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Research Article

Differential effects of enalapril–felodipine versus enalapril–lercanidipine combination drug treatment on sympathetic nerve traffic and metabolic profile in obesity-related hypertension

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Abstract

Scanty information is available on the effects of combination drug treatment based on an ACE inhibitor and a calcium channel blocker on the neurometabolic alterations characterizing obesity-related hypertension (OHT). After 2-week run-in with enalapril (20 mg), 36 OHTs were randomized according to a double-blind crossover design to a combination therapy with either lercanidipine 10 mg (L) or felodipine extended release 5 mg (F), each lasting 8 weeks. Measurements included clinic and ambulatory blood pressure (BP) and heart rate, homeostasis model assessment index, plasma norepinephrine, and muscle sympathetic nerve activity. Patients with uncontrolled BP were then uptitrated to 20 mg/d (L) and 10 mg/d (F) combined with enalapril 20 mg, respectively, for further 8 weeks. For similar BP reductions, enalapril–lercanidipine (EL) caused norepinephrine and MSNA increases significantly less pronounced than those seen with enalapril–felodipine, the lesser sympathoexcitation observed with EL being coupled with a significant improvement in homeostasis model assessment index. This was the case also when L and F were uptitrated in the combination. In OHT, at variance from enalapril–felodipine, EL combination is almost entirely devoid of any major sympathoexcitatory effect and is associated with an improvement in insulin sensitivity. J Am Soc Hypertens 2016;■(■):1–8.

Keywords: Combination drug treatment; lercanidipine; obesity-related hypertension; sympathetic activity.

Introduction

Obesity-related hypertension represents a clinical condition characterized by a high or a very high cardiovascular risk, the abnormal values of body fat depot as well as blood pressure (BP) being frequently associated with major cardiovascular complications and presence of end-organ damage, metabolic abnormalities, insulin resistance, endothelial dysfunction as well as neuroadrenergic activation.[1–10] This latter alteration appears to be of key pathophysiological relevance and a major target of the therapeutic intervention considering that in obesity-related hypertension sympathetic neural mechanisms (1) contribute at the development and progression of the high BP state and the related target organ damage,[3,4,7–10] (2) participate at the occurrence of metabolic alterations,[3,4,7,9,10] and (3) concur with other factors at determining the cardiovascular complications as well as the cardiovascular outcome of the obese state associated with hypertension, including sudden cardiac death.[5,6,9,10] Scanty, however, is the information

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available on the effects of antihypertensive drug treatment on neuroadrenergic function in patients in which hypertension is complicated by obesity.[5–7] This is particularly the case for the combination drug treatment based on an ACE inhibitor and a calcium antagonist, that is, the therapeutic approach recommended by current guidelines and most commonly used in the treatment of this clinical condition.[6]

The present study was designed at providing information on this issue. In particular, the study was aimed at comparing the long-term effects of two different combination drug regimens, both based on an ACE inhibitor and a calcium antagonist, that is, enalapril–felodipine (EF) and enalapril–lercanidipine (EL), on sympathetic cardiovascular drive, as assessed by the only approach available so far to directly and continuously measure in humans sympathetic neural discharge, that is, the microneurographic technique.[2,5,6]

Methods

Study Population

The study population consisted of 45 obese hypertensive patients of both sexes (33 men and 12 women) recruited from our outpatient clinic. However, because of the inability to obtain stable muscle sympathetic nerve activity (MSNA) in all experimental sessions (see below), the study was successfully carried out in 36 patients. They reported BP values consistently higher than 140/90 mm Hg on ACE inhibitor monotherapy at repeated sphygmomanometric measurements and displayed body mass index (BMI, body weight divided by the square of height) between 30 and 40 kg/m^2. All patients were in sinus rhythm, occasionally alcohol drinker, and none was a cigarette smoker. Coronary heart disease, congestive heart failure, cerebrovascular disease, renal insufficiency, diabetes mellitus, respiratory diseases, or other conditions known to affect autonomic function[5,6] were ruled out on the basis of clinical evidence or appropriate biochemical or instrumental work-up. Obstructive sleep apnea of mild-to-moderate degree was detected via overnight polysomnography in 16 of the 36 patients who completed the study. No patient was involved in a physical training or in a body weight reduction program. The protocol of the study was approved by the Ethics Committee of the Istituto Auxologico Italiano and the IRCCS Mutimedica, Sesto San Giovanni, Milan, Italy. All patients gave written consent to the study after detailed explanation of its nature and purpose.

Study Design

After recruitment, patients entered a 2-week run-in period during which they discontinued previous ACE inhibitor treatment and were switched directly to enalapril 20 mg once daily in the morning. The study proper consisted of four identical experimental sessions within a randomized double-blinded crossover design (see below, Figure 1). Following the first experimental session, the patients were randomly allocated according to a computerized list to take a morning oral dose of felodipine extended release (5 mg, 18 patients) or lercanidipine (10 mg, 18 patients) added to the already administered enalapril 20 mg/d for an 8-week period. This was followed by the second experimental session, carried out according to a protocol identical to the one described for the first session (see below). Felodipine or lercanidipine administration was then discontinued, and the patients remained for a 2-week period under enalapril 20 mg/d treatment. This was followed by a second 8-week period during which the patients received at the dosage above mentioned the calcium antagonist drug not taken in the first 8-week period and added to enalapril treatment. A third experimental session was then performed, according to the same protocol of the two previous experimental sessions. A 24-hour ambulatory BP was performed before and at the end of the first 8-week treatment and assessed again following the second 8-week treatment. Finally, in the patients with persistent uncontrolled BP at the visit carried out after the second treatment period, the assigned daily dose of drugs was uptritated to enalapril 20 mg/felodipine 10 mg (n = 14) or enalapril 20 mg/lercanidipine 20 mg (n = 13), according to a single blinded design. This treatment period, lasting again 8 weeks, was followed by a final experimental session, in which, with the exception of 24-hour ambulatory BP monitoring, the previously mentioned variables were reassessed. During each period, patients were seen at a 2-week interval in the outpatient clinic of our hospital. No lifestyle changes were advised. Pills count was performed at each visit with new medications dispensed.

Measurements

Measurements included BMI, waist-to-hip ratio, sphygmomanometric, beat-to-beat finger (Finapres; Ohmeda 2300, Englewood, Florida, USA) systolic BP, diastolic BP, heart rate (HR; electrocardiogram), respiration rate (pneumotachograph), and echocardiographically detected left ventricular mass index, calculated by the Devereux formulae normalized to body surface area.[11,12] They also included multiunit recordings of muscle sympathetic nerve traffic (MSNA) via the microneurographic technique, as previously described,[2,7,13] venous plasma norepinephrine (NE) measured by high-performance liquid chromatography,[14] and fasting plasma glucose and plasma insulin, which were determined from a blood sample taken from an antecubital vein. From a standard formulae (plasma insulin × fasting plasma glucose/22.5), calculation was made of the homeostasis model assessment (HOMA) of

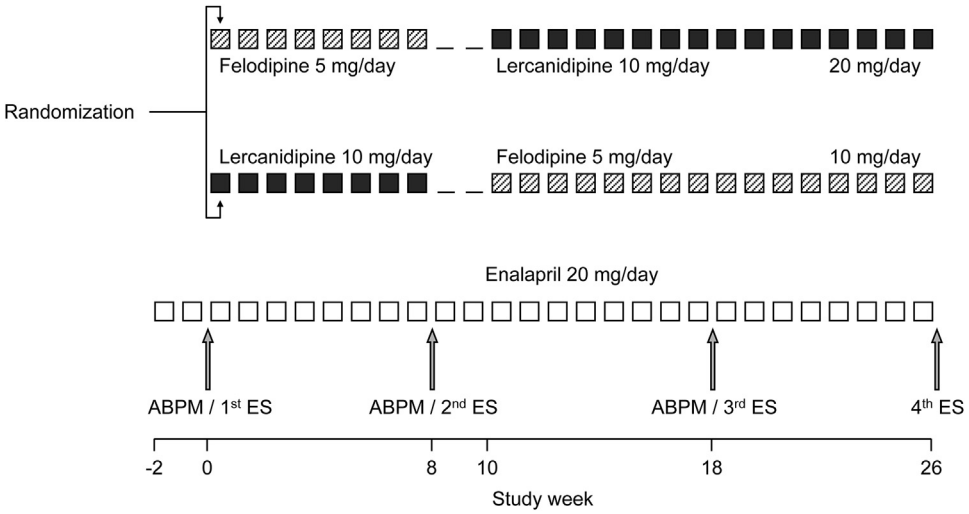

Figure 1. Scheme of the experimental design of the study. For details see Methods. ABPM, ambulatory blood pressure monitoring; ES, experimental session.

insulin resistance, which was used as an estimate of insulin resistance.[15] Ambulatory BP monitoring was obtained over the 24 hours by an oscillometric device (Spacelabs 90,207, Spacelabs, Issaquah, Washington, USA) with the readings set at 15-minute and 20-minute intervals during the daytime (from 07.00 to 23.00 hour) and the nighttime (from 23.00 to 07.00 hour) periods, respectively.[16] The device was applied in the morning, and individuals were allowed to return home with the instruction to attend at their usual activities and to come back to the hospital the following day for device removal. The cutoff BP values for ambulatory BP normality were those mentioned by the international guidelines, that is, a 24-hour average less than 130/80 mm Hg.[6] BP, electrocardiogram, and MSNA were digitized with a sampling frequency of 1000 Hz (PowerLab Recording System Model ML870 8/30; AD Instruments, NSM2153; Bella Vista, New South Wales, Australia). MSNA was quantified over a 30-minute period either as bursts incidence over time (bursts per minute) or as bursts incidence corrected for HR values (bursts per 100 heartbeats). Respiration rate was monitored by a strain gauge pneumograph positioned at midchest level.

Protocol and Data Analysis

Each of the four experimental sessions was carried out as follows. Each individual came to the laboratory in the late morning after a light breakfast and an overnight abstinence from alcohol and coffee consumption. The experimental session was usually carried out 4 to 5 hours following the assumption of the drug treatment which took place around 07.00 o'clock. Patients were placed supine, and BP was measured three times with a mercury sphygmomanometer. They were then fitted with the intravenous cannula and the devices to measure finger BP, HR, and respiration rate. Venous blood samples for plasma NE were taken 30 minutes after putting the venous cannula. After 10-minute interval, BP, HR, and MSNA were continuously measured during a 30-minute period. Data were collected in a semi-dark and quiet room at a constant temperature of 20–22°C. They were analyzed by a single investigator, who was not involved in data collection and was unaware of the experimental design. Values from individual patients were averaged for each group of treatment (EF and EL) and expressed as means ± standard error of the mean. The significance of the differences in mean values was assessed by two-way analysis of variance. The two-tailed t test for paired or unpaired observations was used to locate the difference between the baseline condition and the post-drug period or between drugs using the Bonferroni's correction for multiple comparisons. A P value $< .05$ was taken as the minimal level of statistical significance.

Results

Table 1 shows baseline values recorded in the whole study population. The 36 patients who performed the study showed elevated BMI as well as waist-to-hip ratio values coupled with clinic and ambulatory systolic and diastolic BP values well above the normal range. They also showed normal laboratory values with the exception of HOMA index which was above the normal range. This was also the case for left ventricular mass index, whereas left ventricular ejection fraction was preserved. Plasma NE levels were normal or slightly above the normal range, whereas MSNA values were similar to the ones reported in other studies carried out in obese hypertensive patients and well above the ones detected in other studies performed in normotensive lean subjects with a similar age.[2,7,10]

Table 1
Behavior of hemodynamic, biochemical, echocardiographic, and MSNA values before randomization in the study population

Variable	Value
Sex (male/female)	29/7
Age (y)	48.8 ± 2.1
Body mass index (kg/m^2)	32.9 ± 0.5
Waist-to-hip ratio	0.97 ± 0.01
Clinic SBP/DBP (mm Hg)	153.4 ± 2.1/102.9 ± 1.7
Finger SBP/DBP (mm Hg)	151.1 ± 2.0/101.3 ± 1.8
24-hour SBP/DBP (mm Hg)	147.2 ± 1.9/98.1 ± 1.5
Clinic heart rate (beats/min)	74.3 ± 2.5
Finger heart rate (beats/min)	72.8 ± 2.2
24-hour heart rate (beats/min)	69.6 ± 1.6
Left ventricular mass index (g/m^2)	114.5 ± 1.5
Left ventricular ejection fraction (%)	60.5 ± 0.9
Plasma total cholesterol, mg/dL	214.2 ± 26.4
Plasma HDL cholesterol, mg/dL	47.4 ± 9.1
Plasma triglycerides, mg/dL	172.5 ± 24.8
Plasma glucose, mg/dL	103.7 ± 13.6
Plasma insulin, μU/mL	10.5 ± 0.8
HOMA index (a.u.)	2.59 ± 0.1
eGFR (mL/min per 1.73 m^2)	76.6 ± 3.2
Respiration rate (breaths/min)	17.6 ± 1.3
MSNA (bursts/min)	47.9 ± 2.1
MSNA (bursts/100 heart beats)	61.1 ± 2.8
Plasma norepinephrine (pg/mL)	239.4 ± 21.0

A.u., arbitrary units; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; MSNA, muscle sympathetic nerve traffic; SBP, systolic blood pressure.

Data are shown as means ± standard error.

The effects of the two combination drug treatments tested in the present study, that is, enalapril 20 mg–felodipine 5 mg/d and enalapril 20 mg–lercanidipine 10 mg/d, on hemodynamic, metabolic, neurohumoral, and MSNA values are shown in Figure 2. Both the two combination drug treatments caused significant reductions in both clinic and ambulatory systolic and diastolic BP, the magnitude of the decreases being greater, although not significantly, for the EL than for the EF combination. Both clinic and ambulatory HR values increased during the two combination regimens administration, the magnitude of the increase being greater, although again not significantly, for EF than for EL. HOMA index was almost unchanged during EF treatment, whereas it showed a reduction during EL, the differences between the two drug combinations being statistically significant. Figure 2, middle and right lower panels also show the increases in plasma NE and MSNA values detected during the two drugs combination regimens. The magnitude of both plasma NE and MSNA elevation was, however, significantly less pronounced during the combination treatment based on EL as compared with the one seen during EF.

Figure 3 shows the behavior of clinic systolic and diastolic BP, HR, MSNA, and plasma NE values measured in the 27 patients displaying uncontrolled clinic BP values at the end of the second 8-week treatment with either enalapril 20 mg-felodipine 5 mg (n = 14) or enalapril 20 mg–lercanidipine 10 mg (n = 13) combination treatment. In these patients, uptitration of felodipine and lercanidipine to 10 mg and 20 mg, respectively, in combination with enalapril 20 mg allowed to achieved in all patients a satisfactory clinic BP control. These greater BP reductions were associated with a much more marked increase in HR, plasma NE, and in MSNA in the EF treated rather than in the EL-treated group.

The two combination drug regimens were well tolerated during the entire period of the study, the most frequently occurring treatment-related side effects (almost always detected at the higher doses of the calcium channel blocking drugs) being palpitations (4 in the EF and 2 in the EL-treated group), headache (2 in the EF and 1 in the EL-treated group), and peripheral edema (2 in the EF and 0 in the EL-treated group). They were of mild or moderate degree, however, and in no patient their occurrence required drug treatment discontinuation.

Discussion

Two are the major novel findings of our study. (1) In our obese hypertensive patients, the BP-lowering effects exerted by the two drug combination treatments tested in the present study are associated with a differential effect on adrenergic cardiovascular drive, the EL combination being almost entirely devoid of any major sympathoexcitatory effect, at variance from EF combination which caused a marked adrenergic activation. (2) The two drug combinations tested in the present study trigger different effects on a sensitive marker of glucose metabolism such as HOMA index, the EL combination being capable to improve this metabolic variable, at variance from the EF which left unchanged or even, in some cases, worsened HOMA values. This allows to conclude that in obese hypertensive patients, combination drug treatments based on an ACE inhibitor and a calcium antagonist of the dihydropyridine class may have not necessarily the same sympathetic and metabolic effect, some combinations, such as enalapril/lercanidipine, showing a more favorable impact on the neurometabolic alterations characterizing the obese hypertensive state.[1–5,8,9] A favorable metabolic effect has been also reported with other combination drug treatment based on other ACE inhibitor/calcium antagonist such as trandolapril-slow release verapamil, which in patients with metabolic syndrome have been show to improve insulin sensitivity at variance from the losartan–hydrochlorothiazide drug combination.[17]

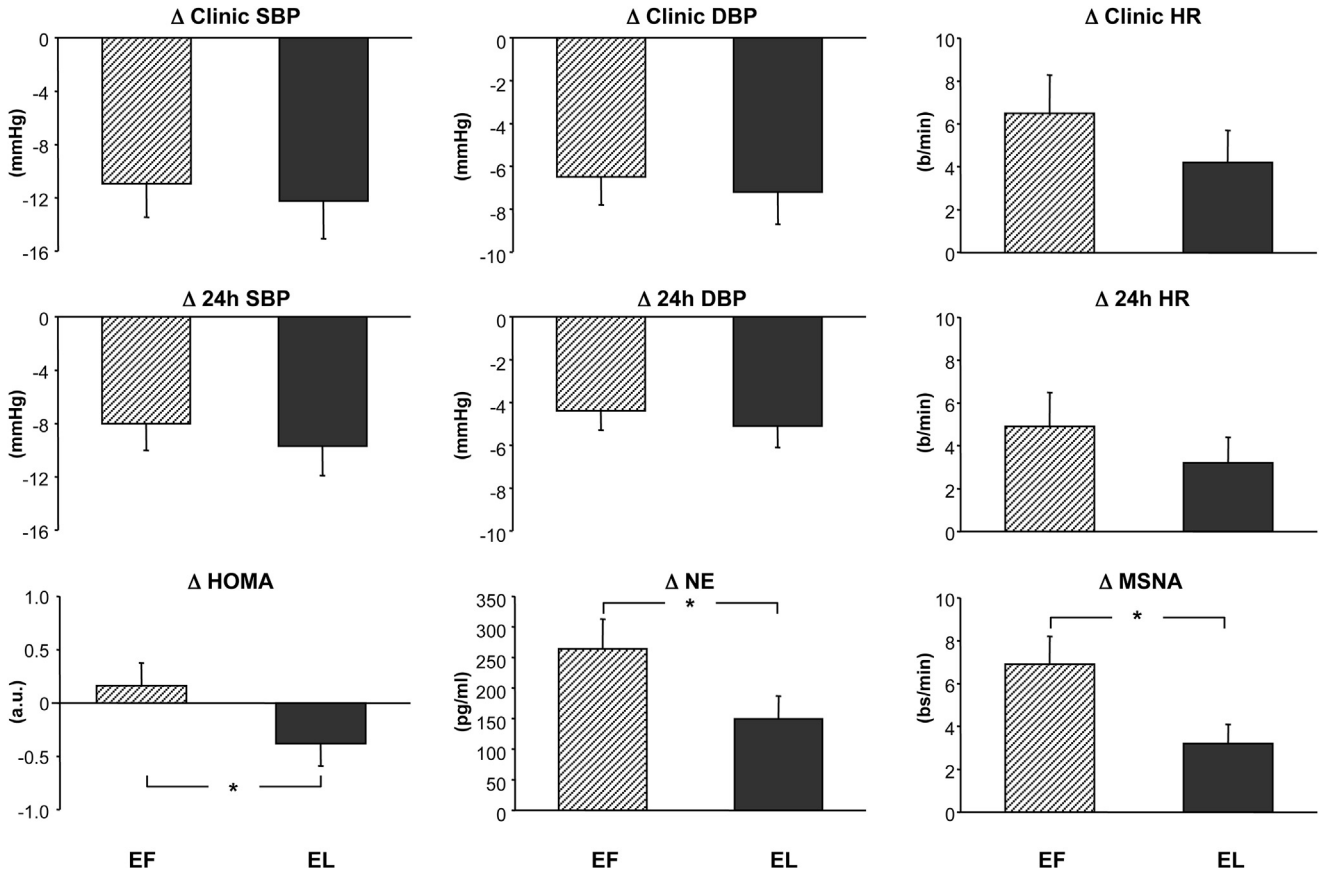

Figure 2. Changes in clinic systolic and diastolic blood pressure (Δ clinic SBP and DBP), clinic heart rate (Δ clinic HR), ambulatory systolic and diastolic blood pressure (Δ 24-h SBP and DBP), ambulatory heart rate (Δ 24 HR), homeostasis model assessment of insulin (Δ HOMA), venous plasma norepinephrine (Δ NE), and muscle sympathetic nerve activity (Δ MSNA) observed after 8 weeks treatment with enalapril 20 mg–felodipine 5 mg day (EF, n = 36 dashed bars) and enalapril 20 mg-lercanidipine 10 mg day (EL, n = 36 black bars). Data are shown as means ± SEM. Asterisks (*$P < .05$) refer to the statistical significance between treatment groups. SEM, standard error of the mean.

Our study does not allow to clarify the mechanisms potentially responsible for the different effects on sympathetic function of the two drug combinations. We can rule out that they depend on a different degree of the BP-lowering effects and thus on a different activation of arterial baroreceptors triggered by the BP decrease induced by the two combination drug regimens[18] because the BP reductions were similar for magnitude in the two combination treatments (or, if anything, slightly greater in the EL treatment which showed, however, a sympathetic activation significantly less for magnitude than the one seen during EF treatment) both when assessed via the sphygmomanometric and the ambulatory BP technique. We can also exclude that they were related to the ACE inhibitor treatment because both the two drug combinations were based on the use of enalapril drug administered at the same daily dosage. We can thus speculate that they were due to the differences in the effects of the calcium channel blocker drug used in the combination, that is lercanidipine and felodipine, on sympathetic neural function, as documented in a previous study published by our group.[13] The difference, however, appears not to be due to a heterogeneity of the pharmacokinetic profile of the two drugs because both lercanidipine and felodipine share a long duration of action that provides a 24-hour BP-lowering effect when given once daily.[19–22] It may rather be due to the greater lipophilicity of lercanidipine, which may favor a direct depressor effect on vasomotor center through its crossing of the blood-brain barrier.[19,22] This has been recently shown for other calcium antagonist drugs, such as azelnidipine.[23]

Three other results of our study deserve to be briefly discussed. First, we found that the different effects of the two drug combination regimens on sympathetic neural function were paralleled by similarly different effects on insulin resistance state, the EL combination, at variance from the EF one, being capable to reduce HOMA index and thus to improve insulin sensitivity. Because sympathetic neural factors are involved in the regulation of insulin metabolism,[7–10] we may speculate that the effects of the two drug combinations are at least in part dependent on their

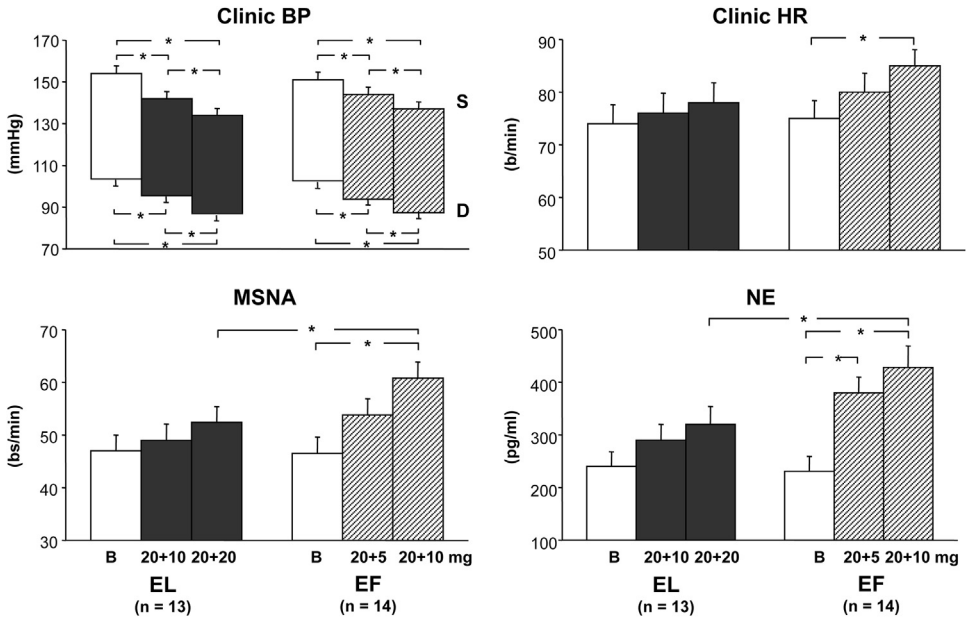

Figure 3. Mean ± SEM values of clinic blood pressure (BP), heart rate (HR), muscle sympathetic nerve activity (MSNA), and venous plasma norepinephrine (NE) values in the patients who completed the 28-week study period (n = 13 and n = 14 in the enalapril–lercanidipine and in the enalapril–felodipine–treated groups). S: systolic; D: diastolic; B: basal values before randomization; EL 20 + 10 mg: values recorded after an 8-week treatment with enalapril 20 mg–lercanidipine10 mg day; E + L 20 + 20 mg: values recorded after a further 8-week treatment with enalapril 20 mg–lercanidipine 20 mg day; EF 20 + 5 mg: values recorded after an 8-week treatment with enalapril 20 mg–felodipine 5 mg day; EF 20 + 10 mg: values recorded after a further 8-week treatment with enalapril 20 mg–felodipine 10 mg day. Asterisks (*$P < .05$) refer to the statistical significance between different treatments. SEM, standard error of the mean.

different sympathetic impact, as also shown for other antihypertensive drugs.[24–27] They may, however, also depend on the fact that the drug combination EL increases intracellular expression of proteins involved in insulin signalling.[28] Second, as documented in the first-line EL treatment study and in other studies,[29–31] greater daily dosages of lercanidipine or felodipine in the combination regimen with enalapril caused a greater reduction in BP with the possibility to achieve a greater BP control. The results of the present study suggest, however, that the potentiation of the BP-lowering effects associated with the higher daily dosage of the calcium channel blockers is accompanied by a further increase in HR, MSNA. and plasma NE, indicating an additional dose-related sympathetic activation. However, the magnitude of this effect was more pronounced when sympathetic drive was assessed by plasma NE than by MSNA recording, presumably because processes other than release (tissue clearance of the adrenergic neurotransmitter, for example) participated in the phoenomenon.[8] The effect was also less marked in the EL combination drug treatment and significantly much greater in the case of the EF combination. The potentiation of the sympathoexcitatory effects exerted by felodipine, even when combined with an ACE inhibitor, appears to be similar for magnitude to what reported with other calcium antagonist, such as amlodipine.[32] Finally, the assessment of the sympathetic effects of the two different drug combinations tested in the present study was based on three independent adrenergic markers, that is, HR, plasma NE, and MSNA. In general, they changed in a similar fashion in response to the long-term administration of the two drug combinations. The agreement between different markers in evaluating the adrenergic responses strengthens the study conclusions and suggests that the changes we observed probably involved the sympathetic function at cardiac as well as at different peripheral vascular levels. However, in line with results of previous studies,[7,10,33] the sympathetic assessment based on MSNA recording displayed a sensitivity greater than HR and plasma NE in detecting changes in sympathetic neural drive. This may be due to a number of factors, including the physiological notion that, at variance from plasma NE and MSNA, HR represents a less specific adrenergic marker, its values depending not only on sympathetic but also on parasympathetic influences to the sinus node.[34]

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