ORIGINAL ARTICLE

High Muscle Sympathetic Nerve Activity Is Associated With Left Ventricular Dysfunction in Treated Hypertensive Patients

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BACKGROUND
The presence of asymptomatic left ventricular diastolic dysfunction (LVDD) in hypertensive patients can be associated with the development of cardiac events. The increase in sympathetic activity may be 1 of the mechanisms that predisposes to this outcome. In this study, we analyzed 2 hypotheses: (i) whether sympathetic activity is higher in the presence of LVDD, independent of blood pressure control and (ii) whether different classes of LVDD have a different effect on sympathetic activity.

METHODS
After analyzing left ventricular function using echo Doppler cardiography, 45 hypertensive patients receiving treatment were allocated into 3 groups: normal function (LV-NF, n = 15), impaired relaxation (LV-IR, n = 15), and pseudonormal or restrictive (LV-P/R, n = 15). An age-, sex-, and body mass index–matched control group of normotensive volunteers (N, n = 14) was included. Muscle sympathetic nerve activity (MSNA), heart rate, and systolic blood pressure variabilities and baroreflex sensitivity were evaluated while the patient was in a supine position.

RESULTS
Blood pressure and antihypertensive drug use were similar among the hypertensive groups. The LV-IR and LV-P/R groups had similar MSNA (33±1 and 32±1 bursts/min, respectively), which was significantly higher than that of the LV-NF and N groups (26±3 and 15±2 bursts/min, respectively). The LV-IR and LV-P/R groups had significantly higher LF-systolic blood pressure variability and significantly lower baroreflex sensitivity compared with the N group.

CONCLUSIONS
The presence of asymptomatic LVDD is associated with increased MSNA, independent of blood pressure control. The sympathetic hyperactivity associated with LVDD is similar in the different patterns of LVDD studied.

Keywords: blood pressure; diastolic dysfunction; hypertension; muscle sympathetic nerve activity.

doi:10.1093/ajh/hpt032

Left ventricular diastolic dysfunction (LVDD), determined using Doppler echocardiography, is frequently detected in the general population, and hypertension is one of the many factors associated with it.[1–5] LVDD has an unfavorable impact on cardiovascular morbidity and mortality,[6,7] even in the absence of clinical features of heart failure.[1] Some patients with preclinical LVDD may eventually experience cardiovascular events and, in almost half the cases, no trigger mechanism can be identified.[8] Sympathetic overactivity seems to act as an underlying trigger that may influence the progression of LVDD. A recently published study[9] involving a group of never-treated hypertensive patients showed that the presence of LVDD was associated with increased muscle sympathetic nerve activity (MSNA). However, it remains unclear whether the same phenomenon occurs in hypertensive patients receiving antihypertensive therapy. Moreover, the peripheral sympathetic drive activities in the different classes or stages of LVDD are not known.

We conducted this study to answer 2 questions: (i) Is sympathetic activity greater in hypertensive patients with LVDD independent of blood pressure (BP) control with antihypertensive drugs? and (ii) Do different classes or "stages" of LVDD have different effects on sympathetic activity in hypertensive patients?

METHODS

Population

Forty-five asymptomatic patients of both sexes, aged 35–60 years old, with primary hypertension diagnosed according to the current guidelines[10] were recruited from the Hypertension Unit of the Heart Institute (InCor) of the Hospital das Clínicas da Faculdade de Medicina da Universidade de Sao Paulo. The patients were carefully examined and found to have a low risk of obstructive sleep

apnea based on their scores on the Berlin Questionnaire.[11] The exclusion criteria used were as follows: body mass index ≥35 kg/m², signs or symptoms of heart failure or history of cardiovascular diseases, increased level of N-terminal prohormone of brain natriuretic peptide (>125 pg/ml), excessive alcohol consumption, current smoking history, diabetes mellitus (random blood sugar level ≥110 mg/dl), hyperlipidemia (total cholesterol >200 mg/dl), alterations in renal function (serum creatinine >0.9 mg/dl), serious comorbidities (organ failure or terminal malignancy), and changes in antihypertensive therapy in the last 6 months.

All of the hypertensive patients were taking antihypertensive drugs, enalapril (angiotensin-converting enzyme inhibitor) and/or amlodipine (calcium channel blockers), and their office BP measurement was controlled according to guidelines (<140/90 mm Hg).

A group of normotensive healthy volunteers (N, n = 14) matched for age, sex, and body mass index was used as controls.

This study was approved by the Ethics Committee of the Hospital and the University of São Paulo (SDC:0091/07; CAPPesq: 2937/07/012) and registered with the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au; ANZCTR:343085). All of the participants agreed to participate and signed an informed consent after being informed about the nature and purpose of the study.

The hypertensive patients were assigned to 3 groups according to the classes of diastolic function identified by transmitral inflow patterns detected with echo Doppler cardiography and tissue Doppler analyses. The LV-NF group (n = 15) consisted of hypertensive patients with normal left ventricular diastolic function. The LV-IR group (n = 15) consisted of hypertensive patients with impaired relaxation LVDD. The LV-P/R group (n = 15) consisted of hypertensive patients with pseudonormal or restrictive classes of LVDD.

Measurements

Echo Doppler cardiographic assessment. Conventional echo Doppler cardiography and tissue Doppler measurements were performed using commercially available equipment (Sequoia Echocardiography System, 512 Acuson; Siemens, Mississauga, CA) and a 3V2c multifrequency transducer with simultaneous electrocardiographic monitoring. End-diastolic and end-systolic left ventricular (LV) internal diameters, interventricular septal thickness, and posterior wall thickness were measured on a 2-dimensional guided M-mode according to American Society of Echocardiography (ASE) guidelines and recommendations.[12] The LV mass index was calculated using Devereux's formula and normalized to body surface area.[13] The LV ejection fraction was measured from the 4-chamber apical projection using the Teichholz method.[12] The diastolic function was assessed using the following methods: pulsed-wave Doppler imaging of the mitral and pulmonary venous flow velocities; tissue Doppler imaging of the septal, lateral, anterior, and inferior mitral annulus; and the average myocardial peak velocity at 4 sites of early diastole (E' peak), late diastole (A' peak), and systole (S' peak).[14]

The values and parameters adopted to assess diastolic function and classify diastolic dysfunction[1] were as follows:

1. Normal diastolic function: 0.75 < E/A < 1.5 (E: peak early filling velocity/A: velocity at atrial contraction); S ≥ D (systolic forward flow > diastolic forward flow); E/e' (E: peak early filling velocity/e': velocity of mitral annulus early diastolic motion) < 10; DT(mitral E velocity deceleration time) > 140 ms.
2. Impaired relaxation (LVDD class I): E/A ≤ 0.75; S > D; E/e' < 10.
3. Pseudonormal (LVDD class II): 0.75 < E/A < 1.5; S < D; E/e' ≥ 10; DT > 140 ms.
4. Restrictive (LVDD class III): E/A > 1.5; S < D; E/e' ≥ 10;DT < 140 ms.

The determination of the LVDD classes required the presence of at least 2 parameters in the same classification.

Muscle sympathetic nerve activity. MSNA was recorded directly from the peroneal nerve using the microneurographic technique.[15] Multiunit postganglionic muscle sympathetic nerve recordings were made using a tungsten microelectrode. The signals were amplified and filtered. Nerve activity was rectified and integrated (time constant = 0.1 s) to obtain a mean voltage display of sympathetic nerve activity, which was recorded on paper. All recordings of MSNA met previously established and described criteria. Muscle sympathetic bursts were identified by visual inspection and were expressed as burst frequency (bursts/min) and burst incidence (bursts/100 heart beats).

BP, heart rate (HR), and autonomic measurements. BP waveforms were obtained with a digital photoplethysmograph device (Finometer; Finapres Medical System BV, Holland) while subjects were awake in a supine position during a 15-minute rest period. A software program (BeatScope) used the BP curves and patient age, sex, weight, and height values to calculate systolic BP (SBP) and diastolic BP and HR. The waveforms were simultaneously recorded on another computer equipped with AT/MCA-CODAS acquisition and conversion of biological signals (DATAC Instruments, Akron, OH). The signal sampling frequency was 1000 Hz. These stored data underwent a routine analysis to provide the HR and BP variability values.

Each heartbeat was identified with a specialized algorithm implemented for the Matlab MT (MATLAB 6.0; Mathworks, Natick, MA), which allows the automatic detection of systolic and diastolic pressure waves. Pulse interval or R-R interval was calculated as the difference between the beginning and endpoints of the cycle ($t_1 - t_0$).

The power spectral density of the R-R interval was obtained with the Fast Fourier Transformation using Welch's method over 16,384 points with a Hanning window and 50% overlap. The spectral bands for humans (very low-frequency: 0.0–0.04 Hz; low-frequency (LF): 0.04–0.15 Hz; high-frequency (HF): 0.15–0.4 Hz) were defined according to the literature.[16] In addition, spontaneous baroreflex sensitivity was evaluated using the LF alpha index, which was calculated as

the square root of the ratio between the pulse interval power and systolic pressure power in the LF band of the spectral analysis.[17]

Study protocol and data analysis

The participants were evaluated at the same time of day (between 7:00 AM and 12:00 PM) while resting in the supine position and breathing spontaneously in a temperature-controlled room (21–23 °C). All of the participants were studied for at least 2 hours after they had consumed a light meal and abstained from alcohol and caffeinated beverages for the preceding 12 hours. BP was continuously monitored and recorded for 15 minutes concurrent with the MSNA recording. Comparisons between groups were made with analysis of variance using the Bonferroni correction for multiple comparisons. Multivariable linear regression was used to check the influence of SBP, LV mass, and the absence or presence of LVDD in MSNA. The results are expressed as means ± SEMs. $P < 0.05$ was considered statistically significant.

RESULTS

Table 1 shows the clinical evaluation data and echo Doppler cardiography measurements according to the previously proposed classifications for all groups.

There were no differences in sex, age, and body mass index among the groups. The office BP values of the treated hypertensive patients showed that SBP was significantly higher in the LV-IR and LV-P/R groups than in the N group. However, diastolic BP was similar among all of the groups. The 3 groups of hypertensive patients with or without diastolic dysfunction had no differences in SBP or diastolic BP measurements. The distribution of the classes of antihypertensive agents was similar among the groups. The percentage of patients on dual therapy, enalapril and amlodipine, was 73%, 80%, and 80% in LV-NF, LV-IR, and LV-P/R groups, respectively. The percentage of patients under monotherapy

with enalapril was 13%, 13%, and 7% in LV-NF, LV-IR, and LV-P/R groups, respectively. The other patients used monotherapy with amlodipine. There was no statistically significant difference among the groups regarding LV ejection fraction and LV mass.

The values for HR and SBP variability are presented in Table 2. There was no difference among the groups with regard to HR variability in the time domain ($P > 0.05$). However, we found a progressive reduction in the variance of the R-R interval in group N compared with that of the LV-P/R group. The values of the components of cardiac sympathetic modulation (LF) were similar among N, LV-NF, and LV-IR groups. The same pattern occurred for the values of cardiac parasympathetic (HF) and cardiac sympathetic modulation (LF/HF ratio).

The SBP variance tended to be higher in the LV-IR and LV-P/R groups compared with the N and LV-NF groups, but the differences among the groups was not statistically significant ($P > 0.05$).

The sympathetic modulation of vascular tone represented by the LF component of SBP variability was higher in the LV-P/R group (11.7 ± 1.2 mm Hg^2; n = 14) and the LV-IR group (12.2 ± 1.3 mm Hg^2; n = 15) than in the N group (6.7 ± 0.6 mm Hg^2; n = 12) but was similar to that of the LV-NF group (9.3 ± 1.1 mm Hg^2; n = 15) (Figure 1a). Moreover, the LV-NF group was not different from the N group. Baroreflex sensitivity, represented by the LF alpha index, was impaired in the LV-P/R (5.07 ± 0.72 ms/mm Hg; n = 10) and LV-IR (4.6 ± 0.6 ms/mm Hg; n = 10) groups compared with the N group (8.2 ± 1.0 ms/mm Hg; n = 13), but it was similar to that of the LV-NF group (6.05 ± 0.55 ms/mm Hg; n = 15). Furthermore, the LV-NF group did not differ from the N group (Figure 1b).

The MSNA values are presented in 2 ways: by frequency (burst/min) (Figure 2) and incidence (burst/100 hearts beats). Groups with hypertension associated with LVDD had higher MSNA values in both forms of presentation (LV-IR group: 33 ± 1 bursts/min, 51 ± 3 bursts/100 heartbeats;

Table 1. Results of anthropometric assessments and echo Doppler cardiography in all groups

Variables	N group (n = 14)	LV-NF group (n = 15)	LV-IR group (n = 15)	LV-P/R group (n = 15)
Age, years	47 ± 2	48 ± 2	53 ± 2	51 ± 2
BMI, kg/m^2	27 ± 1	28 ± 1	29 ± 1	27 ± 1
Men, No.	6	7	7	9
SBP, mm Hg	121 ± 2	134 ± 3	133 ± 5*	136 ± 3*
DBP, mm Hg	72 ± 2	78 ± 2	77 ± 4	79 ± 2
HR, bpm	67 ± 2	71 ± 2	68 ± 3	69 ± 2
LVEF, %	71 ± 2	71 ± 2	67 ± 2	67 ± 2
LV mass, g/m^2	81 ± 3.1	91 ± 4	96 ± 8.9	102 ± 5.8
NTproBNP, pg/ml	23 (6–83)	18 (7–72)	39 (5–105)	30 (2.3–107)

Data are means ± SEMs, except for Men, which is number, and NTproBNP, which is median (minimum–maximum).

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate. LV, left ventricular; LVEF, left ventricular ejection fraction; LV-IR, hypertensive patients with impaired relaxation left ventricular diastolic dysfunction; LV-NF, hypertensive patients with normal left ventricular diastolic function; LV-P/R, hypertensive patients with pseudonormal or restrictive classes of left ventricular diastolic dysfunction; N, normotensive controls; NTproBNP, N-terminal prohormone of brain natriuretic peptide; SBP, systolic blood pressure.

*$P < 0.05$ vs. N group.

Table 2. Heart rate and systolic blood pressure variability in all groups evaluated

	N group (n = 13)	LV-NF group (n = 15)	LV-IR group (n = 15)	LV-P/R group (n = 14)
TPW, ms^2	1,459±349	1,231±201	995±173	1,353±403
VARR R-R, ms^2	2,274±546	1,804±331	1,362±240	1,419±305
LF, ms^2	540±164	369±73	303±72	351±84
HF, ms^2	365±76	388±81	253±38	372±122
% LF	57±4.4	50±5	47±4.4	50±7.3
% HF	43±4.4	50±5	53±4.4	59±7.3
VARR SBP, mm Hg^2	30.6±6	31.6±4	40.2±5	45.2±6

Data are means + SEMs. There were no statistically significant differences ($P > 0.05$).

Abbreviations: HF, high-frequency; LF, low-frequency; LV-IR, hypertensive patients with impaired relaxation left ventricular diastolic dysfunction; LV-NF, hypertensive patients with normal left ventricular diastolic function; LV-P/R, hypertensive patients with pseudonormal or restrictive classes of left ventricular diastolic dysfunction; N, normotensive controls; SBP, systolic blood pressure; TWP, total power; VARR, variance.
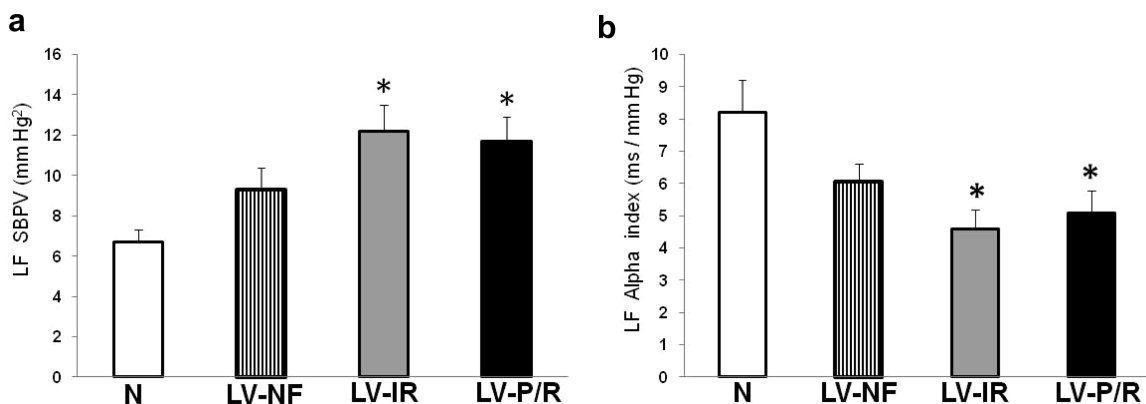
Figure 1. Sympathetic modulation to the blood vessels and baroreflex in all evaluated groups. **(a)** Low-frequency (LF) component of the systolic blood pressure variability (SBPV) in all of the evaluated groups. **(b)** LF alpha index: baroreflex sensitivity in all evaluated groups. LV-IR, hypertensive patients with impaired relaxation left ventricular diastolic dysfunction; LV-NF, hypertensive patients with normal left ventricular diastolic function; LV-P/R, hypertensive patients with pseudonormal or restrictive classes of left ventricular diastolic dysfunction; N, normotensive controls. *$P < 0.05$ vs. N group.

Figure 2. Muscle sympathetic nerve activity (MSNA) values of all evaluated groups, expressed in burst frequency. LV-IR, hypertensive patients with impaired relaxation left ventricular diastolic dysfunction; LV-NF, hypertensive patients with normal left ventricular diastolic function; LV-P/R, hypertensive patients with pseudonormal or restrictive classes of left ventricular diastolic dysfunction; N, normotensive controls. *$P < 0.05$ vs. N group; **$P < 0.05$ vs. LV-NF group.
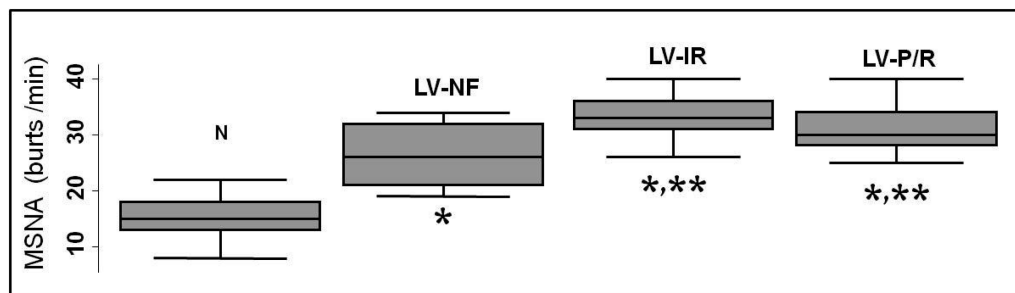
LV-P/R group: 32±1 bursts/min, 47±2 bursts/100 heartbeats) compared with the LV-NF group (26±3 bursts/min, 37±2 bursts/100 heartbeats; $P < 0.05$) and the N group (15±2 bursts/min, 23±2 bursts/100 heartbeats; $P < 0.05$).

Furthermore, the LV-NF group (26±3 bursts/min, 37±2 bursts/100 heartbeats) had higher MSNA values compared with the N group (15±2 bursts/min, 23±2 bursts/100 heartbeats; $P < 0.05$).

Small increases in LV mass and higher BP levels could have an impact on sympathetic activity. To evaluate this possibility, we performed a multiple linear regression analysis, which showed that in this studied population, only the presence or absence of LVDD had a strong association with MSNA ($P < 0.0001$; $r^2 = 0.603$). No association with SBP or LV mass was observed ($P > 0.05$).

DISCUSSION

The main findings of this study are that even with the regular use of antihypertensive medication, hypertensive patients with LVDD have higher MSNA than patients without LVDD and that the classes or stages of LVDD showed no effect on sympathetic activity.

Several variables were controlled to reduce factors that could potentially affect sympathetic activity, such as body mass index, metabolic disturbances, extremes of age, and the presence of signs and symptoms of cardiac heart failure at the time of evaluation. All of the hypertensive patients were on similar antihypertensive medication, and their office BP was considered controlled. A previous study, which evaluated hypertensive patients who had never received treatment for hypertension, showed an increase in MSNA and impaired baroreflex sensitivity associated with diastolic dysfunction.[9] Our data add to these observations, indicating that even with the use of antihypertensive drugs and the control of BP, it is still possible to detect peripheral sympathetic hyperactivity associated with diastolic dysfunction. Furthermore, the classes of LVDD had no effect on the sympathetic drive.

The mechanisms associated with high sympathetic activity are unknown. The medication's interference with sympathetic activity cannot be ruled out in our study. Several studies using different methodologies have evaluated the influence of monotherapy treatment on sympathetic activity. It has been shown that acute and chronic use of angiotensin converting enzyme (ACE) inhibitors decreased MSNA in healthy volunteers[18] and in patients with HF[19] but caused no changes in hypertensive patients.[20] Regarding the effect of chronic dihydropyridine administration, a null effect[21] or a small residual increase in MSNA has been reported in hypertensive patients.[22] Because 80% of our patients were using an ACE inhibitor (enalapril) associated with a dihydropyridine (amlodipine), we can speculate that even if medication had some influence on sympathetic activity, this bias affected all groups of patients similarly.

Although it was not the primary purpose of this study, we demonstrated that hypertensive individuals have higher MSNA than normotensive subjects. Some studies do not support this finding;[23] however, our study is in agreement with previous observations in a different set of patients.[9,24]

The hypertensive patients with LVDD had impaired baroreflex sensitivity as evaluated by the LF alpha index. This may increase BP variability, which is known to intensify the target organ damage.[25] Indeed, the assessment in the time domain of SBP in our study showed a trend toward increased variance in the LV-IR and LV-P/R groups compared with groups N and LV-NF. In an animal model with permanent impairment of the baroreflex sensitivity, BP variability has been shown to have a greater influence on organ damage than the pressure level itself does.[26]

Importantly, the LF component of SBP variability, which is believed to represent sympathetic modulation of vessel tone, was significantly increased in the LV-IR and LV-P/R groups compared with the N group, further indicating increased sympathetic activity to the muscle vessels.

There were no differences in cardiac autonomic modulation inferred from the analysis of HR variability between groups. There was a discrepancy between the sympathetic activity assessed by HR variability and MSNA. Other studies in different populations have shown the same discrepant results[27–29].

Different mechanisms not assessed in this study may explain the greater sympathetic activity detected only in the peripheral territory. One possibility is the alteration in the reflex mediated by cardiopulmonary receptors. This reflex primarily modulates sympathetic activity to the muscles and kidneys and is compromised in situations with cardiac remodeling, such as systolic HF[30] and left ventricular hypertrophy (LVH).[31] The involvement of the cardiopulmonary reflex in hypertensive patients with diastolic dysfunction and without LVH needs to be evaluated.

This study contributes to a better understanding of the pathophysiology of asymptomatic hypertension-related LV dysfunction, a condition that is still poorly understood. The clinical significance of peripheral hyperactivity and baroreflex impairment relies on the higher cardiovascular morbidity and mortality demonstrated in numerous clinical trials and epidemiological studies among different populations.[32–35] The hyperactivity of the sympathetic nervous system has been considered a major component of the development of cardiac structural and functional changes in hypertension.[36] The decrease and control of BP is related to reduced cardiovascular risk.[37] However, even when hypertensive patients treated in the public health service exhibit control of their BP levels, the higher sympathetic activity persisted, which can represent a continued risk of cardiovascular events.

In conclusion, asymptomatic hypertensive patients with LVDD with a positive profile of cardiac remodeling exhibit a persistent increase in MSNA and baroreflex impairment despite an acceptable level of BP control with antihypertensive drugs. The hyperactivity of the sympathetic system is independent of the class of LVDD. The sympathetic overdrive associated with LVDD may account for the increased cardiovascular risk in these patients.

The patients did not undergo 24-hour ambulatory BP monitoring. Although all of the hypertensive groups registered similar office BPs, it is possible that differences in BP circadian rhythm exist among these groups. Loss of circadian rhythm is related to higher sympathetic activity.[38]

Diastolic dysfunction is a chronic process with a poor known pathophysiology. The role of specific treatments for this condition per se is unclear; consequently, treatment is directed to the root of its origin, such as hypertension. Because drugs with a positive effect on ventricular remodeling, such as angiotensin-converting enzyme inhibitors and calcium channel blockers, may not overcome the sympathetic hyperactivity associated with LVDD, drugs that can decrease sympathetic activity should be considered DD treatment.

ACKNOWLEDGMENT

DISCLOSURE

The authors declared no conflict of interest.

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