
Adjusted model: with adjustment for age, BMI, and B-blockers													
Women	Low	1.00	.0071	1.00	<.0001	1.00	.0021	1.00	<.0001	1.00	.6171	1.00	.0752
Women	High	1.94		2.45		2.11		2.69		1.19		1.53	
Men	Low	2.88		3.90		3.22		4.91		1.38		1.77	
Men	High	3.82		5.35		4.34		7.13		1.56		2.01	
Adjusted model: with adjustment for age, BMI, and all antihypertensive drugs													
Women	Low	1.00	.0056*	1.00	<.0001	1.00	.0017*	1.00	<.0001	1.00	.5726	1.00	.0658
Women	High	1.98		2.48		2.15		2.72		1.21		1.55	
Men	Low	2.95		3.96		3.31		4.45		1.43		2.10	
Men	High	3.93		5.44		4.46		6.17		1.64		2.65	

Note: Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

p for interaction between sex and catecholamine

*$p < .1$.

**$p < .05$.

TABLE 5 Baseline characteristics of the patients according to sex in the propensity-matched cohort

	Men (*n* = 43)	Women (*n* = 43)	*p*-value
Age, years	40.9 ± 7.8	40.0 ± 7.0	.429
BMI, kg/m^2	26.3 ± 3.1	25.9 ± 3.6	.498
Office SBP, mm Hg	129.0 ± 14.1	127.3 ± 15.1	.610
Office DBP, mm Hg	87.7 ± 12.7	85.3 ± 13.4	.397
24-h SBP, mm Hg	126.5 ± 12.5	123.6 ± 14.5	.303
24-h DBP, mm Hg	85.4 ± 9.5	82.1 ± 12.1	.183
24-h HR, bpm	75.2 ± 10.9	75.7 ± 10.6	.829
Awake SBP, mm Hg	129.9 ± 12.9	126.9 ± 14.8	.316
Awake DBP, mm Hg	88.5 ± 9.9	84.4 ± 12.7	.122
Awake HR, bpm	79.1 ± 12.0	79.1 ± 11.4	.993
Asleep SBP, mm Hg	115.5 ± 13.6	113.9 ± 15.1	.571
Asleep DBP, mm Hg	75.4 ± 9.9	75.2 ± 11.7	.927
Asleep HR, bpm	62.7 ± 9.3	65.1 ± 9.3	.249
Urine catecholamine[a]			
Epinephrine, μg/24 h	8.1(5.9)	5.8(4.1)	.011
Norepinephrine, μg/24 h	39.3(15.2)	35.2(11.4)	.061
Total catecholamine, μg/24 h	49.5(19.3)	40.1(11.7)	.013

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

[a]Expressed as median and interquartile range.

TABLE 6 The association between 24-h urine total catecholamine and ambulatory blood pressure in the propensity-matched cohort

	Men (*n* = 43)		Women (*n* = 43)	
	r	*p-value*	*r*	*p-value*
24-h SBP	0.308	.044	0.239	.123
24-h DBP	0.410	.006	0.184	.238
24-h HR	0.391	.009	−0.016	.919
Awake SBP	0.330	.031	0.194	.213
Awake DBP	0.436	.003	0.155	.321
Awake HR	0.374	.014	−0.041	.795
Asleep SBP	0.217	.163	0.320	.036
Asleep DBP	0.294	.056	0.232	0.134
Asleep HR	0.477	.001	−0.005	.976

Note: Abbreviations: DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

Total catecholamine concentrations were log-transformed.

r = Pearson's correlation coefficients.

p = .009), awake HR (*r* = 0.374, *p* = .014), and asleep HR (*r* = 0.477, *p* = .001) (Table 6). However, in women with untreated hypertension, 24-h urine total catecholamine levels were only correlated with asleep SBP (*r* = 0.320, *p* = .036). There was no correlation between 24-h urine total catecholamine levels and 24-h SBP or 24-h DBP (Table 6).

In order to examine whether the effect of SNS activity on 24-h ambulatory BP was independent, multivariate linear regression was performed. In men with untreated hypertension, total catecholamine was independently associated with 24-h DBP (β = 28.54, 95% CI 9.26–47.83, *p* = .005), awake SBP (β = 27.37, 95% CI 0.06-54.68, *p* = .050), awake DBP (β = 30.89, 95% CI 11.09–50.70, *p* = .003), and asleep DBP (β = 21.94, 95% CI 0.77–43.11, *p* = .043). In women with untreated hypertension, total catecholamine was not associated with ambulatory BP parameters (Table 7).

4 | DISCUSSION

This study revealed that in a cohort of young hypertensive patients, men had higher SNS activity than women. Furthermore, SNS activity was independently associated with 24-h ambulatory BP in men rather than in women. These findings are consistent in the total cohort and propensity-matched untreated hypertensive patients.

Sex differences exist in CVD clinical manifestations, management, and outcomes.[9] In younger age groups, hypertension prevalence was higher in men than women. However, in the age group above 60 years, hypertension was more prevalent in women than in men.[3,4] The clinical characteristics of young hypertensive patients were unique and different, varying according to sex. A previous study revealed that serum triglyceride levels were correlated with BMI, serum cholesterol, and glucose levels in men, but not in women, suggesting the sex-specific presence of metabolic syndrome in young hypertensive patients.[12] In the present study, we found that hypertensive men had higher office BP, ambulatory BP, and BMI than hypertensive women.

Hypertension control rates are usually lower in young men than in young women.[3,4] Data from the National Health and Nutrition Examination Surveys in the USA showed that hypertension awareness, treatment, and control were lower among young adults (age, 18–39 years), especially in young adult men.[3] Data from the Korean National Health and Nutrition Examination Survey also showed that the overall hypertension control rate was lower in men (44.8%) than women (51.3%), especially in men <60 years.[4] These findings suggest that sex-specific approaches should be recommended for effective hypertension management.

There are great differences in the association between sex and SNS activity among different studies. Some studies showed higher SNS activity in men, compared to women, as measured by plasma or urinary catecholamines.[13,14] One study showed no sex difference.[15] In the Multi-Ethic Study of Atherosclerosis (MESA), however, women had higher urine norepinephrine and dopamine levels than men.[16] In the present study, we found that sex differences exist in stress hormone levels, as young hypertensive men had higher urinary catecholamines than young women. Different from the MESA study,[16] our study subjects were relatively young (age 20–50 years) and 24-h urine catecholamines were collected. The MESA study

TABLE 7 Linear regression for 24-h blood pressure in men and women with untreated hypertension in the propensity-matched cohort

	Men (*n* = 43)		Women (*n* = 43)	
	β (95% CI)	*p*-value	β (95% CI)	*p*-value
24-h SBP				
Log (Total catecholamine)	24.99 (−1.78, 51.76)	.066	23.48 (−28.18, 75.15)	.364
24-h DBP				
Log (Total catecholamine)	28.54 (9.26, 47.83)	.005	17.19 (−26.05, 60.43)	.426
Awake SBP				
Log (Total catecholamine)	27.37 (0.06, 54.68)	.050	13.49 (−39.28, 66.26)	.608
Awake DBP				
Log (Total catecholamine)	30.89 (11.09, 50.70)	.003	11.26 (−33.36, 55.89)	.613
Asleep SBP				
Log (Total catecholamine)	17.93 (−11.89, 47.75)	.231	46.07 (−7.07, 99.20)	.087
Asleep DBP				
Log (Total catecholamine)	21.94 (0.77, 43.11)	.043	29.57 (−12.62, 71.76)	.164

Note: Abbreviations: CI, confidence interval; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Adjusted for age and body mass index.

Total catecholamine concentrations were log-transformed.

β = Unstandardized coefficients.

included only 654 patients out of 6814 multi-ethnic participants with variable CVD risk factors. The mean age was 61.5 ± 10.1 years old. Moreover, urine was collected only for 12-h overnight; therefore, the data may not reflect daily stress exposures.[16] Our findings are further supported by a recent study of healthy normotensive adults in which SNS activity, based on the measurement of muscle sympathetic nerve activity (MSNA), was lower in women than men until age 50.[17]

Previous studies investigating the association between SNS activity and BP are conflicting.[18–21] One study revealed that urinary norepinephrine and epinephrine excretion rates are heritable, but not associated with office and ambulatory BP.[18] Another study revealed no relationship between 24-h urinary catecholamine metabolites and either 24-h SBP or clinic SBP.[19] The Medical Research Council's mild hypertension trial reported a correlation between clinic SBP and 24-h urine adrenaline and noradrenaline concentrations in controls, but not in hypertensive patients.[20] Data from 115 consecutive normotensive and mildly hypertensive volunteers showed that the SNS is involved in regulating circadian BP variations and urinary sodium excretion; urinary norepinephrine and epinephrine were significant predictors of dipping BP patterns.[21] Recently, a meta-analysis showed a direct and significant relationship between SNS activity, based on the measurement of MSNA, and office BP and 24-h ambulatory BPs.[7] In the present study, we also found that SNS activity, based on the measurement of 24-h urinary catecholamine, was correlated with 24-h ambulatory BP in a cohort of young Chinese hypertensive patients. Furthermore, we found that SNS activity was correlated with awake but not asleep BP in the total cohort. These findings suggest that there were more stress challenges during awake, which might increase SNS activity and result in higher BP.

Even though a previous study claimed that HR values were a marker of cardiac sympathetic function,[5] more recent research has found that they are not a reliable indicator of SNS activity.[6–8] A meta-analysis showed that HR was inversely correlated with MSNA,[7] which might be due to the combined effects of both sympathetic drive and vagal influences on the sinus node. A recent study demonstrated that patients with masked uncontrolled hypertension had higher out-of-clinic SNS activity than patients with controlled hypertension; patients with masked uncontrolled hypertension had similar 24-h HR, awake HR, and asleep HR when compared to patients with controlled hypertension.[8] In the present study, men had higher ambulatory BP but similar 24-h HR and awake HR than women in the total cohort. Importantly, we found that HR was positively correlated with SNS activity in the total cohort and the propensity-matched cohort, which was consistent with a previous study.[6] However, due to the contradictory results of the aforementioned meta-analysis,[7] further studies are still needed to investigate the relationship between HR and SNS activity.

Interestingly, we found that an association between SNS activity and BP was notable in hypertensive men rather than in

hypertensive women. Sex differences in SNS activity and BP had been reported in different populations.[22,23] One study conducted in 54 healthy young adults showed that resting MSNA was related to changes in mean arterial pressure in men but not women.[22] Another study compared changes in MSNA and cardiovascular variables during leg cycle exercise, with increased inspiratory muscle resistance, in seven men and eight women. During the leg cycle exercise with inspiratory resistive breathing, MSNA burst frequency increased, accompanied by an increase in mean arterial pressure in both men and women. However, women had lesser increase in mean arterial pressure and MSNA burst frequency than men.[23]

Although some studies showed that beta-blockers (BBs) are more frequently prescribed to women,[24] older studies have reported that BBs were more effective in men than in women.[24,25] Fletcher et al showed that BBs improved survival only in hypertensive men, but not in women.[25] Similarly, coronary events and mortality were reduced only in men in the β-Blocker Heart Attack Trial.[26] Recently, one animal study reported the sex effects of beta-1 adrenergic blocker, landiolol, on cardiac performance and energy metabolism in septic rats. Landiolol improved in vivo cardiac performance in septic male rats; however, deleterious effects were reported in females.[27] Our findings are also supported by sex differences in BB response.[25–27]

There are some possible reasons for the sex effects in SNS activity and BP. Sex hormones have unique impacts on hypertension development and affect women and men in different periods of their lives. Estrogen may modulate adrenergic reactivity of macrovasculature, resulting in weaker α-adrenergic vasoconstriction in women than men. One animal study revealed that vessels of females express more dilatory beta-adrenoceptors, which counteract the constrictive effects of alpha-adrenoceptors.[28] Further studies are needed to clarify our findings.

4.1 | Limitations

The present study has some limitations. First, we only enrolled relatively young hypertensive patients (age 20–50 years). Further studies are required to clarify whether these findings can be applied to older hypertensive patients. Second, we measured urinary catecholamines instead of urinary metanephrines or MSNA. In physiologic research settings, MSNA or norepinephrine spillovers are often used to assess autonomic system function.[29] Catecholamines are released into the bloodstream, and the kidneys filter a relatively constant proportion into urine, thus providing a noninvasive method to measure their levels.[30] In epidemiologic research and clinical practice, plasma and urinary catecholamines are used to assess autonomic activity. Although 24-h urinary metanephrine is a better indirect measurement to assess sympathetic activity than 24-h urinary catecholamines, urinary catecholamine measurement has been successfully applied to delineate altered sympathetic activity in various populations.[31,32] Therefore, the findings of this study are particularly relevant to clinical settings. Because 24-h urinary metanephrines can be used as a cross-check for 24-h urinary catecholamines, combining both methods will confirm our findings in the future. Thirdly, the study was not designed to measure BP or HR variabilities. Further studies with more accurate measurements of BP and HR variability are needed. Fourthly, our hypertensive patients were only the Chinese Han population in Taiwan. SNS activities may vary among different ethnicities.[32,33] Some previous studies have shown that catecholamines may be pivotal in racial variations in BP. For example, African Americans had better receptor sensitivity than European Americans.[33] Further studies are needed to verify the current findings in other ethnic cohorts.

5 | CONCLUSIONS

In young Chinese hypertensive patients, men had higher SNS activity than women, and SNS activity was independently correlated with 24-h ambulatory BP. The findings suggest that young hypertensive men may preferentially benefit from medications or interventional procedures that target sympathetic output to improve BP control and prevent the development of CVD.

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CONFLICT OF INTEREST

The authors declared no conflicts of interest.

AUTHOR CONTRIBUTIONS

Chin-Chou Huang was the main conductor of this study and contributed to the study conception and design, implementation, statistical analysis, interpretation, the preparation and finalization of the manuscript. Chia-Min Chung contributed to the study conception and design, implementation, statistical analysis, and the preparation of the manuscript. Hsin-Bang Leu, Po-Hsun Huang, Tao-Cheng Wu, and Liang-Yu Lin contributed to the study conception and design, and data collection. Shing-Jong Lin and Wen-Harn Pan contributed to the study conception and design. Jaw-Wen Chen contributed to the study conception and design, implementation, statistical interpretation, and the preparation of the manuscript. All authors approved the final manuscript for publication.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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