ORIGINAL RESEARCH

Impact of Percutaneous Transluminal Renal Angioplasty on Autonomic Nervous System and Natriuresis in Hypertensive Patients With Renal Artery Stenosis

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BACKGROUND: We investigated the early postoperative effect of percutaneous transluminal renal angioplasty on ambulatory blood pressure (BP) and the circadian characteristics of natriuresis and autonomic nerve activity.

METHODS AND RESULTS: A total of 64 patients with hypertension with hemodynamically significant renal artery stenosis (mean age, 60.0±21.0 years; 31.3% fibromuscular dysplasia) who underwent angioplasty were included, and circadian characteristics of natriuresis as well as heart rate variability indices, including 24-hour BP, low-frequency and high-frequency (HF) components, and the percentage of differences between adjacent normal R-R intervals >50 ms were evaluated using an oscillometric device, TM-2425, both at baseline and 3 days after angioplasty. In both the fibromuscular dysplasia and atherosclerotic stenosis groups, 24-hour systolic BP (fibromuscular dysplasia, −19±14; atherosclerotic renal artery stenosis, −11±9 mm Hg), percentage of differences between adjacent normal R-R intervals >50 ms, HF, brain natriuretic peptide, and nighttime urinary sodium excretion decreased (all *P*<0.01), and heart rate increased (both *P*<0.05) after angioplasty. In both groups, revascularization increased the night/day ratios of percentage of differences between adjacent normal R-R intervals >50 ms (both *P*<0.01) and HF, and decreased those of low frequency/HF (all *P*<0.05) and nighttime urinary sodium excretion (fibromuscular dysplasia, 1.17±0.15 to 0.78±0.09; atherosclerotic renal artery stenosis, 1.37±0.10 to 0.99±0.06, both *P*<0.01). Multiple logistic regression analysis indicated that a 1-SD increase in baseline low frequency/HF was associated with at least a 15% decrease in 24-hour systolic BP after angioplasty (odds ratio, 2.30 [95% CI, 1.03–5.67]; *P*<0.05).

CONCLUSIONS: Successful revascularization results in a significant BP decrease in the early postoperative period. Intrarenal perfusion might be a key modulator of the circadian patterns of autonomic nerve activity and natriuresis, and pretreatment heart rate variability evaluation seems to be important for treatment success.

Key Words: blood pressure monitoring ■ brain natriuretic peptide ■ heart rate variability ■ natriuresis ■ percutaneous transluminal renal angioplasty ■ renal artery stenosis

Renal artery stenosis is associated with secondary hypertension, which is often resistant to antihypertensive medication. The most common cause of renal artery stenosis is atherosclerotic stenosis (ARAS), and fibromuscular dysplasia (FMD) comprises most of the remaining causes. Treatment of hypertension because of renal artery stenosis includes medical therapy and revascularization. Previous randomized clinical trials, which compared medical therapy with percutaneous transluminal angioplasty (PTA) in patients with ARAS, could not prove the superiority of the latter for controlling hypertension and preserving

CLINICAL PERSPECTIVE

What Is New?

- This study demonstrated the effect of percutaneous transluminal angioplasty treatment on ambulatory blood pressure response, heart rate variability, natriuresis, and brain natriuretic peptide in patients with hypertension with hemodynamically significant renal artery stenosis.

What Are the Clinical Implications?

- Intrarenal perfusion might be a key modulator of the circadian pattern of autonomic nerve activity and natriuresis.
- Pretreatment evaluation of heart rate variability is important to screen for ideal candidates for renal percutaneous transluminal angioplasty treatment.

Nonstandard Abbreviations and Acronyms

%RR50	percentage of differences between adjacent normal R-R intervals >50 ms
ARAS	atherosclerotic renal artery stenosis
FMD	fibromuscular dysplasia
HF	high-frequency
LF	low-frequency
ln	log-transformed
PSV	peak systolic velocity
PTA	percutaneous transluminal angioplasty
SBP	systolic blood pressure

renal function[1–3]; however, these trials had significant design flaws,[4] and the selection of ideal candidates for PTA is a controversial topic.

In the mechanisms of development of renovascular hypertension, the renin–angiotensin system is generally recognized as the primary mediator; however, previous experimental evidence proved that efferent renal sympathetic nerve activity has an important role in the development and maintenance of elevated blood pressure (BP) by modulating renin secretion and renal tubular sodium reabsorption.[5] In renovascular patients with hypertension, the sympathetic nervous system is activated in relation to activation of the angiotensin system.[6–8]

Successful PTA may result in a significant BP decline relatively early[9]; however, evidence of a BP-lowering effect of PTA on out-of-office BP in the early postoperative period is limited. Other than inactivation of the renin–angiotensin system, the precise

pathophysiological mechanisms of the BP change after renal PTA remain unclear. In the present study, we first examined the early postoperative effects of renal PTA on ambulatory BP. Second, the pathophysiological mechanisms of BP changes were investigated through evaluation of cardiorenal indicators and the circadian characteristics of natriuresis and heart rate variability indices, which are the most promising markers of sympathetic or parasympathetic nerve activity,[10] and whether autonomic nerve activity is involved in this BP change was examined. Finally, we examined whether pretreatment assessment of autonomic nerve activity has clinical implications in the consideration of renal PTA in patients with hypertension with renal artery stenosis.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. The study protocol was approved by the ethics committee of our institution (M28-124). All of the subjects enrolled in this study were Japanese and gave informed consent to participate in this study.

Study Subjects

This study enrolled 64 patients with hypertension with hemodynamically significant renal artery stenosis who underwent renal PTA between April 2011 and January 2019 at our institution (the National Cerebral and Cardiovascular Center), and all patients included in this study were in stable sinus rhythm. From 2000 onward, all of the patients with hypertension who had been referred to our hospital attended the renal sonographic laboratory, and renal sonographic data were routinely collected.[11–13] In our hospital, PTA treatment was recommended for patients with hypertension with hemodynamically significant renal artery stenosis with any of the following criteria: (1) FMD with hypertension, (2) resistant hypertension with failure of or intolerance to antihypertensive medication, (3) recurrent heart failure or sudden-onset flash pulmonary edema, or (4) progressive renal function decline because of bilateral lesions or a solitary kidney. Hemodynamically significant renal artery stenosis in this study was defined as >80% confirmed by digital subtraction angiography for ARAS, or resting mean translesional systolic gradient ≥20 mm Hg for FMD.[14,15] Hypertension was defined as systolic BP (SBP) ≥140 mm Hg or diastolic BP ≥90 mm Hg on at least 2 separate office visits or receiving antihypertensive treatment. Other inclusion criteria were de novo renal artery stenosis, good-quality renal sonographic recordings, and kidney length of the affected side ≥8.0 cm. Exclusion criteria were mild-to-moderate renal artery stenosis, non–sinus rhythm,

receiving hemodialysis or erythropoietin therapy, previous kidney transplantation, life expectancy of <1 year, known hemorrhagic diathesis or hypercoagulable state, contraindication to receiving heparin, myocardial infarction and/or stroke within 30 days, current pregnancy, and malignancy.

Clinical Characteristics

Basal measurements were performed on the 2 days before PTA. After overnight fasting, venous blood sampling from all subjects was performed. Height and body weight were measured, and body mass index was calculated. Estimated glomerular filtration rate was calculated using the Japanese coefficient-modified Chronic Kidney Disease Epidemiology Collaboration equation in milliliters per minute per 1.73 meters squared.[16,17] Daytime (6:00 AM to 9:00 PM) and nighttime (9:00 PM to 6:00 AM) urine samples were collected to estimate the circadian characteristics of urinary creatinine and sodium excretion rates as well as urine volume, both 2 days before and 3 days after renal PTA. All patients consumed a standardized diet that contained 100 mmol/d of sodium during the study period. Brain natriuretic peptide was measured by a validated chemiluminescent immunoassay (sensitivity 5.8 pg/mL; Abbott Diagnostics) both 2 days before and 3 days after renal PTA. Diabetes was defined according to the American Diabetes Association criteria.[18] Smoking status was determined by interview and defined as never smoker, former smoker (smoked ≥100 cigarettes in his/her lifetime, but had not smoked for >1 year at the time of interview), and current smoker. Previous cardiovascular disease was defined as a history of stroke, myocardial infarction, or heart failure requiring hospitalization.

Diagnostic and Revascularization Procedures

Ultrasonographic examinations were performed using duplex Doppler sonography in the supine or lateral position; the ultrasonographic procedure that we adopted has been described previously.[11–13] After Doppler angle correction by <50°, peak systolic velocity (PSV) was measured in the aorta and at the site of the stenosis, and was interpreted as indicative of stenosis when the renal/aortic ratio within the stenotic lesion was ≥3.5, and when the absolute PSV within the lesion was >180 cm/s with poststenotic turbulence.[19]

An intra-arterial bolus of 3000 to 5000 U of heparin was administered during angiography. The procedure was performed in a standard fashion via the transfemoral approach, with angiographic images at different angles to best visualize the renal artery. The severity of stenosis was assessed by the percent degree of stenosis calculated as minimum lumen diameter divided by reference lumen diameter multiplied by 100 in ARAS, or by the resting translesional mean pressure gradient in FMD. FMD was considered to be present in patients with a nonatherosclerotic stenotic lesion affecting the trunk or branches of the renal arteries in the absence of aortic wall thickening or biochemical evidence of inflammation, and in the absence of known syndromic arterial disease such as type 1 neurofibromatosis or Alagille syndrome. ARAS was defined as a reduction in the luminal diameter of the renal artery within 1 cm of the aortic wall in the presence of atherosclerotic change in the aorta, detected by digital subtraction angiography. Bilateral stenosis was defined as stenosis on both sides, unilateral stenosis with contralateral occlusion, or a solitary kidney with stenosis.

The first-line revascularization technique in FMD-related renal artery stenosis was PTA without stenting, and in ARAS was PTA with stenting. Balloons were sized to the diameter of the normal vessel, and the patient's symptoms were assessed during each balloon inflation. A balloon expandable stent (Palmaz, Palmaz Genesis, or Palmaz Corinthian; Cordis, Miami Lakes, FL) was inserted at minimum balloon inflation pressure of 6 to 13 atm. In FMD, stenting was performed following PTA if needed because of periprocedural dissection. The final diameter of the stent was determined by the diameter of the fully inflated delivery balloon. Proper positioning of the stent was verified in multiple fluoroscopic views, and the goal was to reduce the stenosis to <30% angiographic stenosis and abolish the translesional pressure gradient to 0. To confirm success of the intervention, post-PTA arteriography of the renal artery was performed, and if needed, the pressure gradient was also assessed.

For all patients, 81 to 100 mg aspirin and additional antiplatelet agents (clopidogrel or an alternative) were administered on the day of PTA.

Office and Ambulatory BP Measurements and Power-Spectral Analysis of R-R Intervals

Office BP was measured twice by a physician, 1 minute apart, in each patient, with an appropriate arm cuff and a sphygmomanometer on the left arm after a resting period of ≥10 minutes in the sitting position; the mean of the 2 measurements was used.

Ambulatory brachial BP and indices of heart rate variability (low-frequency [LF] component, high-frequency [HF] component, and the ratio of LF to HF [LF/HF]) were obtained every 30 minutes using a commercially available, validated platform that uses established methodology, the TM-2425 (A & D, Tokyo, Japan), a noninvasive, automated oscillometric ambulatory BP monitoring device, both 2 days before and 3 days after renal PTA. This device satisfied the criteria

of the Association for the Advancement of Medical Instrumentation and the British Hypertension Society,[20] and the usefulness of this recorder in clinical hypertension research was previously reported[20–23]; the patients were asked to carry the device for 25 hours, and the first hour of recordings were omitted from the analysis.

The TM-2425 monitored R-R interval of the electrocardiogram. The procedures for power-spectral analysis of R-R intervals with this device were previously reported in detail.[21] Briefly, electrocardiogram tracings were obtained with a pericardial lead (V5). All R-R intervals were recorded at a resolution of 7.8 ms throughout a 24-hour period. Ectopic beats and artifacts were excluded automatically. After these procedures, spectral R-R interval variability was computed with the autoregressive model from every 5-minute block over a 24-hour period. The ranges of 0.05 to 0.15 Hz and 0.15 to 0.40 Hz were computed as the LF component and HF component, respectively. The percentage of differences between adjacent normal R-R intervals >50 ms (%RR50) was one of the time domain indices and was calculated as a marker of parasympathetic nerve activity.[10] Heart rate was calculated on the basis of continuous electrocardiogram recordings. Physical activity was measured by the ceramic acceleration-pickup sensor incorporated into the BP recorder. The quantity of acceleration was detected at 18-ms intervals at frequencies in the range 1 to 10 Hz, with a sensitivity of 4.2×10^{-4} g per bit, and cumulative values for 1-minute intervals were recorded for 24 hours.[23]

Statistical Analysis

Summary statistics are presented as mean±standard deviation (SD) for continuous variables and percentage for categorical variables unless otherwise specified. Log transformation was performed before analysis for variables with a skewed distribution. The subjects were divided into 2 groups according to whether they had FMD or ARAS, and then the significance of any differences between the groups was evaluated using an unpaired t test. Differences in variables from before PTA to 3 days after PTA are presented as absolute change±SD. The Wilcoxon signed rank test was used to compare paired measurements within groups before and after PTA, and the Friedman test was used to determine the significance of differences in parameters induced by PTA between subgroups. The correlations among percent change in 24-hour SBP after PTA and baseline heart rate variability indices were obtained by the least-squares method. Logistic regression analysis was used to determine the odds ratio (OR) of –15% or more change in 24-hour SBP after PTA. Multivariate stepwise regression analysis (forward–backward stepwise selection) was performed to identify significantly associated determinants of percent change in 24-hour

SBP after PTA or of a –15% or more change in 24-hour SBP after PTA; probability criteria to be entered or excluded from the models in stepwise regression were set at 0.05 and 0.1, respectively. All P values were 2-sided, and those <0.05 were considered statistically significant. All calculations were performed using a standard statistical package (SPSS version 24.0; IBM, Armonk, NY).

RESULTS

Baseline Characteristics

Baseline clinical characteristics of the study subjects are listed in Table 1. Mean age was 60.0±21.0 years (range, 16–85 years), and 53.1% were men. As expected, patients with FMD showed a significantly lower male ratio, lower prevalence of previous cardiovascular disease, and younger age than those with ARAS; however, baseline office SBP and urinary albumin/creatinine ratio were not significantly different between the groups. Major complications, including hemorrhage, dissection, stent migration, vessel thrombosis, and emboli, were not seen in any patient, and no patient with FMD received stenting. In patients with both FMD and ARAS, PSV and renal/aortic ratio had decreased significantly at early assessment within 5 days after PTA (FMD: PSV, 86±38 cm/s; renal/aortic ratio, 1.04±0.80; ARAS: PSV, 80±69 cm/s; renal/aortic ratio, 1.89±0.57; P<0.01, respectively).

Effects of PTA on 24-Hour BP and Heart Rate

At baseline, except for nighttime values of SBP and heart rate, patients with FMD showed higher ambulatory BP and heart rate than those in patients with ARAS (Table 2 and Figure 1). Three days after PTA, in both FMD and ARAS, all ambulatory BP parameters had decreased (all P<0.01), and heart rate had increased (all P<0.05). Except for nighttime SBP (P=0.11), BP changes in FMD were greater than those in ARAS (all P<0.01), but changes in heart rate did not differ between the groups (daytime: P=0.47, nighttime: P=0.94). At both baseline and after PTA, physical activity quantified by an acceleration sensor did not differ between the groups and did not change significantly.

Effects of PTA on Heart Rate Variability Indices

Baseline LF and 24-hour LF/HF in patients with FMD were higher than those in patients with ARAS (Table 3). In both groups, %RR50 as well as HF decreased after PTA, but 24-hour LF in FMD, nighttime LF and 24-hour LF/HF in patients with ARAS, and nighttime LF/HF in

Table 1. Baseline Clinical Characteristics of Study Subjects

Variables	Total	FMD	ARAS
No.	64	20	44
Age, y	60.0±21.0	32.0±11.8	72.8±7.2[*]
Men, %	53.1	10.0	72.7[*]
Body mass index, kg/m^2	23.1±3.6	20.8±3.2	24.1±3.4[*]
Former or current smoker, %	62.5	25.0	79.5[*]
Duration of hypertension, y	11.5±10.8	5.8±7.1	14.1±11.5[*]
Previous CVD, %	45.3	0	65.9[*]
Diabetes, %	20.3	0	29.6[*]
Office systolic BP, mm Hg	148±24	154±26	144±22
Office diastolic BP, mm Hg	82±16	92±13	77±15[*]
Office heart rate, bpm	70±16	75±17	67±15
LDL-cholesterol, mmol/L	2.75±0.74	2.91±0.90	2.70±0.69
Hemoglobin A1c, %	5.54±0.61	5.13±0.47	5.74±0.58[*]
eGFR, mL/min per 1.73 m^2	58.1±30.2	94.1±20.7	41.8±16.6[*]
Urinary albumin/creatinine ratio, mg/g creatinine	317.5±868.9	46.0±77.6	443.8±1029.7
hs-CRP, mg/L	3.45±7.49	0.69±1.01	4.66±8.72
Left kidney, cm	10.4±1.2	10.7±1.2	10.2±1.2
Difference in left/right kidney size, cm	1.1±1.0	1.0±0.9	1.2±1.0
Renal aortic ratio	5.03±2.14	4.20±1.44	5.52±2.29[†]
PSV in segments with RAS, cm/s	308±86	326±91	301±85
Severity of stenosis, mm Hg for FMD, % for ARAS	…	57.6±24.4	87.4±10.9
PTA for bilateral RAS, %	12.5	10.0	13.6
No. of antihypertensive drugs	2.3±1.3	1.3±1.0	2.7±1.2[*]
Statin use, %	50.0	5.0	70.5[*]

Values are mean±SD. ARAS indicates atherosclerotic renal artery stenosis; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; FMD, fibromuscular dysplasia; hs-CRP, high-sensitivity C reactive protein; LDL, low-density lipoprotein; PSV, peak systolic velocity; PTA, percutaneous transluminal angioplasty; and RAS, renal artery stenosis.

[*]$P<0.01$ and [†]$P<0.05$ vs FMD.

both groups did not change significantly; however, no significant difference in change in heart rate variability indices between the groups was found.

Figure 2 shows the effect of PTA on night/day ratios of heart rate variability indices. In both groups, night/day ratios of %RR50 and HF increased, and that of LF/HF decreased after PTA, and no significant difference in changes in night/day ratios of heart rate variability indices between the groups was found.

Effects of PTA on Natriuresis and Brain Natriuretic Peptide

Except for baseline 24-hour urinary creatinine excretion rate, baseline nighttime urinary creatinine excretion rate as well as baseline urinary sodium excretion rate did not differ between the groups. In both groups, urinary creatinine as well as sodium excretion rate in the nighttime period decreased after PTA, and no significant difference in these changes between groups was found (Table 3).

Figure 2 shows the effect of PTA on night/day ratios of creatinine and sodium excretion, and brain natriuretic peptide. In both groups, brain natriuretic peptide and night/day ratios of creatinine and sodium excretion decreased after PTA.

Predictive Value of Baseline Heart Rate Variability Indices

We examined the correlations between percent change in 24-hour SBP (FMD: −11.9±8.2% versus ARAS: −7.6±9.3%, $P<0.01$) and baseline heart rate variability indices, and found that percent change in 24-hour SBP after PTA was correlated with baseline log-transformed (ln) %RR50, ln LF, ln HF, and ln LF/HF (Figure 3). The results of multivariate stepwise regression analysis suggested that baseline 24-hour SBP and ln LF/HF were associated with percent change in 24-hour SBP after PTA (Table 4).

After PTA, a total of 10 (6 FMD) patients had a decrease in SBP of >15%. Univariate logistic regression

Table 2. BP, Heart Rate, and Physical Activity Before and Changes After Transluminal Renal Angioplasty

	FMD	ARAS
Daytime		
Systolic BP, mm Hg		
Baseline	151±23	138±14*
After PTA	132±14	128±14
Change after angioplasty	−19±14	−10±9*
Diastolic BP, mm Hg		
Baseline	91±16	73±9*
After PTA	80±12	69±8*
Change after angioplasty	−11±11	−4±4*
Heart rate, beats/min		
Baseline	67±11	60±10†
After PTA	69±10	64±10
Change after angioplasty	2±4	4±11
Physical activity, g/min		
Baseline	0.014±0.011	0.009±0.004
After PTA	0.012±0.008	0.010±0.005
Change after angioplasty	−0.002±0.08	0.001±0.004
Nighttime		
Systolic BP, mm Hg		
Baseline	144±24	134±17
After PTA	125±15	121±15
Change after angioplasty	−19±15	−13±12
Diastolic BP, mm Hg		
Baseline	84±17	71±9*
After PTA	69±13	64±8*
Change after angioplasty	−14±11	−7±6*
Heart rate, beats/min		
Baseline	61±12	58±10
After PTA	63±13	59±10
Change after angioplasty	2±5	2±9
Physical activity, g/min		
Baseline	0.003±0.003	0.002±0.002
After PTA	0.003±0.003	0.002±0.002
Change after angioplasty	−0.001±0.003	0.001±0.002

*$P<0.01$ and †$P<0.05$ vs FMD. Values were log-transformed for analysis. ARAS indicates atherosclerotic renal artery stenosis; BP, blood pressure; FMD, fibromuscular dysplasia; g/min, gravitational acceleration/min, and PTA, percutaneous transluminal angioplasty.

analysis found that age (OR, 0.83 for 1-SD increase [7.1 years for FMD, 11.2 years for ARAS [95% CI, 0.69–0.99]; $P=0.048$), FMD (OR, 4.29 for yes [95% CI, 1.07–18.97]), and baseline 24-hour ln LF/HF (OR, 2.16 for 1-SD increase [0.34 for FMD, 0.26 for ARAS] [95% CI,

1.02–5.31]; both $P<0.05$) were significantly associated with a −15% or more change in 24-hour SBP after PTA. The results of multivariate stepwise logistic regression analysis suggested that FMD as well as baseline ln LF/HF were associated with a −15% or more change in 24-hour SBP after PTA (Table 4).

DISCUSSION

The present study demonstrated that in both FMD and ARAS, a significant ambulatory BP decrease and heart rate increase were found 3 days after PTA. In both groups, %RR50, HF, nighttime urinary sodium excretion rate, and brain natriuretic peptide decreased after revascularization. In addition, revascularization increased the night/day ratios of %RR50 and HF, and decreased those of LF/HF and urinary creatine and sodium excretion. Baseline ln %RR50 and heart rate variability indices were correlated with percent change in 24-hour SBP after PTA, and baseline LF/HF was an independent predictor of a −15% or more change in 24-hour SBP after PTA.

Our results indicate that successful PTA results in a significant out-of-office BP decrease in the early postoperative period after PTA. Measurement of serum brain natriuretic peptide level is widely used in the diagnosis of heart failure,[24] and provides information about the intravascular volume status.[25] Nocturnal sodium excretion is associated with BP level.[26] Therefore, apart from inactivation of the renin–angiotensin system, the rapid BP decline after PTA seems to be induced via decreased volume status and nocturnal natriuresis.

Of the heart rate variability indices applied in this study, %RR50 and HF are known to be markers of parasympathetic nerve activity, and LF/HF is considered to mirror sympathovagal balance or to reflect sympathetic modulation. With respect to the LF component, controversy exists as to whether LF is a quantitative marker of sympathetic modulation or reflects both sympathetic activity and vagal activity.[10] Physical activity is a major factor influencing autonomic nerve activity, but in this study, it was not significantly changed by PTA. Our findings of the serial changes in autonomic activities indicated that sympathetic nerve activity other than 24-hour LF/HF was unchanged in patients with FMD, and in both groups, parasympathetic nerve activity decreased after PTA. Decreased BP and volume status could affect the arterial baroreflex sensors located in the carotid sinus and the aortic arch by regression of the vessel wall, and lead to a decrease in afferent input to central autonomic nuclei. These sympathetic influences act in conjunction with parasympathetic influences on the sinoatrial node to increase heart rate.[27] Therefore, our obtained results of decreased parasympathetic nerve activity and increased heart rate after PTA can be attributed to the
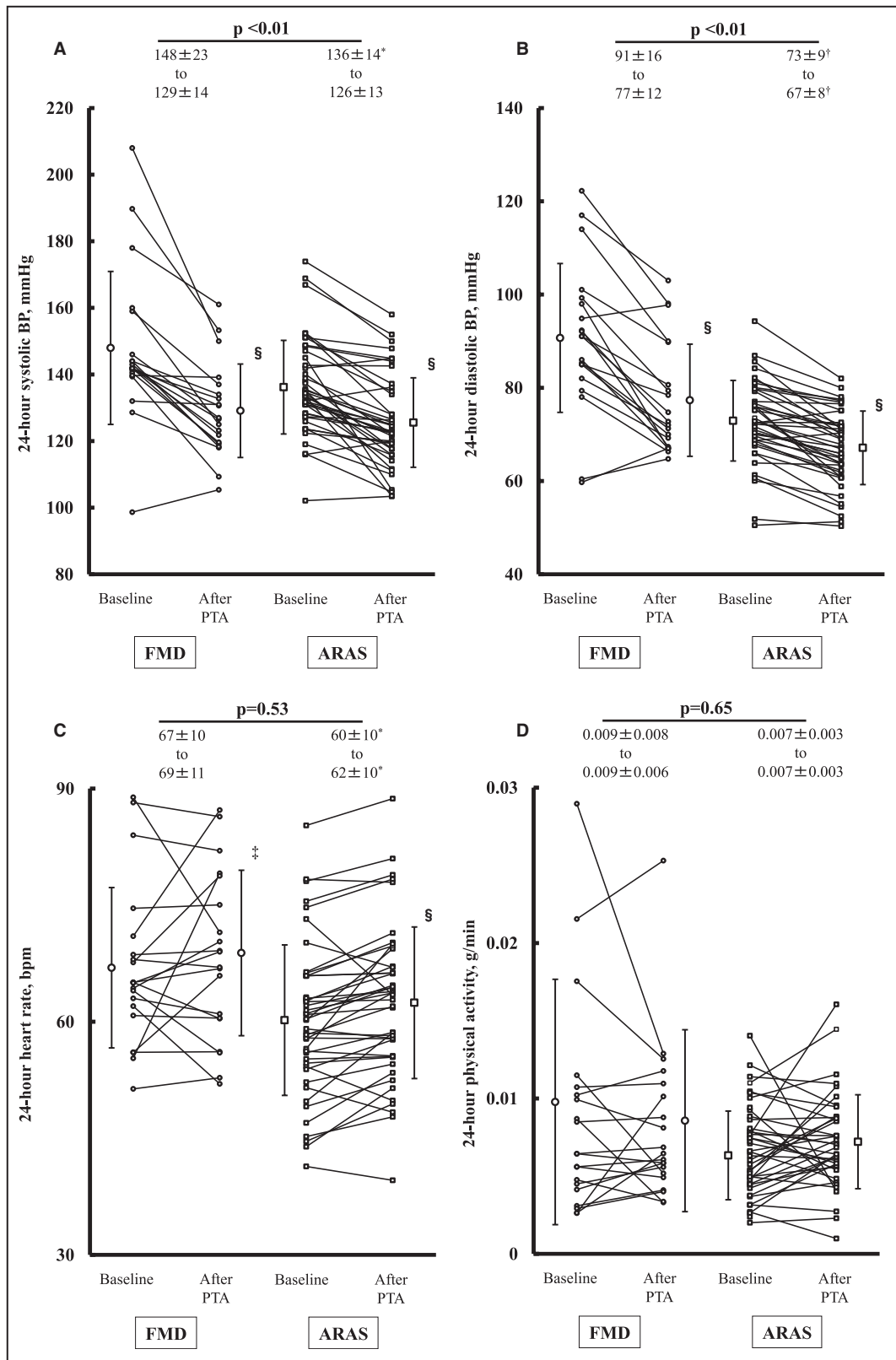
Figure 1. **Changes in 24-hour systolic (A) and diastolic (B) blood pressure, heart rate (C), and physical activity (D) by renal angioplasty.**

Data are presented as individual plots and mean±SD. Open circles indicate patients with FMD. Open squares indicate patients with ARAS. ARAS indicates atherosclerotic renal artery stenosis; BP, blood pressure; FMD, fibromuscular dysplasia; and PTA, percutaneous transluminal angioplasty. *$P<0.05$ and †$P<0.01$ vs FMD. ‡$P<0.05$ and §$P<0.01$ vs baseline.

Table 3.   Time Domain and Frequency Domain Measures of Heart Rate Variability and Urinary Creatinine and Sodium Excretion Before and After Transluminal Renal Angioplasty

	Baseline	After PTA	P value*	P value†
%RR50, %				
24-h				
FMD	10.80±6.76	7.05±5.97	<0.01	0.79
ARAS	9.02±8.84	5.78±5.99	<0.01	
Nighttime				
FMD	11.83±7.27	9.71±7.63	<0.05	0.89
ARAS	8.33±9.08	5.92±6.62‡	<0.05	
LF, ms²				
24-h				
FMD	118.3±86.2	101.2±82.6	0.18	0.52
ARAS	98.8±143.4‡	65.8±96.8‡	<0.01	
Nighttime				
FMD	123.4±95.6	96.5±90.8	0.048	0.55
ARAS	102.7±171.6‡	97.7±215.9‡	0.08	
HF, ms²				
24-h				
FMD	125.8±105.8	88.3±88.4	<0.01	0.55
ARAS	147.0±241.5	81.9±121.5	<0.01	
Nighttime				
FMD	169.1±144.6	126.8±121.5	<0.05	0.74
ARAS	154.1±258.9	137.9±372.5‡	<0.05	
LF/HF				
24-h				
FMD	2.16±0.77	2.51±1.26	<0.01	0.29
ARAS	1.78±0.45‡	1.90±0.59‡	0.08	
Nighttime				
FMD	1.74±0.48	1.88±0.82	0.62	0.63
ARAS	1.83±0.73	1.76±0.59	0.78	
Urinary creatinine excretion rate, mg/h				
24-h				
FMD	66.9±34.3	51.8±22.0	<0.05	0.10
ARAS	50.2±22.0‡	46.4±24.5	0.14	
Nighttime				
FMD	75.6±53.5	40.8±24.4	<0.01	0.08
ARAS	56.4±35.3	40.7±19.3	<0.01	
Urinary sodium excretion rate, mmol/h				
24-h				
FMD	4.85±2.20	5.08±2.36	0.52	0.10
ARAS	4.97±2.06	4.11±1.87	<0.05	
Nighttime				
FMD	5.18±2.91	3.75±2.01	<0.05	0.61
ARAS	5.55±3.45	3.66±1.69	<0.01	

%RR50 indicates the percentage of differences between adjacent normal R-R intervals >50 ms; ARAS, atherosclerotic renal artery stenosis; FMD, fibromuscular dysplasia; HF, high-frequency; LF, low-frequency; PTA, percutaneous transluminal renal angioplasty.

*P values of Wilcoxon signed-rank test.

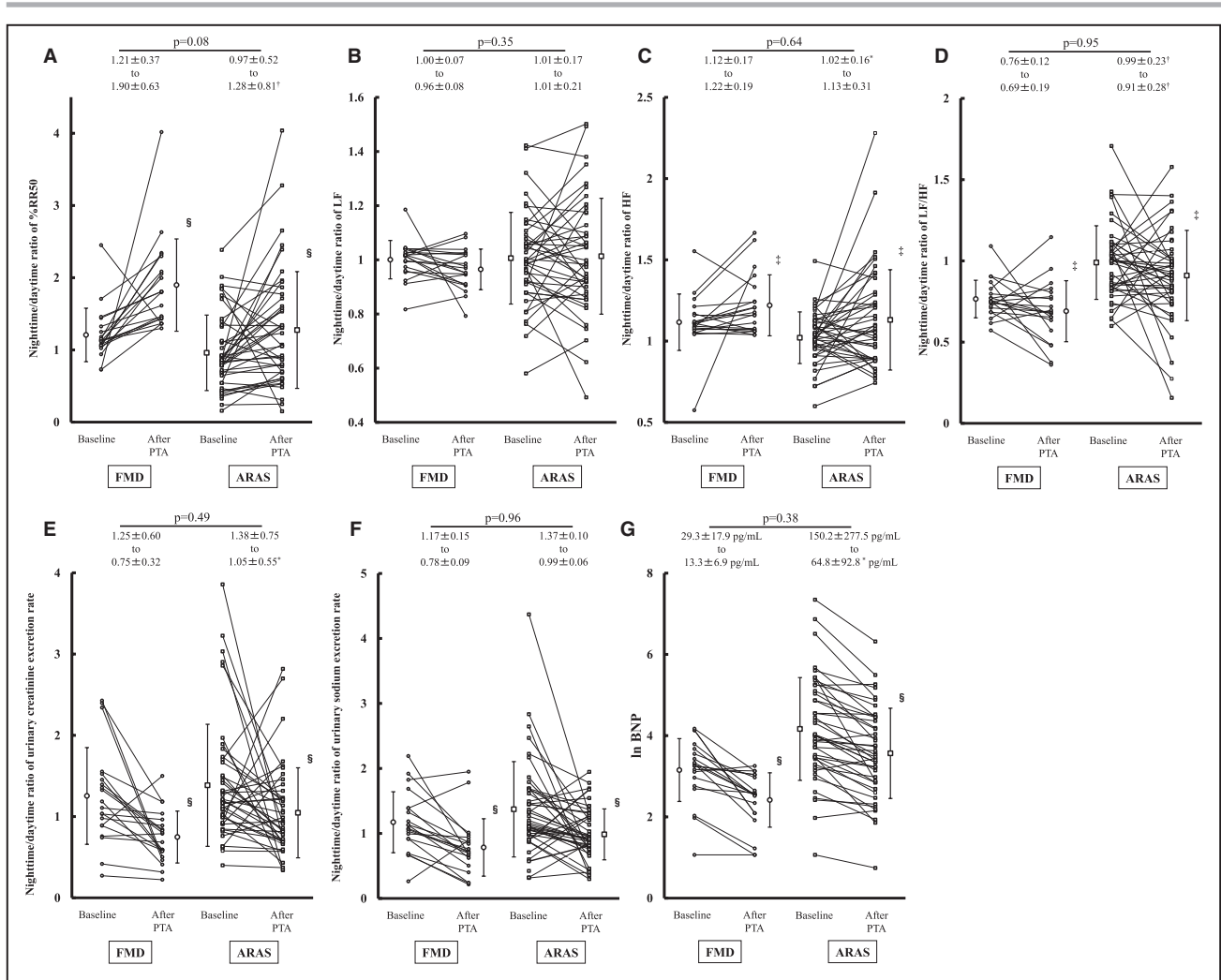†P values of Friedman test.

‡P<0.05 vs FMD.

Figure 2. Changes in night/day ratios of %RR50 (A), LF (B), HF (C), LF/HF (D), urinary creatinine (E) and sodium (F) excretion, and brain natriuretic peptide (G) by PTA.

Data are presented as individual plots and mean±SD. Open circles indicate patients with FMD. Open squares indicate patients with ARAS. %RR50 indicates the percentage of differences between adjacent normal R-R intervals >50 ms; ARAS, atherosclerotic renal artery stenosis; BNP, brain natriuretic peptide; FMD, fibromuscular dysplasia; HF, high frequency; LF, low frequency; ln, log-transformed; and PTA, percutaneous transluminal renal angioplasty. *$P<0.05$ and †$P<0.01$ vs FMD. ‡$P<0.05$ and §$P<0.01$ vs baseline.

reflex activation brought about by the unloading of arterial baroreceptors in response to an acute BP drop or volume loss.[28,29]

On the other hand, our findings might be opposite to the generally accepted concept that sympathetic and parasympathetic nerve activity exhibit reciprocal fluctuation. Although decreased muscle sympathetic nerve activity by renal PTA has been reported,[8] in this study, we could not find common changes in cardiac sympathetic nerve activity indices after PTA. The concept of a central nervous system set point that is separate from the baroreflex and involves central autonomic mechanisms has been proposed. These are central neural mechanisms that set the BP level by providing input to sympathetic promotor neurons in the rostral ventrolateral medulla via mechanisms

independent of baroreceptor afferent input.[30,31] Sympathetic nerve activity usually increases in the first few days after the administration of antihypertensive drugs.[29] On the other hand, muscle sympathetic nerve activity is not necessarily increased by lifestyle modifications; it is reduced by body weight loss and increased by a low salt diet, though these modifications reduce BP.[32] Reduced volume status and natriuresis by PTA might affect cardiac sympathetic nerve activity in a conflicting manner. Our findings may lead to the notion that cardiac autonomic nerve activity seems to be involved in the mechanism of the acute BP fall in the early postoperative period, but might act in an opposing manner by decreasing parasympathetic nerve activity and increasing or not changing sympathetic nerve activity.
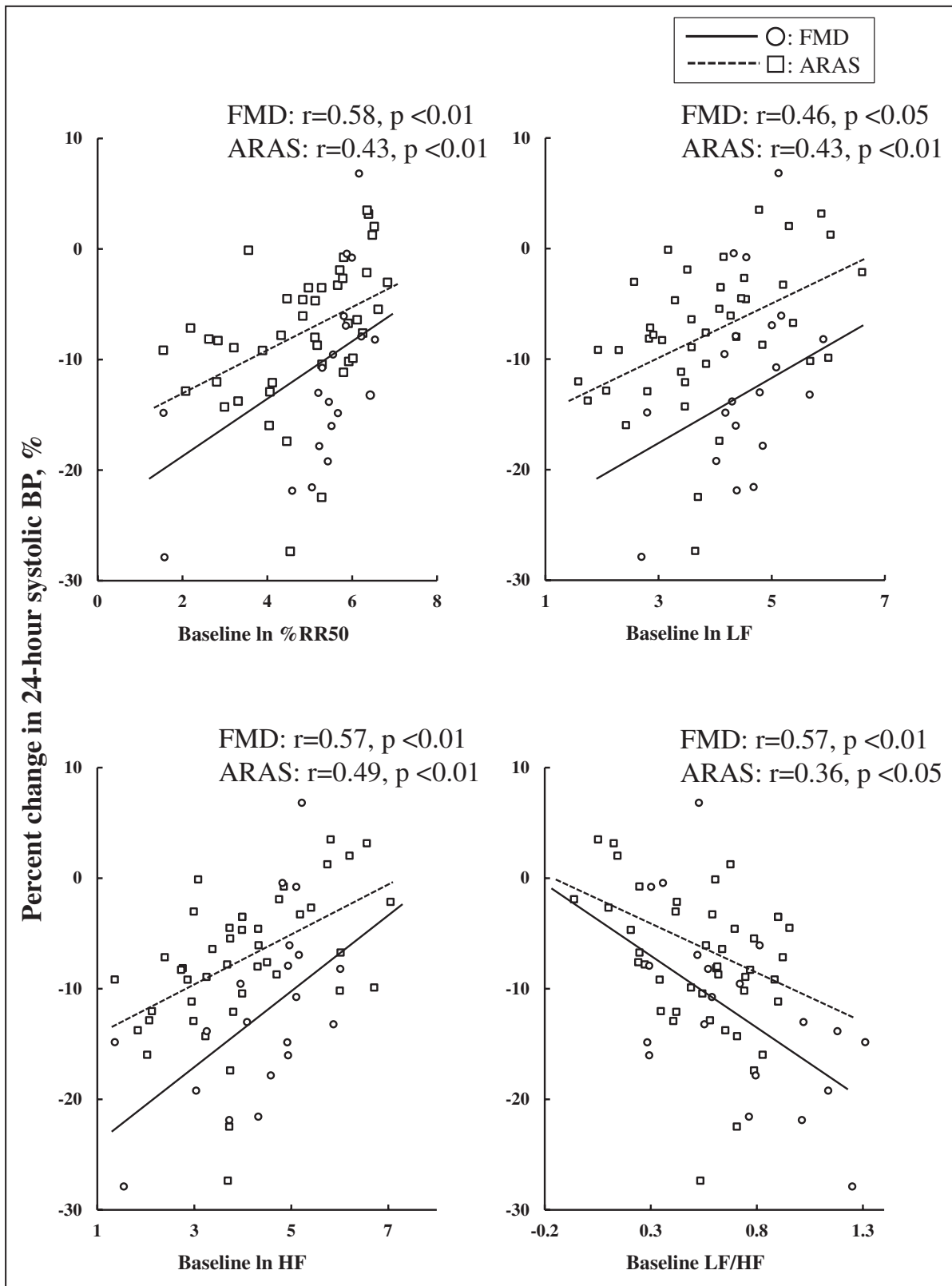
Figure 3. **Relationship between baseline ln %RR50 (A), ln LF (B), ln HF (C), and LF/HF (D), and percent change in systolic blood pressure after PTA.**
Open circles indicate patients with FMD. Open squares indicate patients with ARAS. %RR50 indicates the percentage of differences between adjacent normal R-R intervals >50 ms; ARAS, atherosclerotic renal artery stenosis, BP, blood pressure; FMD, fibromuscular dysplasia; HF, high frequency; LF, low frequency; ln, log-transformed; and PTA, percutaneous transluminal renal angioplasty.

Table 4. Multiple Stepwise Regression Analysis

Variables associated with percent change in 24-hour SBP after PTA , R^2=0.369			
Variable	β	95% CI	*P* value
Baseline 24-h SBP	−0.395	−0.247 to −0.068	<0.001
Baseline 24-h ln LF/HF	−0.325	−13.145 to −2.413	<0.01
Variables associated with –15% or more change in 24-hour SBP after PTA, R^2=0.192			
Variable, unit of increase	Odds ratio	95% CI	*P* value
FMD, yes	4.66	1.10–22.34	<0.05
Baseline 24-h ln LF/HF, 1 SD (0.34 for FMD, 0.26 for ARAS)	2.24	1.03–5.67	<0.05

ARAS indicates atherosclerotic renal artery stenosis; FMD, fibromuscular dysplasia; ln LF/HF, log-transformed low-frequency/ high-frequency; PTA, percutaneous transluminal renal angioplasty; and SBP, systolic blood pressure.

In normal subjects, autonomic nerve activity exhibits a circadian pattern, with higher sympathetic nerve activity in the daytime and higher parasympathetic nerve activity at nighttime. It is also well known that hypertensive subjects have a blunted circadian pattern of sodium excretion compared with normotensive subjects, with a greater fraction of daily sodium output occurring at night.[26] In this study, the night/day ratio of sodium excretion and heart rate variability indices other than LF showed a significant change after PTA and moved closer to a normal pattern. Thus, the circadian changes in the autonomic nervous system as well as sodium excretion in patients with renovascular hypertension seem to be disturbed, and renal perfusion could be one of the key modulators of these mechanisms. On the other hand, 24-hour sodium excretion in patients with ARAS decreased after PTA, and we cannot exclude the possibility that there might be different limits to sodium excretory capacity between subjects and that low sodium intake because of a hospital diet might have affected these results.

Previous studies on predictors of improved out-of-office BP after PTA are limited,[33–35] but in most clinical guidelines, the indications for renal PTA consistently include hemodynamically significant renal artery stenosis and hypertension.[14,36,37] Studies of translesional pressure gradient in human subjects indicate that an aortic–renal pressure gradient of 10% to 20% is necessary to detect increased renin release,[38] which corresponds to a translesional peak gradient of at least 20 mm Hg and luminal stenosis of at least 70%.[39] All patients included in this study met the criteria for stenosis severity, but the BP-lowering effect of PTA varied among patients. The pathophysiology of renovascular hypertension involves increased sympathetic nerve activity, and accumulating evidence suggests interactions between renal nerves and the renin–angiotensin–aldosterone system, and the renin–angiotensin–aldosterone system itself is influenced and modulated by the sympathetic nervous system.[5] Sympathetic input to other vascular beds may also occur, and increased total body norepinephrine spillover and muscle sympathetic nerve activity have been reported in renovascular patients with hypertension.[6,8] Therefore, patients with hypertension with both severe renal artery stenosis and increased sympathetic nerve activity may be suggested to have pathophysiologically accepted renovascular hypertension, and could be ideal candidates for renal PTA treatment. If our results were confirmed in a subsequent randomized clinical trial, measurement of autonomic nerve activity could serve as a widely available biomarker for patients who may benefit clinically from renal PTA.

Our study design does not allow us to draw conclusions about the renal sympathetic nerve activity change by renal PTA, and increased cardiac sympathetic nerve activity does not necessarily mean that the activation includes renal sympathetic fibers. This study included patients with treated hypertension at the start of the study, and was performed during hospitalization. Our results could underestimate the involvement of BP itself, or the impact of hospitalization itself on BP and sodium excretion. Other limitations were primarily a lack of patient randomization, lower prevalence of male patients in the FMD group, and the likelihood of selection bias.

In conclusion, a significant out-of-office BP decline in the early postoperative period might be induced via reduced volume status and natriuresis, accompanying reduced parasympathetic nerve activity. Intrarenal perfusion might be a key modulator of the circadian pattern of autonomic nerve activity and natriuresis. Even in patients with hypertension with significant renal artery stenosis, the BP response after PTA depends on pretreatment cardiac autonomic activity, and for treatment success, evaluation of heart rate

variability is important to screen for ideal candidates for renal PTA treatment. A large prospective randomized controlled trial will be important to confirm our preliminary observations.

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Disclosures

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