

The sympathetic nervous system in hypertension: assessment by blood pressure variability and ganglionic blockade

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Objective To determine if the contribution of the sympathetic nervous system to blood pressure could be evidenced by low-frequency oscillations of systolic blood pressure (LF_{SBP}), reflecting vascular sympathetic modulation, or by the decrease in blood pressure after autonomic blockade.

Design We studied multiple system atrophy (MSA) patients, in whom supine hypertension is maintained by residual sympathetic tone ('positive controls'); pure autonomic failure (PAF) patients, in whom supine hypertension is largely independent of sympathetic tone ('negative controls'); essential hypertensive patients (HTN) and normotensive subjects (NTN).

Results Supine systolic blood pressure (SBP) was 204 ± 8 , 185 ± 6 , 177 ± 9 and 130 ± 4 mmHg in MSA, PAF, HTN and NTN, respectively. LF_{SBP} was higher in MSA and HTN (5.7 ± 1.5 and 5.8 ± 1.4 mmHg²) compared to NTN and PAF (3.3 ± 0.5 and 1.1 ± 0.5 mmHg²). Trimethaphan 2–4 mg/min induced complete autonomic blockade and lowered SBP below 125 mmHg in all NTN and all but one MSA (to 111 ± 3 and 97 ± 9 mmHg). SBP remained elevated in PAF (164 ± 7 mmHg). Responses in HTN were variable; SBP decreased below 125 mmHg in three and remained elevated in four patients. The decrease in LF_{SBP} correlated with the reduction in SBP, with a steeper slope in MSA and HTN compared to NTN (29.0 ± 5.5 , 8.4 ± 1.6 and 3.6 ± 1.2 mmHg/mmHg², respectively).

Conclusion Ganglionic blockade, alone or coupled to LF_{SBP}, discriminated between human models of sympathetic-dependent (MSA) and independent (PAF) hypertension. This approach may aid in assessing the contribution of the sympathetic nervous system in essential hypertension, in which sympathetic dependence is variably expressed. *J Hypertens* 21:1677–1686 © 2003 Lippincott Williams & Wilkins.

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Introduction

The sympathetic nervous system is pivotal to short-term cardiovascular regulation and buffers acute blood pressure changes [1]. It may also contribute to the long-term maintenance of hypertension (HTN). Several approaches have been used to explore this possibility. Sympathetic activity has been quantified directly using postganglionic sympathetic fiber recordings [2,3] and norepinephrine spillover measurements [4,5].

The contribution of the sympathetic nervous system to HTN can be examined by gauging the decrease in blood pressure produced by acute sympathetic withdrawal during ganglionic blockade [6–10]. This 'intrinsic' blood pressure would be normalized in hyper-

tensive conditions driven by sympathetic drive, and would remain elevated in those caused by other mechanisms. For example, we have used ganglionic blockade to examine the mechanism of supine hypertension in patients with autonomic failure [10]. We found that in patients with multiple system atrophy (MSA), also termed the Shy-Drager syndrome, blood pressure was uniformly and dramatically reduced. This finding implied that residual sympathetic activity accounted for most of the hypertension in these patients. In contrast, ganglionic blockade had little or no effect in patients with pure autonomic failure (PAF). This finding indicated that mechanisms other than sympathetic tone were responsible for hypertension in PAF patients [10]. One of the objectives of this study was to

compare the results obtained in these unique patient groups to patients with essential hypertension.

It would also be advantageous to use non-invasive methods to gauge the sympathetic contribution to blood pressure. Spectral analysis of blood pressure is thought to reflect sympathetic modulation of vasomotor tone [11–14], and could be applied to explore this issue [15]. Systolic blood pressure fluctuations with a 10-s periodicity, or low-frequency band (LF_{SBP}), which are also termed ‘Mayer’ waves, may provide an index of sympathetic tone [16,17]. LF_{SBP} is increased by maneuvers that induce sympathetic activation, such as the upright posture [13,18], lower-body negative pressure [19] and infusion of depressor substances [20]. The mechanism of formation of Mayer waves is not completely understood. It has been proposed that this rhythm is initiated within the central nervous system neurons where sympathetic tone originates [21–25]. It has also been proposed that the baroreflex creates a ‘resonance’ phenomenon that contributes to these blood pressure fluctuations [26,27]. Patients with multiple system atrophy may be uniquely useful in examining this process. They have preserved sympathetic outflow that is not modulated by baroreflex function, as this is completely absent.

Methods

Study subjects

We studied a total of 32 subjects. Seventeen patients had primary autonomic failure; nine with MSA [four females, 67 ± 1 years old, body mass index (BMI) $25.57 \pm 0.42 \text{ kg/m}^2$], and eight with PAF (three females, 73 ± 4 years old, BMI $22.59 \pm 0.95 \text{ kg/m}^2$). We followed diagnostic criteria for PAF (isolated failure of the autonomic nervous system) and MSA (autonomic failure associated with Parkinsonism or cerebellar ataxia) as previously published [28,29], and patients with secondary causes of autonomic failure were excluded. In addition, we studied seven patients with HTN (three females, 51 ± 4 years old, BMI $25.64 \pm 1.55 \text{ kg/m}^2$) and a group of eight healthy normotensive (NTN) subjects (three females, 28 ± 3 years old, BMI $23.51 \pm 0.97 \text{ kg/m}^2$). Written informed consent was obtained, and all studies were approved by our local institutional review boards.

Protocol

Studies were conducted at the Vanderbilt University General Clinical Research Center and at the Clinical Research Center at the Franz Volhard Clinic. Vasoactive medications and fludrocortisone were discontinued for at least five half-lives before testing. Patients were given a 150 mEq sodium and 70 mEq potassium diet. Studies were conducted at least 2.5 h after a meal, and patients did not drink 90 min before testing [30].

Ganglionic blockade

Subjects were studied in the supine position. Heart rate was monitored continuously using surface electrocardiogram. Blood pressure was measured by sphygmomanometer in all cases, and monitored continuously either by the finger volume clamp method (Finapres; Ohmeda, Englewood, Colorado, USA), or through a radial artery catheter. After the subject had rested quietly for at least 20 min, ganglionic blockade was induced by continuous infusion of trimethaphan (Cambridge Labs., Newcastle upon Tyne, England). The infusion was begun at 0.5 or 1 mg/min and increased at 6-min intervals until one of the following endpoints was reached: an infusion-rate of 8 mg/min, appearance of symptoms related to excessive hypotension, no further decrease in blood pressure with increased infusion rates, or achievement of complete ganglionic blockade [10].

Spectral analysis

The data were recorded using a WINDAQ data acquisition system (DI220; DATAQ, Akron, Ohio, USA; 14 Bit, 500 Hz) and processed off-line using custom-written software in PV-Wave language (PV-Wave; Visual Numerics Inc., Houston, Texas, USA). Beat-to-beat values of detected R–R intervals and blood pressure values were interpolated, low-pass filtered (cutoff 2 Hz) and resampled at 4 Hz. Data segments of 128 s recorded at the end of each infusion step were used for spectral analysis. Linear trends were removed and power spectral density was estimated with the FFT-based Welch algorithm using three segments of 256 data points with 50% overlapping and Hanning window [31]. The power in the frequency range of low frequencies (LF: 0.04 to < 0.15 Hz), and high frequencies (HF: 0.15 to < 0.40 Hz) was calculated following Task Force recommendations [32]. Variability was also expressed as a percentage of total power or as normalized units (nu) to total power minus the power in the very-low-frequency range (< 0.04 Hz). Additionally, the power of blood pressure variability was normalized to squared systolic blood pressure multiplied by 100 000.

Baroreflex: cross-spectral analysis

Cross spectra, coherence and transfer function analysis were used to capture inter-relationships between R–R interval and systolic blood pressure. Baroreflex gain was defined as the mean magnitude value of the transfer function in the low-frequency band with negative phase and squared coherence value greater than 0.5 [33].

Regression analysis

Slope ($S_{SBP/LF}$) and intercept (SBP_0) of the relationship between blood pressure and blood pressure variability were calculated by linear regression model:

$$SBP = (S_{SBP/LF} \times LF_{SBP}) + SBP_0 \quad (1)$$

Paired values of LF_{SBP} and SBP obtained at each trimethaphan dose were used to approximate individual regression lines for each subject. Averaged slope and intercept values were calculated using individual values for each patient group.

Statistics

Data were tested for Gaussian distribution. If it was normally distributed, it was subjected to one-way analysis of variance (ANOVA) followed by Newman-Keuls multiple comparison testing. Otherwise, non-parametric tests were used. A value for $P < 0.05$ was considered to be statistically significant. All data are expressed as means \pm SEM.

Results

Baseline cardiovascular and spectral parameters

Supine systolic blood pressure was significantly elevated in patients with MSA, PAF and HTN (204 ± 8 , 185 ± 6 , 177 ± 9 mmHg, respectively), compared to healthy NTN subjects (130 ± 4 mmHg, $P < 0.001$).

Supine heart rate was significantly higher in patients with MSA (75 ± 3 bpm, $P < 0.01$ by ANOVA) compared to that of NTN subjects (60 ± 3 bpm). The heart rate of patients with PAF and HTN (69 ± 3 and 69 ± 3 bpm, respectively) was similar to that of normal controls (Table 1).

No significant differences were observed in the HF component of blood pressure variability and respiration between subject groups at baseline (Table 1). In contrast, patients with MSA and HTN had greater blood pressure variability in the LF component compared to NTN controls (LF_{SBP} , 5.7 ± 1.5 and 5.8 ± 1.4 versus 3.3 ± 0.5 mmHg², respectively, $P < 0.05$). The relatively low values of LF_{SBP} in normal subjects are consistent with the low sympathetic tone expected in the supine posture. PAF patients had lower LF blood pressure variability (1.1 ± 0.5 mmHg²), but adequate spectral analysis could not be obtained in four patients with PAF because of frequent premature ventricular contractions, a problem not observed in the other groups. The differences in LF_{SBP} values between MSA and PAF were lost if LF_{SBP} was normalized to total

Table 1. Cardiovascular changes induced by autonomic blockade

	Baseline				Ganglionic blockade			
	NTN	HTN	MSA	PAF	NTN	HTN	MSA	PAF
Systolic BP (mmHg)	129.7 \pm 3.8	176.5 \pm 9.4	204.1 \pm 7.8	185.1 \pm 6.0	110.6 \pm 3.1	129.4 \pm 7.5	96.6 \pm 8.8	164.3 \pm 7.1
Diastolic BP (mmHg)	67.5 \pm 2.5	87.5 \pm 5.8	97.4 \pm 4.5	81.0 \pm 7.1	62.3 \pm 2.6	70.7 \pm 5.7	55.8 \pm 4.0	74.2 \pm 7.9
Heart Rate (beats per min)	60.1 \pm 2.9	69.0 \pm 2.7	75.1 \pm 3.1	68.5 \pm 2.9	86.9 \pm 5.3	80.0 \pm 3.5	75.6 \pm 4.0	67.9 \pm 3.3
BRS (ms/mmHg)	14.0 \pm 2.6	8.8 \pm 2.2	3.3 \pm 0.9	4.2 \pm 1.4	1.9 \pm 0.5	2.7 \pm 0.5	2.1 \pm 0.4	1.4 \pm 0.6
Respiratory Rate (breaths per min)	17.3 \pm 1.7	16.5 \pm 1.1	17.6 \pm 1.8	16.9 \pm 1.1	14.9 \pm 1.4	15.7 \pm 0.9	16.1 \pm 1.5	14.1 \pm 0.6
Tidal Volume (% of baseline)					92.9 \pm 9.4	93.4 \pm 7.5	109.2 \pm 10.2	123.0 \pm 12.0
SD _{RRI} (ms ²)	48.8 \pm 3.9	31.4 \pm 3.7	17.1 \pm 2.0	9.3 \pm 1.2	8.9 \pm 1.4	12.1 \pm 2.2	6.0 \pm 0.7	5.8 \pm 0.8
RMSSD (ms)	54.5 \pm 6.6	24.5 \pm 5.0	13.9 \pm 2.2	10.0 \pm 0.7	7.0 \pm 1.8	6.3 \pm 1.2	7.9 \pm 1.5	6.6 \pm 1.2
LF _{RRI} (ms ²)	495.8 \pm 73.2	265.6 \pm 79.2	59.1 \pm 25.6	11.4 \pm 1.3	4.2 \pm 1.1	7.9 \pm 3.2	3.9 \pm 0.9	2.2 \pm 0.4
HF _{RRI} (ms ²)	585.2 \pm 190.1	115.1 \pm 35.3	29.9 \pm 12.1	21.8 \pm 5.4	8.2 \pm 2.0	7.6 \pm 3.6	10.0 \pm 3.4	13.4 \pm 6.4
TP _{RRI} (ms ²)	1607.8 \pm 308.1	746.7 \pm 215.6	158.8 \pm 35.4	60.3 \pm 18.9	42.4 \pm 9.8	93.2 \pm 32.2	23.3 \pm 15.7	22.1 \pm 6.3
LF _{RRI} / HF _{RRI}	1.6 \pm 0.5	3.3 \pm 0.7	2.1 \pm 0.8	0.6 \pm 0.1	0.6 \pm 0.1	2.1 \pm 2.1	0.9 \pm 0.3	0.3 \pm 0.1
LF _{RRI} (% of TP)	33.0 \pm 3.3	35.1 \pm 1.3	31.4 \pm 7.1	24.0 \pm 5.7	11.4 \pm 1.6	9.9 \pm 2.1	17.3 \pm 3.2	12.4 \pm 3.7
HF _{RRI} (% of TP)	33.9 \pm 6.8	14.9 \pm 3.6	18.9 \pm 4.7	39.0 \pm 3.5	21.4 \pm 2.8	10.1 \pm 5.1	40.1 \pm 10.0	55.8 \pm 14.4
LF _{RRI} (normalized to TP-VLF)	52.1 \pm 7.6	72.0 \pm 5.2	59.4 \pm 7.6	36.6 \pm 4.0	34.6 \pm 3.5	56.9 \pm 7.8	37.8 \pm 8.3	19.7 \pm 4.5
HF _{RRI} (normalized to TP-VLF)	47.9 \pm 7.6	28.0 \pm 5.2	40.6 \pm 7.6	63.4 \pm 4.0	65.4 \pm 3.5	43.1 \pm 0.0	62.2 \pm 8.3	80.3 \pm 4.5
LF _{SBP} (mmHg ²)	3.3 \pm 0.5	5.8 \pm 1.4	5.7 \pm 1.5	1.1 \pm 0.5	1.3 \pm 0.3	1.2 \pm 0.4	0.6 \pm 0.2	1.7 \pm 0.5
HF _{SBP} (mmHg ²)	1.8 \pm 0.4	2.0 \pm 0.3	2.7 \pm 0.7	0.7 \pm 0.1	3.0 \pm 1.3	3.8 \pm 1.0	3.4 \pm 1.1	1.0 \pm 0.3
TP _{SBP} (mmHg ²)	14.2 \pm 2.2	17.2 \pm 5.7	18.8 \pm 4.3	11.7 \pm 5.8	9.8 \pm 3.4	8.2 \pm 1.8	7.4 \pm 1.5	10.3 \pm 2.7
LF _{SBP} / HF _{SBP}	3.9 \pm 1.9	3.4 \pm 1.0	3.4 \pm 1.0	1.3 \pm 0.4	0.7 \pm 0.2	0.3 \pm 0.1	0.3 \pm 0.8	0.9 \pm 0.3
LF _{SBP} (% of TP)	27.2 \pm 4.7	36.6 \pm 4.1	29.3 \pm 3.6	16.2 \pm 5.8	19.1 \pm 4.3	12.5 \pm 2.4	11.1 \pm 3.2	18.1 \pm 3.3
HF _{SBP} (% of TP)	15.9 \pm 4.4	19.5 \pm 6.2	22.7 \pm 8.6	15.7 \pm 6.6	34.7 \pm 6.4	47.9 \pm 7.9	42.9 \pm 8.8	11.4 \pm 3.2
LF _{SBP} (normalized to TP-VLF)	63.2 \pm 6.7	69.7 \pm 6.8	64.1 \pm 9.2	53.6 \pm 6.5	36.5 \pm 3.5	22.7 \pm 5.0	25.6 \pm 6.6	62.1 \pm 8.9
HF _{SBP} (normalized to TP-VLF)	36.8 \pm 6.7	30.3 \pm 6.8	35.9 \pm 9.2	46.4 \pm 6.5	63.5 \pm 0.1	77.3 \pm 5.0	74.4 \pm 6.6	37.9 \pm 8.9
LF _{SBP} (normalized to SBP ² \times 100 000)	19.58 \pm 3.12	18.69 \pm 4.35	14.21 \pm 4.11	3.20 \pm 1.64	10.99 \pm 2.43	7.39 \pm 2.78	6.88 \pm 2.47	6.84 \pm 2.81
HF _{SBP} (normalized to SBP ² \times 100 000)	10.74 \pm 2.30	6.23 \pm 0.69	7.00 \pm 2.05	2.08 \pm 0.51	23.36 \pm 8.47	20.84 \pm 4.22	40.1 \pm 18.1	3.61 \pm 1.42
Slope $S_{SBP/LF}$ (mmHg/mmHg ²)					3.6 \pm 1.2	8.4 \pm 1.6	29.0 \pm 5.5	2.3 \pm 2.0
Intercept SBP ₀ (mmHg)				107.6 \pm 3.8	127.4 \pm 9.9	97.1 \pm 10.0	164.3 \pm 12.6	

Mean \pm SEM calculated from eight patients with pure autonomic failure (PAF), nine patients with multiple system atrophy (MSA), seven patients with essential hypertension (HTN), and eight healthy normotensive subjects (NTN) during baseline and ganglionic blockade. Spectral analysis could not be performed in four PAF patients due to frequent premature ventricular contractions. PAF, pure autonomic failure; MSA, multiple system atrophy; HTN, essential hypertension; NTN, healthy normotensive subjects; RRI, R-R interval; SBP, systolic blood pressure; SD, standard deviation; RMSSD, square root of mean squared successive differences; BRS, baroreflex slope; LF, low frequency; HF, high frequency; TP, total power.

power or to the square of systolic blood pressure (Table 1), suggesting that normalization of LF_{SBP} did not discriminate between conditions characterized by intact (MSA) and absent (PAF) sympathetic modulation of blood pressure. For this reason, only absolute LF_{SBP} was used in all subsequent analysis.

High-frequency variability of heart rate was significantly blunted in HTN, MSA and PAF (115 ± 35 , 30 ± 12 and 22 ± 6 ms², respectively, Table 1), compared to NTN (585 ± 190 ms²). Low-frequency variability of heart rate was also significantly blunted in HTN, MSA and PAF (266 ± 79 , 59 ± 26 and 11 ± 1 ms², respectively), compared to NTN (496 ± 73 ms²).

Effects of ganglionic blockade on cardiovascular and spectral parameters

Baroreflex function

Baseline baroreflex sensitivity was significantly lower in HTN patients (8.8 ± 2.2 ms/mmHg) compared to NTN controls (14 ± 2.6 ms/mmHg), and was virtually absent in PAF (4.2 ± 1.4 ms/mmHg) and MSA (3.3 ± 0.9 ms/mmHg). Trimethaphan decreased baroreflex function in a dose-dependent manner (Fig. 1a). A decrease $> 95\%$ in baroreflex function was obtained at infusion rates of 2–4 mg/min. We considered, therefore, that complete autonomic blockade was obtained at these doses.

Blood pressure variability

Trimethaphan had no effect on high-frequency variability of blood pressure, but produced a dose-dependent decrease in LF_{SBP} in patients with MSA and HTN (Fig. 1b). At doses of 2–4 mg/min, trimethaphan decreased LF_{SBP} in MSA (-3.92 ± 0.95 mmHg², $P < 0.05$), in HTN (-4.55 ± 1.23 mmHg², $P < 0.05$) and in NTN controls (-1.97 ± 0.76 mmHg²), but had no consistent effect in patients with PAF (Fig. 1, Table 1).

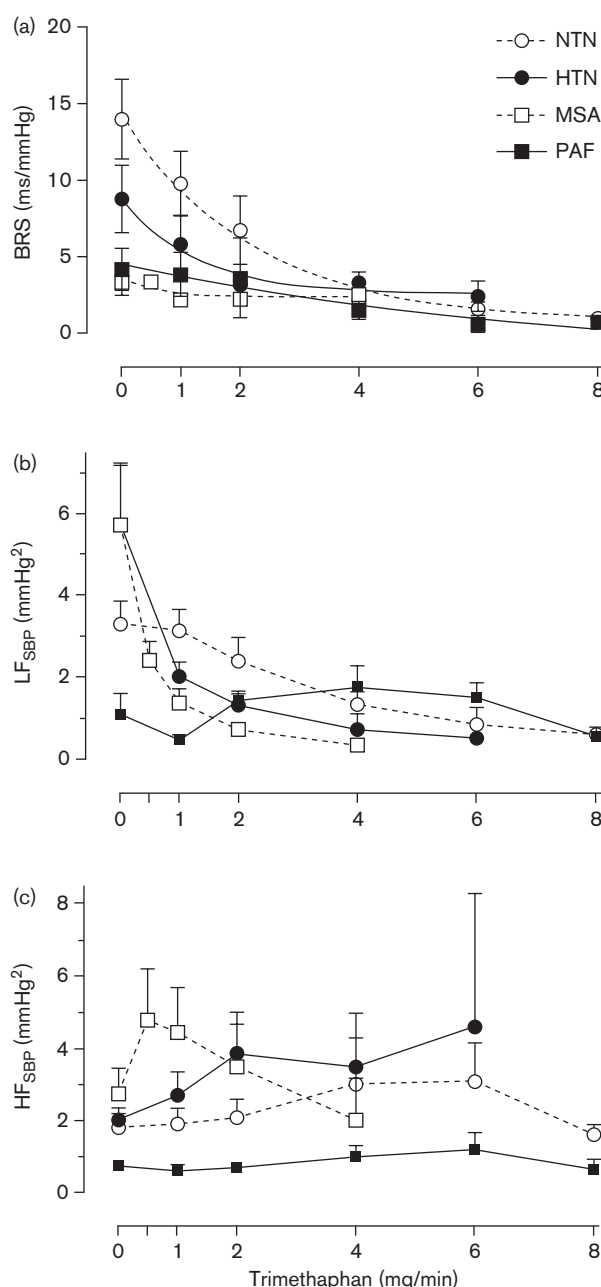
Heart-rate variability

Both low- and high-frequency heart rate variability were significantly reduced by ganglionic blockade in all groups (Fig. 2). The ratio between low and high heart rate variability (LF/HF_{RR}) was greater in HTN and MSA. These findings mirrored those of low-frequency blood pressure variability, which was also increased in these patient groups (LF_{SBP} , Fig. 2).

Blood pressure levels and heart rate

All normal subjects tolerated 8 mg/min trimethaphan, the highest dose used. At this dose, systolic blood pressure decreased by 24 ± 5 mmHg (Fig. 3) and heart rate increased by 26 ± 2 bpm. In contrast, trimethaphan had to be stopped at a dose of 2.6 ± 0.4 and 4 ± 0.8 mg/min in patients with MSA and HTN, respectively, because of dramatic and symptomatic falls in blood pressure (-110 ± 9 and -52 ± 6 mmHg, respec-

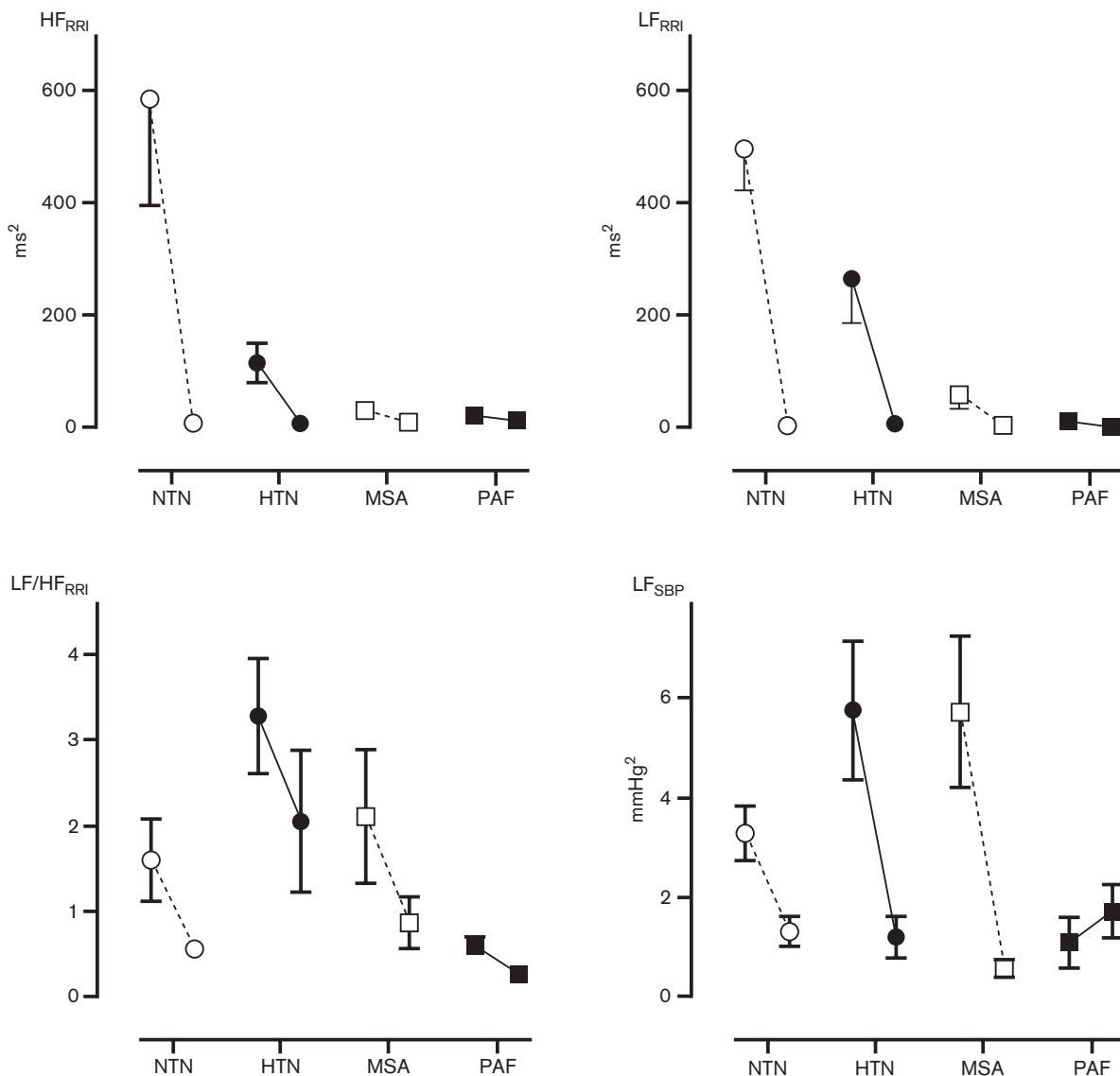
Fig. 1



Effect of increasing doses of trimethaphan in normal subjects (NTN), and in patients with essential hypertension (HTN), multiple system atrophy (MSA) and pure autonomic failure (PAF) on: (a) baroreflex sensitivity (BRS); (b) low-frequency component of blood pressure variability (LF_{SBP}); and (c) high-frequency component of blood pressure variability (HF_{SBP}).

tively). Heart rate did not change in MSA (-1 ± 3 bpm), but increased slightly in HTN (10 ± 3 bpm). All PAF patients tolerated a 8 mg/min trimethaphan infusion rate. This dose produced a reduction in systolic blood pressure (-32 ± 6 mmHg) similar to that observed in NTN controls, but significantly less

Fig. 2



High-frequency component of heart rate variability (HF_{RRI}), low-frequency component of heart rate variability (LF_{RRI}), the ratio between these components of heart rate variability (LF/HF_{RRI}) and low-frequency component of blood pressure variability (LF_{SBP}) found in normal subjects (NTN), and in patients with essential hypertension (HTN), multiple system atrophy (MSA) and pure autonomic failure (PAF). Each data pair denotes values at baseline and during ganglionic blockade.

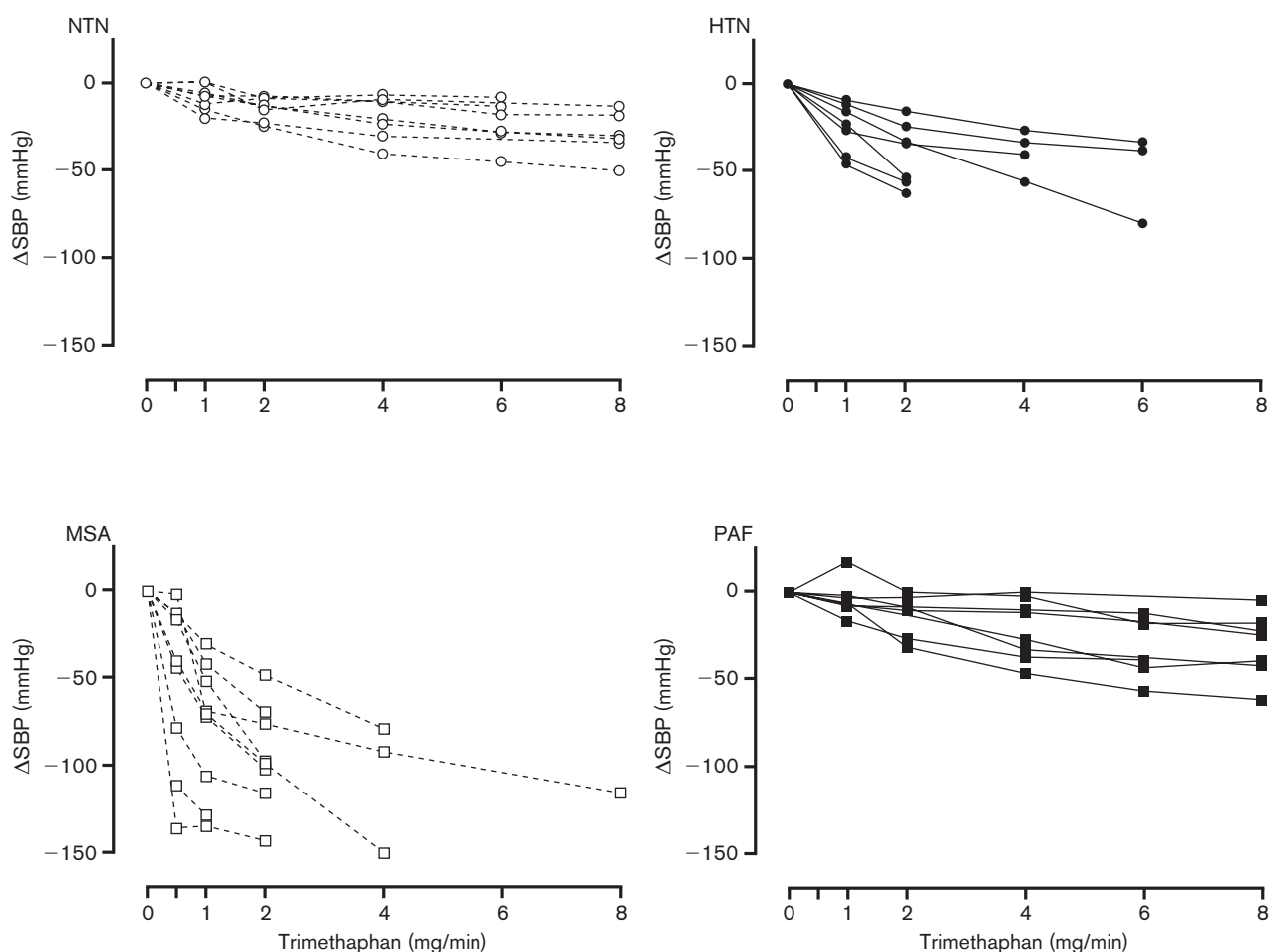
than that produced in patients with MSA or HTN. Heart rate did not change significantly in PAF (-2 ± 2 bpm).

Relationship between LF_{SBP} and blood pressure

To examine the relationship between LF_{SBP} and blood pressure, we performed linear regression analysis between LF_{SBP} and blood pressure using the values obtained at each trimethaphan dose (Equation 1, Fig. 4). The decrease in blood pressure correlated with the decrease in LF_{SBP} particularly well in patients with MSA, HTN and NTN. In contrast, there was no correlation in patients with PAF. The average slope

($S_{SBP/LF}$) calculated from the individual values of this relationship was steeper in MSA and HTN (29.0 ± 5.5 and 8.4 ± 1.6 $mmHg/mmHg^2$) compared to NTN (3.6 ± 1.2 $mmHg/mmHg^2$; $P < 0.02$ for both). The slopes in PAF showed values around zero (2.3 ± 2.0 $mmHg/mmHg^2$). The intercept values (SBP_0) in MSA and NTN were 97.1 ± 10.0 and 107.6 ± 3.8 $mmHg$, respectively. The intercept values were higher in HTN and PAF (127.4 ± 9.9 and 164.3 ± 12.6 $mmHg$) compared to NTN. The estimated intercept values (SBP_0) were similar to the measured blood pressure values at doses of trimethaphan (2–4 mg/min) that induced complete autonomic blockade. Regression analysis of these

Fig. 3



Decrease in systolic blood pressure (Δ SBP) produced by intravenous infusion of trimethaphan in normal subjects (NTN), and in patients with essential hypertension (HTN), multiple system atrophy (MSA) and pure autonomic failure (PAF).

two parameters revealed a tight linear correlation ($r^2 = 0.086$, $P < 0.0001$) with a slope approximating the line of identity (0.98 ± 0.08), indicating that the theoretical blood pressure when LF_{SBP} is zero (SBP_0) is nearly identical to the pharmacologically-induced 'intrinsic' blood pressure.

Cardiovascular parameters during complete autonomic blockade

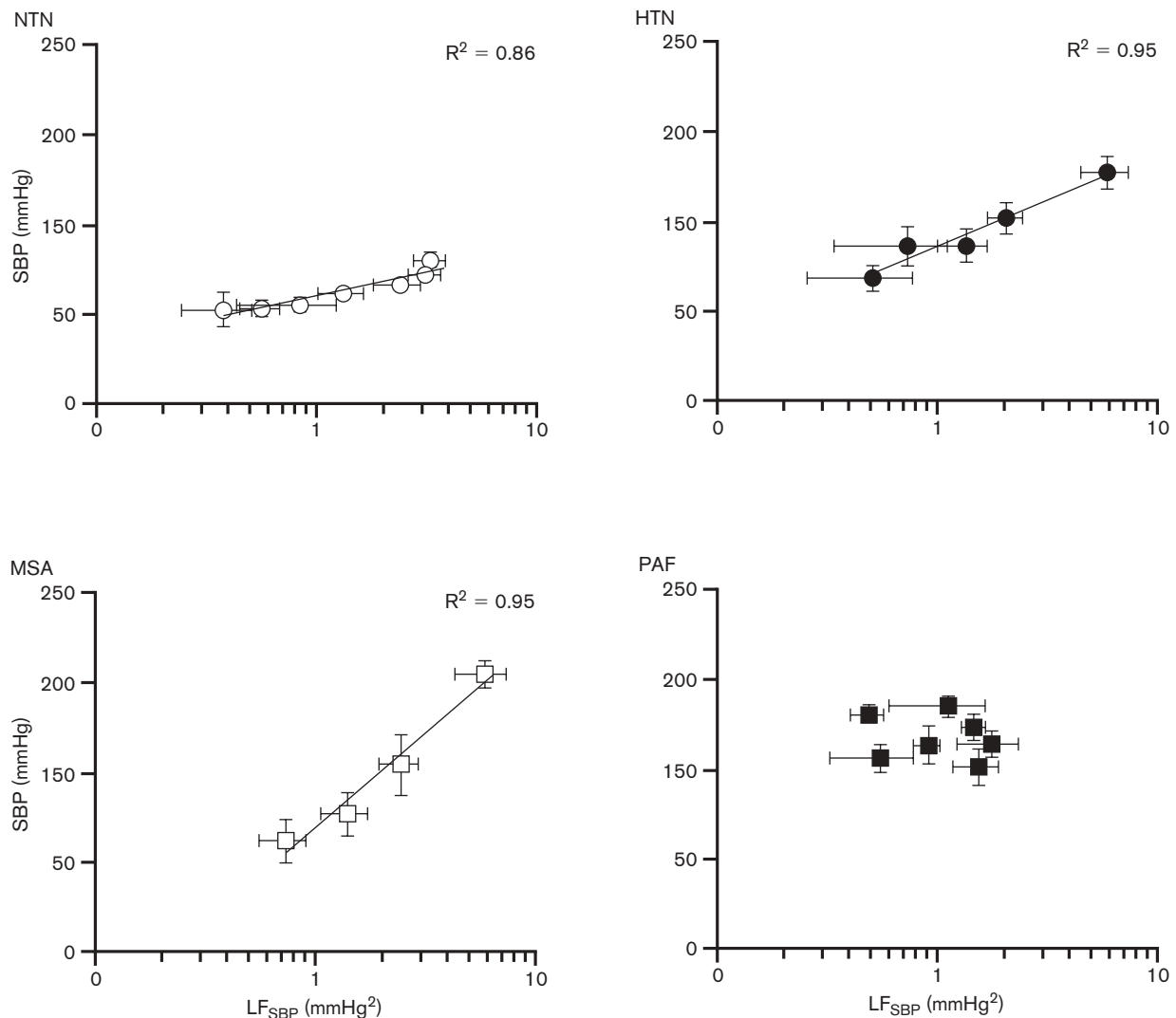
At doses (2–4 mg/min) that produced complete autonomic blockade, trimethaphan decreased systolic blood pressure in patients with MSA and NTN subjects (to 97 ± 9 and 111 ± 3 mmHg, respectively, Fig. 5, Table 1). In contrast, systolic blood pressure remained elevated in PAF during trimethaphan (164 ± 7 mmHg). In HTN patients, systolic blood pressure was 129 ± 8 mmHg during complete autonomic blockade, but individual responses were varied; systolic blood pressure dropped below 125 mmHg in three patients, and

remained elevated in four. Pharmacologically-induced 'intrinsic' blood pressure was superior at discriminating individuals with MSA from PAF than LF_{SBP} . The slope of the LF_{SBP}/SBP relationship, and the calculated intercept when LF_{SBP} is zero also discriminated between these two groups of patients (Fig. 5).

Discussion

In this study, we took advantage of the unique characteristics of patients with autonomic failure and the pathophysiological differences between MSA and PAF regarding sympathetic regulation. The presence of hypertension in patients with autonomic failure seems paradoxical, because orthostatic hypotension dominates their clinical picture. However, supine hypertension can be severe, with systolic blood pressure exceeding 200 mmHg in many patients, and can be associated with end-organ damage [34]. The mechanisms driving the hypertension depend on the underlying pathophy-

Fig. 4



Relationship between the decreases in LF_{SBP} (log power) and systolic blood pressure during trimethaphan infusion in normal subjects (NTN), and in patients with essential hypertension (HTN), multiple system atrophy (MSA) and pure autonomic failure (PAF).

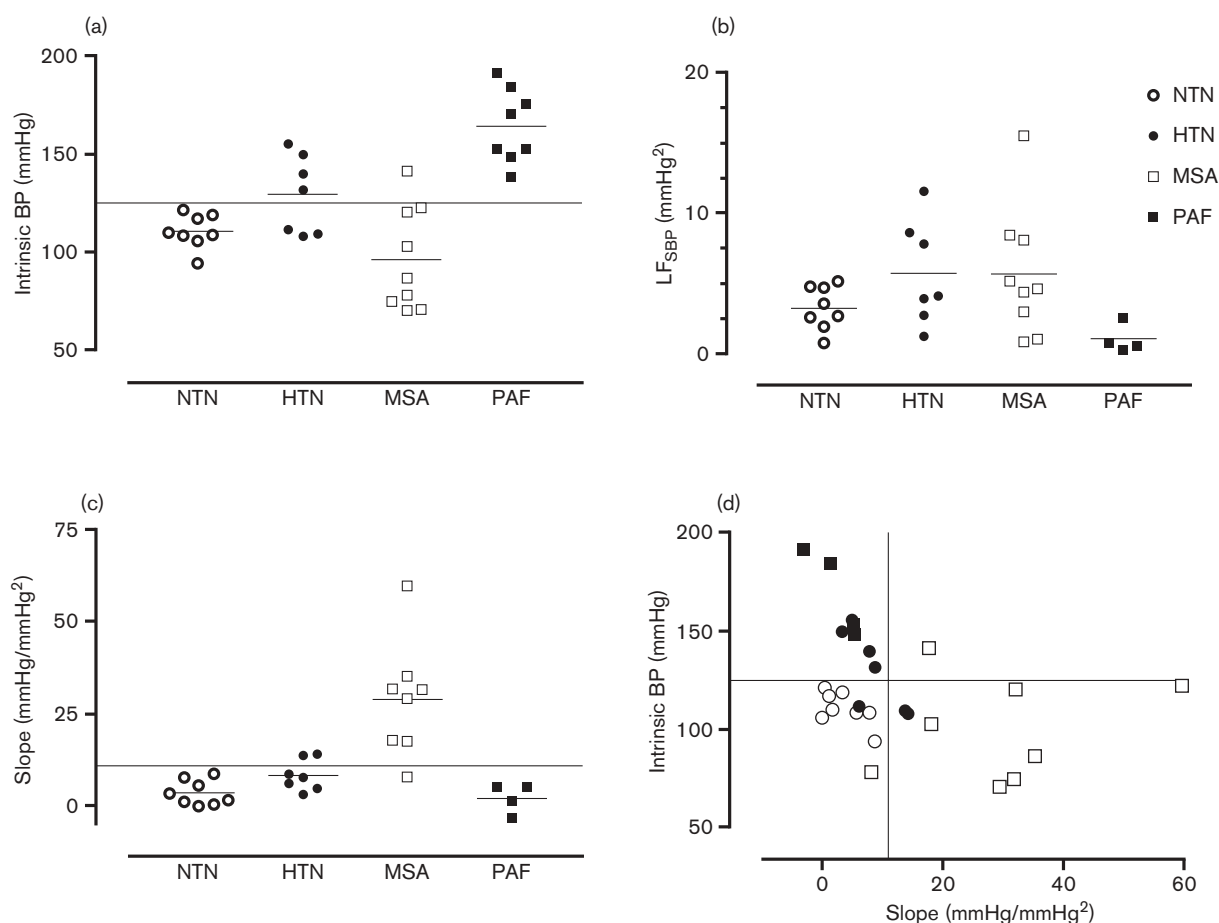
siology. In MSA, the lesion resides within the central nervous system and involves the neural connections responsible for baroreflex modulation of sympathetic tone. The neurons that tonically discharge sympathetic activity (e.g. those residing in the rostral ventrolateral medulla or in the spinal cord) and distal pathways (e.g. spinal tracts and post-ganglionic noradrenergic fibers) appear to be intact. Accordingly, MSA patients have normal or only slightly reduced supine plasma norepinephrine concentrations [35] and intact noradrenergic innervation to the heart [36]. Because trimethaphan produces a dramatic depressor response in MSA patients, their hypertension can be explained by residual sympathetic tone unopposed by the absence of baroreflex mechanisms. They are not able, however, to engage and modulate sympathetic tone as required,

thus the inability of these patients to maintain orthostatic hemodynamics.

In PAF patients, the neural damage involves more distal structures compared to MSA. The sympathetic tracts in the intermediolateral column of the spinal cord and post-ganglionic noradrenergic fibers are lost. This state of affairs is evidenced by the very low plasma levels of norepinephrine found in these patients [35], and the lack of flurodopa uptake by the heart [36]. Consequently, residual sympathetic tone is not a major determinant of PAF patients, who nevertheless are hypertensive.

Because of the pathophysiological differences between MSA and PAF, these patients might shed light about

Fig. 5



Individual data points of (a) intrinsic blood pressure after autonomic blockade; (b) initial low-frequency power of systolic blood pressure oscillations (LF_{SBP}); (c) slope of the fall in blood pressure during autonomic blockade per unit of LF_{SBP} ; and (d) the relation between intrinsic blood pressure and the SBP/LF_{SBP} slope in normal subjects (NTN), and in patients with essential hypertension (HTN), multiple system atrophy (MSA) and pure autonomic failure (PAF). All normal subjects had intrinsic blood pressure < 125 mmHg and slopes < 11 mmHg/mmHg² (dotted lines) during autonomic blockade.

the origin of cardiovascular rhythms that characterize heart rate and blood pressure oscillations. They can also be used as models for sympathetically dependent (MSA) and independent (PAF) hypertension. In the present study PAF patients had greatly reduced LF_{SBP} , in agreement with previous reports [37,38], with no consistent change during trimethaphan infusion. In contrast, LF_{SBP} power was highest in patients with MSA, and was profoundly reduced with trimethaphan. Our results, therefore, confirm the utility of LF_{SBP} as a measurement of sympathetic modulation of blood pressure. In contrast, we found that trimethaphan had no effect on HF_{SBP} , confirming previous studies reporting no relationship between sympathetic tone and high-frequency variability of blood pressure [39].

Our observations in MSA patients are important to our understanding of the origin of LF_{SBP} . It has been

proposed that LF_{SBP} oscillations are the result of resonance phenomena determined by loop properties of the baroreflex. For example, brief selective stimulation of arterial baroreceptors generates an oscillation in blood pressure in the LF range of blood pressure variability [40]. However, we found that LF_{SBP} oscillations exist, and their power is even increased, in MSA patients, in whom there is total absence of baroreflex function, suggesting that these oscillations can originate in brainstem or spinal cord neurons.

The results of this study are also illustrative with regard to the significance of heart rate variability. It is widely accepted that high-frequency variability of heart rate is the result of parasympathetic modulation of sinus node function. Not surprisingly, HF_{RRI} was very low in PAF patients and was reduced to PAF levels in NTN during ganglionic blockade. Patients with MSA also had very

low HF_{RRI} , suggesting that cardiac parasympathetic modulation is impaired, despite the relative preservation of sympathetic vasomotor modulation.

In comparison to HF_{RRI} , there is less agreement about the significance of low-frequency heart rate variability. It is believed that both sympathetic and parasympathetic tone influences LF_{RRI} , and the ratio between low- and high-frequency heart rate oscillations (LF/HF_{RRI}) has been proposed as an index of cardiac sympathovagal balance [41]. This concept, however, remains controversial [42]. We found that LF_{RRI} was abolished during ganglionic blockade in NTN, indicating the autonomic origin of this rhythm. Based on this finding alone, we cannot determine the relative contribution of sympathetic and parasympathetic activities to LF_{RRI} . It is of interest, however, that the LF/HF_{RRI} ratio was increased in HTN and MSA. These groups also had increased LF_{SBP} , reflecting increased sympathetic vasomotor modulation, and decreased HF_{RRI} , reflecting decreased cardiac parasympathetic modulation (Fig. 2). These results suggest that LF/HF_{RRI} reflects, to some degree, sympathetic cardiovascular modulation.

Our results seem to support the hypothesis that the sympathetic nervous system contributes to essential hypertension. As a group, hypertensive patients had elevated LF_{SBP} power, as reported recently [43]. This increased LF_{SBP} was comparable to that of MSA patients, who have sympathetically driven hypertension, and significantly greater than that of normotensive controls and PAF patients. Furthermore, the decrease in LF_{SBP} produced by trimethaphan in hypertensive patients correlated with the decrease in blood pressure, and the slope of this relationship was significantly steeper in MSA and HTN compared to NTN. In most HTN patients, the 'intrinsic' blood pressure was normal during autonomic blockade.

We explored the feasibility of using spectral analysis of blood pressure variability and ganglionic blockade to gauge the contribution of the sympathetic nervous system to hypertension in *individual* patients. We looked at three parameters in particular: 'intrinsic' blood pressure (the absolute blood pressure during ganglionic blockade; i.e. in the absence of autonomic influences), LF_{SBP} , and the slope of the relationship between the blood pressure fall and change of LF_{SBP} induced by ganglionic blockade. We reasoned that the ideal parameter should discriminate between MSA (used as a model of sympathetically dependent hypertension) and PAF (used as a model of sympathetically independent hypertension).

Examination of our individual data suggests that the response to trimethaphan is heterogeneous in HTN

patients (Fig. 5). Blood pressure during ganglionic blockade was reduced in three patients to levels similar to those seen in MSA patients, in whom hypertension is driven by sympathetic tone. In contrast, blood pressure remained elevated in four HTN patients to levels comparable to those observed in PAF patients, a model of hypertension independent of the autonomic nervous system. It is not surprising that essential hypertension, which has diverse and genetically distinct etiologies, appears to present heterogeneous responses to sympathetic withdrawal. We found that pharmacologically induced 'intrinsic' blood pressure and the slope of blood pressure over LF_{SBP} were better in discriminating between MSA and PAF than LF_{SBP} (Fig. 5). Examination of the relationship between intrinsic blood pressure and blood pressure/ LF_{SBP} slope (Fig. 5d) suggests that an intrinsic blood pressure above 125 mmHg, and a slope < 11 mmHg/mmHg² are indicative of patients with sympathetically independent hypertension. A potential limitation of our study is the relatively small number of patients with essential hypertension studied. Increasing the number of observations will not affect the conclusion that responses to ganglionic blockade were heterogeneous; inclusion of more patients will only widen these differences. A larger number of subjects would help us determine whether there is internal agreement between the parameters proposed to identify patients with sympathetically driven hypertension (i.e. high basal LF_{SBP} , normalization of blood pressure with trimethaphan, and a steep slope of the change in blood pressure per LF_{SBP}).

In summary, the combined use of ganglionic blockade with trimethaphan, and human models of sympathetically dependent (MSA) and independent (PAF) hypertension provided insight about the autonomic origin of cardiovascular rhythms. It confirmed the usefulness of LF_{SBP} as an estimate of sympathetic modulation of vasomotor tone, and demonstrated that these rhythms, which are seen in blood pressure recordings as Mayer waves, are present in patients devoid of baroreflex function, suggesting that they originate in cardiovascular centers in the brainstem or spinal cord. We also found that the LF/HF_{RRI} ratio, also referred to as a 'sympathovagal balance', was elevated in the group of patients (HTN and MSA) that had increased sympathetic tone, suggesting that this ratio is influenced by sympathetic modulation. Finally, ganglionic blockade can be used to determine the 'intrinsic' blood pressure in the absence of autonomic influences. This approach, alone or combined with spectral analysis of blood pressure, can be used to study the contribution of the sympathetic nervous system in patient populations. More studies are needed to determine whether this approach can be used in phenotyping patient subsets, in which the sympathetic contribution may be variable. The inclusion of patients with autonomic failure char-

acterized by sympathetically mediated (multiple system atrophy) and sympathetically independent (pure autonomic failure) hypertension provides unique positive and negative control groups. This approach underscores the utility of unusual diseases to dissect autonomic mechanisms.

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